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CONTENTS

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EDITORIAL

Visit to South Africa: 1st—10th April, 1959

The Secretary for Health of the Union of South Africa kindly welcomed a visit from the Editor to see something of the leprosy work in Westfort Institution, Pretoria. It was possible to spend 10 days there, and it was a very stimulating experience, for the work under Dr. A. R. Davison, the Medical Superintendent, is of the highest quality. Westfort is an institution containing over 900 patients. Dr. Davison is assisted by Dr. Egnal, Dr. Doevendans, and Miss Kellerman, the matron, with four sisters and 15 European female nursing assistants, and Mr. Tilley and Mr. Banks for the management. There is a holiday home on the coast called the Lady Mary Baring Home. The results of the work have been good as there have been definite signs of a reduction in the intake of new cases of European and coloured patients. The average intake of all cases is about 600 per annum. There have been great increases in the number of discharges but so far no decrease in total notifications. In the whole of the Union there are four institutions with a total of 1,613 patients. The equipment, housing and buildings of Westfort are first class, and there is complete availability of all drugs and special procedures necessary for all features of leprosy morbidity. Dr. Davison kindly gave up his time to make thorough demonstrations of the patients and of his method of treating them. Research projects go on at Westfort and it has participated recently in the therapeutic evaluation projects of the Leonard Wood Memorial. It became clear, as the cases were demonstrated day after day during the visit, that the type of leprosy in this region should be placed further to the left of the spectrum of leprosy which has lepromatous on the left than the leprosy of countries like East Africa or Nigeria. There was a far greater tendency here to all forms of lepra reaction, and in particular erythema nodosum leprosum. Dr. Davison has had great success with the protection and management of patients in these reactions, and his great contribution has been the demonstration of the value of the antimalarial type of drug (mepacrine and camoquin) in conjunction with ACTH and other corticosteroids. Of particular interest were some signs of the Lucio phenomenon, and of the pellagra factor.

It became quite clear that the work of leprosy in the Union is of the highest standard and humanely carried out. It is hoped that the other sections of work in the Union may be seen on a subsequent visit.

Visit to Brazzaville for the WHO Conference for African Leprologists on Leprosy in Africa: 14th—22nd April, 1959

This congress was organised by WHO, the secretary being Dr. J. Gay Prieto, Chief of the Leprosy Section of the Division of

Communicable Diseases of WHO. It was attended by over 40 leprosy workers and the Chairman elected was Médecin-Général Richet, with Dr. Davison of South Africa as Vice-Chairman. The great value of this conference was the opportunity of so many leprosy workers in Africa getting together and getting to know each other's point of view and hearing about each other's work. There was an opportunity during the conference of seeing the work at Dolisie in French Equatorial Africa and the work at Leopoldville in the Belgian Congo, both of which were very instructive to all the visitors.

With Africa in a ferment of political changes in progress and to come, it was of great value for such a meeting to be held. Each country differs from the other considerably in local conditions and in resources with which to fight leprosy. It was impossible to lay down a hard and fast rule for the control of leprosy in Africa, and it was fascinating to see how each country had applied the principles of leprosy control with adaptability and commonsense. Apart from the more advanced countries where leprosy is well integrated into the Department of Public Health, it became evident that the control of leprosy in Africa would continue best in those countries where trouble had been taken to instruct and train nationals of that country to assist in the leprosy campaign.

Further News of Macrocyclon (See *Lep. Rev.* **29,** 2; Apr. 1958, p. 68)

Macrocyclon is one of the polyoxyethylene ethers which are surface-active agents. Dr. J. A. McFadzean has given a preliminary report, as at 12th September, 1958, to the Leprosy Sub-committee of the Colonial Medical Research Committee, London, on a trial on human leprosy. There were 6 adult males with lepromatous leprosy, balanced with 6 similar cases on DDS. All patients were given a high protein diet throughout the trial, and for a month before it. The macrocyclon patients were given weekly intravenous injections of the drug at 25 mg./kilo for 14 weeks, thereafter gradually increased to 50 mg/kilo over a period of 8 weeks. The control patients were given 400 mg. of DDS in oil weekly intramuscularly in a divided dose for 5 weeks, raised to 600 mg. weekly thereafter. Full laboratory observations were done, and included the assessment of bacterial index by biopsy (by Dr. D. S. Ridley, of the Hospital for Tropical Diseases, London). In one patient there was a fall in the B.I. of 95% but in the other cases it seemed that macrocyclon was clinically much inferior to DDS, this being supported to some extent by the biopsies. There was evidence that macrocyclon produces a mild degree of renal damage. All the patients showed a constant albuminuria which improved after cessation of the dosage. The trial was therefore brought to an end. Dr. McFadzean suggests that further trials of macrocyclon alone are not warranted, but there might be value in a

trial of it at 25 mg./kilo in combination with DDS, and compared to sulphone alone. This trial will probably be carried out by his successor, Dr. M. F. R. Waters, at Sungei Buloh Research Centre in Malaya.

The Nature of the Mitsuda Reaction

We directly requested Dr. R. Kooij to state his present lines of thought on his very interesting work on the nature of the lepromin and allied reactions, and he has responded as follows:

"In my ensuing remarks I leave aside the Fernandez reaction of the lepromin test and confine myself to the Mitsuda reaction which is read 3 or 4 weeks after the intradermal injection of lepromin. I have shown that not only the leprosy bacilli are responsible for the evoking of the Mitsuda reaction, but that also the tissue component plays a role and that even with normal tissue suspensions without bacilli, positive reactions of Mitsuda type are obtained in tuberculoid leprosy, and negative ones in lepromatous leprosy. This explains why the lepromin reaction is not a specific reaction for leprosy and fails to be of diagnostic use. It is of use for the classification of leprosy. The typical feature of the Mitsuda reaction is not its positivity in the tuberculoid leprosy, but its negativity in the lepromatous type. Most adult healthy people show a positive Mitsuda reaction to standard lepromin.

The negative Mitsuda reaction in the lepromatous type is probably due to the inability of patients of that type to break down the leprosy bacilli. This perhaps may be the fault of the reticuloendothelial system, expressed as a lack of special enzyme systems in individual constitutions. The lack of reactivity to lepromin among infants and the gradually developing response among growing children may be interpreted as a manifestation of a normal maturation cycle. Contact with leprosy bacilli is not necessary for this reactivity to lepromin (Kooij and Rutgers, Internat. J. of Leprosy, **26,** 24, 1958; Swerts, Ann. Soc. Belge Med. Trop. **35,** 801, 1955). However, Kooij and Rutgers showed that the reaction to lepromin was accelerated and intensified by leprosy and tuberculosis. Probably these facts might give an explanation of the conversion of negative lepromin reactions to positive by BCG vaccination, perhaps owing to the non-specific Dienes effect, although cross sensitization cannot be ruled out with certainty.

The possible protective influence of BCG vaccination against leprosy could also be explained by the non-specific Dienes effect. The Mitsuda reaction is an unusual type of reaction. There is only one similar reaction in clinical use. This is the Kveim reaction in sarcoidosis. We also found that similar reactions could be obtained with normal tissue suspensions.

The above three reactions have many things in common; they

have the same method of preparation, evoke the same histological picture, and the active principle is bound to the particulate matter.

Probably we are dealing with a kind of foreign body reaction or isomorphic (isopathic) phenomenon of certain individuals due to their individual constitution. With the above three reactions we can detect this mode of response in individual constitutions.

More knowledge about the nature of these reactions may lead to a better understanding of the pathogenesis of leprosy and sarcoidosis. Not much is known about the nature of these so-called foreign-body reactions; they are not easily evoked, very special conditions being required. Several attempts in the past have been made with normal tissue to evoke a positive Mitsuda reaction in patients with tuberculoid leprosy, but without success until my recent work. Furthermore, many experiments have been carried out with normal tissue suspensions to evoke a positive Kveim reaction in patients with sarcoidosis (by Danbolt, among others), usually with negative results. The reason for this is that probably the preparations were not concentrated enough and did not contain sufficient particles of a certain size and chemical composition. Attempts at evoking positive reactions in patients with sarcoidosis by injecting particulate and other elements into the skin, e.g., catgut (Danbolt), silicate (Refvem), talc and aleuronate (Hathausen), Indian ink and paraffin oil (Schauman and Seeberg) have given negative results.

It seems that very special conditions are required for evoking the Mitsuda type or Kveim type of reaction.

It is of the utmost importance to obtain more knowledge of these conditions for the understanding of leprosy and sarcoidosis. Although in the disease leprosy the leprosy bacillus is essential to the occurrence of the disease, it is not the only factor. The severity of the infection, or even whether or not the disease will become manifest, is chiefly determined by other factors, particularly by the mode of reaction due to the individual constitution. In leprosy we should begin to introduce the polyvalent concept into our thinking about the cause of the disease and to study the constitutional aspects of it more intensively.

Leprosy can evoke pictures indistinguishable from sarcoidosis. The study of the pathogenesis of the *syndrome* sarcoidosis (including silicosis) might be of value for a better understanding of leprosy and *vice versa.* The study of the conditions and nature of the Mitsuda reaction, the Kveim reaction, and the reaction to normal tissue suspensions might be very helpful in this respect; most value will lie in further studies of the required conditions of the reaction to suspensions of normal tissue."

We also asked certain workers for comments and so far the following has come from Dr. F. Sagher, of Jerusalem:

"*On the nature of the isomorphic and isopathic reactions in*

leprosy. As far as we know only leprosy and sarcoidosis react to injection of materials taken from patients with these diseases with a reaction after 3-5 weeks. This reaction is histologically of the same nature as the original disease process and therefore it can be called an isomorphic or Koebner's phenomenon. The difference from the original Koebner's phenomenon, as typical in psoriasis and lichen planus, is only that in the first two diseases the histological reaction is a granulomatous one whereas in both latter diseases a great part of the changes is found in the epidermis. In contrast to the isomorphic phenomenon is the isopathic phenomenon[1, 2, 3, 4] which is a reaction caused by living organisms and is producing a granuloma similar to leproma and not to a tubercle after injection of BCG or leishmania after injection of flagellates of *Leishmania tropica*.

These facts have been worked out mainly in lepromatous and in arrested cases but not enough experience has been gathered in the tuberculoid or indeterminate form.

This leproma-like reaction could be elicited also by leishmanin, tuberculin, milk, or peptone injection or sand-fly bites and Richter[5] was able to elicit reaction after injection of Indian ink. The occurrence of the isopathic changes was found by him also in an indeterminate case and he suggests a possible diagnostic importance in bacillus-poor cases.

Also Waaler[6] from Bergen could find an isopathic response in two patients, one of them with active leprosy and one with residual, and a non-characteristic reaction in further two residual or subsidial patients. He also made an attempt to induce isopathic reaction in his own skin by adding a suspension of skin from one of the leprosy patients to tuberculin, but a passive transfer of the isopathic ability did not occur.

Very thorough speculations concerning these facts were pointed out by Wade in an Editorial of the International Journal of Leprosy[7]. It appears from this observation that in lepromatous leprosy (tuberculoid and indeterminate cases have not been studied in a sufficient number) there is a profound specific alteration of the tissue reactivity of the host which causes various substances to elicit changes characteristic of the disease process irrespective of bacilli at the sites. This alteration may persist long after a case is bacteriologically negative. There is no relation to the patient's reactivity to tuberculin or lepromin and the nature of the injected material seems to be of little consequence.

It is interesting to note that also in sarcoidosis some authors have claimed sarcoid reactions after the injection of tissue from normal spleen but others have not found a reactivity to material other than from sarcoid lesions.

The isopathic reaction can be used to find out whether the skin of a contact of leprosy is already reactive with a lepromatous or

prelepromatous reaction, and this could give some hint whether such a contact will develop the disease or not. But this problem is certainly a long term one and difficult to prove. The reactions seems not to subside by the arrest of the disease following treatment over many years.

Kooij[8] pointed out that the leprosy bacillus although essential for the occurrence of leprosy is not the only factor determining the occurrence and development of the disease and this experimental observation may speak in favour of his opinion.

With all the knowledge today accumulated by the various experiments only some of the problems have been touched but much remains to be learned before we shall have a complete explanation of all these humoral responses."

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This subject remains open for discussion, and contributions are welcome. See abstract of another article by KOOIJ in Dermatologica, **117**, 5, 1958, which is given in this issue of *Leprosy Review*, p. 198.

DIETHYL DITHIOLISOPHTHALATE (ETIP or 'Etisul') IN THE TREATMENT OF LEPROSY

A SECOND PROGRESS REPORT

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Introduction

The early stages of a pilot trial of 'Etisul' in the treatment of leprosy were described in a progress report published at the beginning of this year (Davey and Hogerzeil, 1959). At that point experience justified the following observations.

1. No signs of toxicity were found in the 65 patients taking part in the trial.

2. Administered on its own, Etisul was found to possess chemotherapeutic action which was variable, but in some patients was very marked.

3. Its activity was shortlived, most evident during the first two or three months of treatment. When administered for longer periods, evidence of drug resistance appeared, particularly in patients who through inadequate inunction had received a low dosage.

4. When standard oral chemotherapy was initiated after a short course of Etisul, progress continued to be better than average.

The close observation of the patients concerned has continued. In addition, particular attention has been given to the use of Etisul in combination with oral chemotherapy, both early and late in the course of treatment. Here it is proposed to report on the following.

A. The continued progress of patients on oral chemotherapy following shorter and longer courses of Etisul.

B. The effect of a short course of Etisul late in oral chemotherapy with DDS.

C. The progress during the first six months of patients receiving Etisul in combination with DDS.

D. The progress during the first four months of patients receiving Etisul in combination with DDS and Ciba 1906.

Mode of Administration

The reader is referred to the earlier report for a short review of the properties of ETIP. The drug is presented in 'Etisul' in the form of a perfumed 75% cream, which we have administered by inunction in a dose of 3-6 ccs. twice weekly. Poor results in the earlier stages of the trial following light and localised inunction led to the routine use of widespread inunction with good massage, using a dose of 6 ccs. twice weekly in adults. Inunction is followed by a rest for 2-3

hours, after which the patient takes a warm bath, using scented soap. This routine has proved entirely acceptable.

Toxicity

133 patients have now received courses of Etisul, and no evidence of any toxic action has been found. Dermatitis has not been encountered. Frequent examinations of blood and urine have shown no abnormality. There has been no gastro-intestinal upset. Euphoria has been usual, doubtless due in part to the psychological stimulus supplied by inuncting an unknown substance, but in many patients also indicating a genuine sense of well-being based on real improvement in their physical condition.

Assessment of progress

In the pilot trial of new drugs, it has been our practice to assess progress on a basis of clinical, histological, and bacteriological changes. Of these the third is the least subject to fallacy, and can yield valuable information during a relatively short period of trial. This gives it particular importance in the present trial, in which we are concerned with progress in terms of weeks rather than of months or years. In considering the bacteriological picture, based always on multiple smears, two aspects are important. (*a*) Changes in bacterial index, and (*b*) Changes in bacterial morphology.

By Bacterial Index we mean the average of the findings on a single occasion at 10 sites including both ear lobes and nostrils, at each of which the concentration of bacilli is reckoned from 0 to a maximum of 4 plus, very scanty bacilli being counted as 0.5 and 4 plus indicating a smear with innumerable bacilli in every field. The Bacterial Index is at best an estimate, but experience proves its value. It is in any case a conservative basis for assessment, for a 4 plus reading will be found equally from sites at which lepromatous infiltration is still moderate and those where the skin is saturated with it, so that a marked reduction in the concentration of bacilli will have taken place in advanced cases before any change is discernable under the microscope.

Too little attention has as yet been given to the degenerative changes in bacterial morphology which take place during chemotherapy. Although in reactive states and in borderline leprosy a proportion of the bacilli in routine smears may be abnormal in shape or in staining properties, this does not alter the fact that during successful chemotherapy a progressive decline invariably takes place in the proportion of bacilli of normal shape and staining properties in routine smears. This change occurs early, and may be pronounced before any decline occurs in the Bacterial Index. The proportion of bacilli showing degenerative changes can often actually be counted, and this affords the most precise method of

observing short term changes in the situation as far as the bacilli are concerned. We have made use of it in this work, and can give with some accuracy the time taken in any patient for the proportion of normal bacilli to fall by 50% and by 100%.

The entire bacteriological findings here reported have been assessed by one specialist technician, who, unaware of the details of treatment, has lacked any bias that may inevitably have coloured the judgement of the clinician.

For control purposes we have used the standard graphs of decline in Bacterial Index which have been developed at this unit, and provide a form of control which is least open to objection. The detailed observation of morphological changes is a comparatively recent development, and records of DDS treatment during the past 10 years do not give sufficient detail to provide the reliable standard now called for where this aspect is concerned. Those covering the trial of Ciba 1906 do, however, provide a valuable basis for comparison. As we have found Ciba 1906 more speedily effective than DDS in the early stages of treatment, it is most unlikely that DDS would induce morphological changes more rapidly than did Ciba 1906.

It is worth emphasising that the principles of random selection have been applied in this work, patients being attached to the trial strictly in order of admission.

We now consider the progress of the four groups of patients.

A. The continued progress of patients on oral chemotherapy following shorter or longer courses of Etisul.

(*a*) *Short course of Etisul.*

The original pilot trial group of nine lepromatous and nine tuberculoid cases received approximately three months of inunction with ETIP (non-perfumed) in a dose of 3 ccs. twice weekly. This was followed by standard oral chemotherapy, 4 patients receiving the two drugs together for the second three months. The group has now been observed for 18 months. The last six months have done nothing to alter the impression previously gained that in these patients acceleration of the expected effect of oral chemotherapy had taken place as a result of the Etisul course.

A later group (Group 3) of ten lepromatous and five non-lepromatous cases received Etisul in a dose of 6 ccs. twice weekly for 10–12 weeks, and then continued with standard DDS therapy. They included some very severe lepromatous cases. This group has now been observed for nine months. Clinically and histologically their progress has been very satisfactory, the resolution of lepromatous infiltration being uniformly evident, accompanied by a pronounced sense of well-being. No complications have been witnessed, apart from mild and brief reactive phases in two patients.

Bacterial Index

The average decline in Bacterial Index for the two groups is given in Figure 1. It will be observed that in both cases a rapid initial decline took place, most marked during the first two months. This was succeeded by a period of diminished progress. In the second group this persisted for three months, i.e. during the period when the dosage of DDS was being built up to its standard maintenance dose, progress then being resumed, so that at nine months it is still well in advance of what would have been expected using DDS alone. This phase of slower progress during the second three months was not so obvious in the first group, four of whom received combined treatment during this period.

Morphology of Bacilli in Routine Smears

The time taken in months for the proportion of normal bacilli in routine smears to fall by 50% and 100% from the figure at the onset is given in Table 1.

TABLE 1

Decline in proportion of normally staining bacilli

	Group 1 3 ccs ETIP b.w. for 3 months		Group 3 6 ccs Etisul b.w. for 3 months	
	50% decline	100% decline	50% decline	100% decline
Within 1 month	2	–	2	2
,, 2 months	7	3	4	–
,, 3 ,,	–	2	1	–
,, 4 ,,	–	–	1	1
,, 5 ,,	–	–	1	–
,, 6 ,,	–	1	1	1
,, 9 ,,	–	1	–	1
Over 9 ,,	–	2	–	5
	9	9	10	10

The most significant point here is that in 100% of Group 1 (milder cases) and 70% of Group 3 (more severe cases) a decline in the proportion of normal bacilli by 50% occurred during the first three months, *when Etisul was being used alone.*

(*b*) *Longer course of Etisul.*

A brief reference only is called for in regard to the group of 14 lepromatous and 8 tuberculoid cases (Group 2) who received from three to six months of Etisul treatment, using light inunction over a limited area of the body, with inadequate absorption, i.e. low dosage for a long period. It was in this group that evidence

FIG 1. Decline in Bacterial Index during chemotherapy

A short course of ETIP followed by standard chemotherapy with DDS or DDSO (two patients only in Group 1).

The DDS standard is represented by dotted lines:

Group 1 is the original pilot trial.

Group 3 is treatment by ETIP for 10 to 12 weeks, followed by DDS.

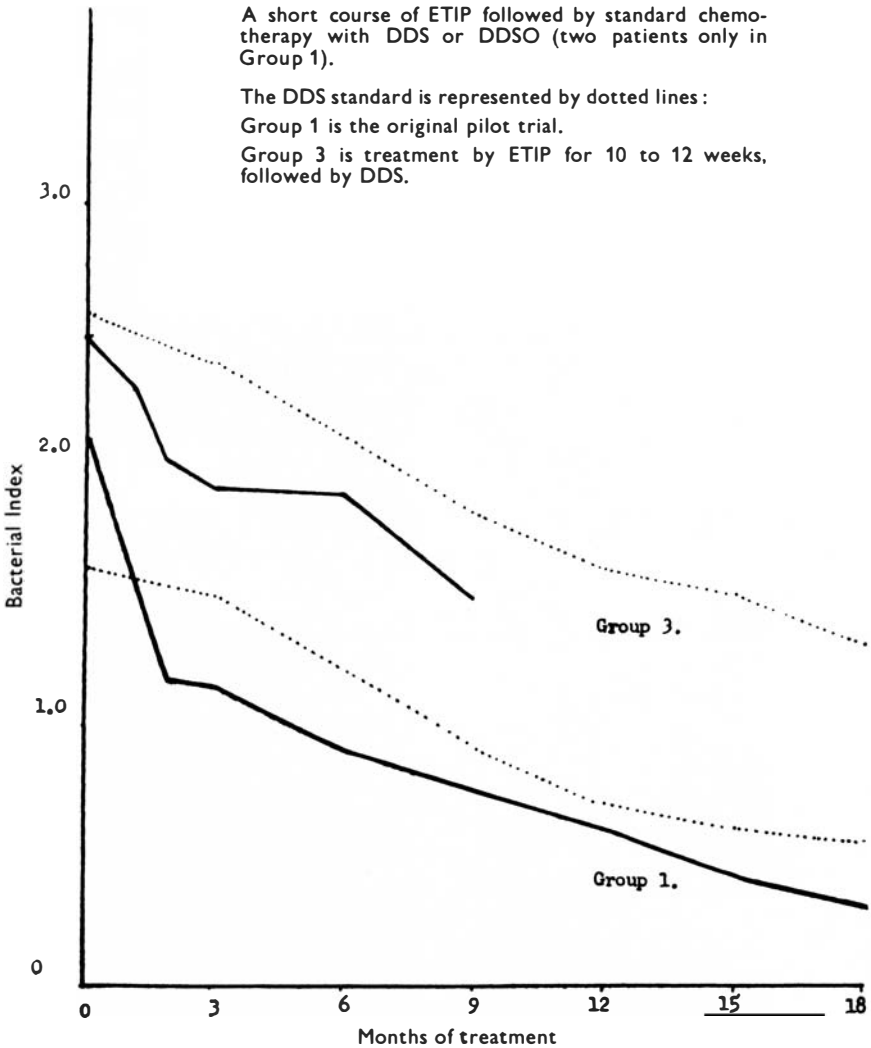

FIG. 1

of drug resistance was encountered. When transferring the patients concerned to oral chemotherapy it was considered appropriate to give them the drug with speediest action and least toxicity known to us, namely Ciba 1906. This was given immediately in full dosage.

With an average Bacterial Index of 3.0 it is evident that the group included a high proportion of severe cases, but their progress, while good in five cases, was on the whole decidedly inferior to that of the two groups already described, as judged both by the rate of decline in Bacterial Index during Etisul treatment and also by the time taken for a decline by 50% in normal bacilli.

Continuing treatment with Ciba 1906 proved satisfactory but not outstanding. Its lack of toxicity was an obvious virtue, but bacteriological progress was not appreciably better than would have been expected with DDS during the same period, and in one or two patients was not as good. It is possible that the chemical relationship between Ciba 1906 and Etisul is sufficiently close to have affected to some extent the usefulness of Ciba 1906 in cases beginning to develop drug resistance to Etisul.

Experience with this group stresses the importance of adequate inunction in treatment with Etisul.

This earlier work led to three new groups of patients, the progress of whom is now reported for the first time.

B. The effect of a short course of Etisul late in oral chemotherapy.

A course of Etisul lasting two months was given to 15 lepromatous cases who displayed persistently positive bacteriological findings after three or four years of DDS treatment.

In two cases smears became negative within three months, but in the remainder no effects could be observed as a result of the course of Etisul other than those of a subjective nature. In all these patients the bacilli were in a granular condition. The mechanical effect of inunction and massage may very well have stimulated absorption of bacillary material, but there was no evidence that Etisul had any chemotherapeutic effect in these cases.

At the same time, a course of Etisul was given to five patients of similar type after two years of treatment with Ciba 1906. The drug had no observable effect.

Etisul is thus of interest only in the early stages of treatment. The temporary check in bacteriological improvement observed when Etisul treatment is followed by oral chemotherapy suggested its trial in combination with DDS, and during the past six months attention has been concentrated on this.

C. Etisul in combination with DDS. Progress during the first six months.

Twenty-four lepromatous cases are taking part in this trial.

They have been divided into two groups. (*a*) In ten previously untreated patients the two drugs were administered together from the start, so that they received Etisul during the period when the maintenance dose of DDS was being built up. (*b*) In the remaining 14 patients DDS treatment was either initiated by us and Etisul added when the dose of DDS had reached 400 mg. weekly, or else the patient had received a short course of DDS privately before consulting us. At first a short course of Etisul was visualised in each group, but the importance of determining the influence of combined treatment on drug resistance led to the continuance of Etisul treatment beyond the three months originally envisaged. In most cases it has been continued throughout the period of trial.

Clinically, the progress of patients in both groups has been eminently satisfactory, with steady and rapid improvement without any complications. In several cases repeated biopsies have also shown well marked resolution histologically. In both these respects there is so far nothing to choose between the two groups. Their bacteriological progress will be considered separately.

Group (a) Etisul and DDS starting concurrently.

The ten patients in this group had had no previous chemotherapy, their statements in this respect being supported by bacteriological findings, repeated where thought desirable after an interval of a few weeks during which no treatment was given. Details of their bacteriological progress once treatment was initiated are given in Table 2.

TABLE 2

Bacteriological status of patients receiving Etisul and DDS concurrently

	Bacterial Index								*Morphology of Bacilli Months taken for reduction in normal bacilli by:*	
	0	1	2	3	4	5	6	7	50%	100%
A.O.	1.7	0.9	1.1	1.0	1.6	1.6	1.1	0.6	<1	7
N.	3.5	3.5	3.1	3.1	2.9	2.5	2.1	1.8	1	6
O.A.	0.6	0.3	0.3	0.1	0.2	0.2	0	0	<1	4
N.A.	2.9	2.8	2.5	2.4	2.3	2.5	1.4		2	6
O.M.	0.3	0.2	0.1	0	0	0	0		2	3
E.A.	1.6	1.5	1.5	0.7	1.2	0.5			2	5
D.O.	2.2	2.2	1.4	1.3	1.4	1.1			2	5
O.O.	0.3	0.3	0.1	0	0	0			2	3
P.O.	1.1	0.7	0.4	0.3	0.5	0.4			1	> 5 persisting (nose only)
I.U.	2.2	1.2	0.9	0.7	0.7				1	> 4 persisting (nose only)
Avge.	1.6	1.4	1.1	0.95	1.0					

Where Bacterial Index is concerned, previous experience with Etisul alone was reproduced here, with a very marked reduction in Bacterial Index during the first two months which was greatly in

excess of the DDS standard. During the third and fourth month slowing down of progress was again evident, and it is clear that the combination of DDS with Etisul did not succeed in obliterating this phase. In those whose period of observation has extended beyond this time, progress has been resumed, and has been very satisfactory.

The action of the combined treatment on the morphology of bacilli is very striking. Within 1 month, in 5 out of 10 cases, the proportion of normal bacilli in routine smears had fallen by 50%, and in the entire group this point was reached within two months. Even more remarkable is the fact that within the short period of this trial normally staining bacilli have entirely disappeared from all skin sites examined, though in one case they linger in the nose.

Group (b) Short course of DDS preceding combined treatment with Etisul

In this group of 14 patients, 7 had had no previous chemotherapy when they first consulted us. These were given 100 mg. DDS twice weekly, raised then to 200 mg. twice weekly, and Etisul treatment introduced at this point. This meant that the maintenance dose of 300–400 mg. DDS twice weekly was attained within the first two months of Etisul treatment. The remaining 7 patients had all had short periods of DDS therapy lasting from 3–12 months either privately or at an out-patient clinic, and were admitted to the trial because of the obvious activity of their disease. Details of their bacteriological progress are given in Table 3.

TABLE 3

Bacteriological status of patients receiving a short course of DDS before starting combined treatment with Etisul

	Bacterial Index during combined treatment									Previous DDS treatment in months	Morphology of Bacilli Months taken for reduction in normal bacilli by	
	0	1	2	3	4	5	6	9			50%	100%
P.O.*	2.0	2.2	1.1	1.05	1.1	1.6	1.6	1.2		1	1½	6
G.N.*	2.3	2.1	1.3	1.2	1.4	1.5	2.1	1.5		1	2	6
J.U.	3.8	3.3	3.0	3.0	2.6	2.5	2.2			10	1	5
O.O.	1.3	0.9	0.8	0.7	0.5	0.2	0.1			12	1	2
A.I.	1.6	1.1	0.6	0.6	0.8	0.6				6	0	0
M.O.	2.7	2.3	2.3	2.2	1.9	1.9				3	2	5
I.U.	0.8	0.4	0.1	0.2	0	0				1	3	3
S.I.	1.5	1.4	1.4	1.0	1.0	0.7				7	0	0
A.A.	2.1	1.9	1.1	1.0	1.0					3	3	> 5 persisting (nose only)
E.S.	3.2	3.3	3.3	2.9	2.4					5	1	5
O.O.	2.0	1.8	0.9	0.9						1	1	2
S.A.	0.6	0.7	0.7	0.5						1	1	3
O.U.	1.6	1.6	1.2	0.8						1	2	3
N.	0.1	0.1	0	0						1	2	2

* Etisul for first 3 months only.
Average (4 months combined treatment).
2.2 1.9 1.5 1.4 1.3

In this group also progress during the first two months was very satisfactory, and though some slowing down in the decline of Bacterial Index then occurred, there was no real check to its continued fall. Nothing was lost in these patients by giving them a few weeks course of DDS before starting Etisul, and coming months will show whether there was in fact an advantage.

The position of those who had longer periods of DDS treatment is interesting. Four of them had considerable numbers of normally staining bacilli in their smears in spite of several months of DDS treatment. In them all rapid improvement both clinical and bacteriological followed the administration of combined treatment.

In neither group have any signs yet appeared suggestive of drug resistance. The proportion of normal bacilli in routine smears has fallen continuously and regularly, not only during the first three months, but after that period in patients who have continued taking the drugs together.

D. Etisul in combination with DDS and Ciba 1906 (*DPT*).

With Etisul falling off in effectiveness at about the third month, and DDS requiring 3 months or thereabouts for the attainment of its maintenance dose, it appeared to be worth while experimenting with the use of Ciba 1906 in conjunction with the other two, for its speedy action would bring it into effect during the third month when neither of the other two may be at optimum efficiency.

Fifteen lepromatous cases, some of them severe, are taking part in this most recent part of the trial. None had had any previous chemotherapy. They received full doses of Ciba 1906 from the start, (2.0 gms. daily), 6 ccs. Etisul twice weekly, and DDS was built up on a twice weekly basis following the usual routine. 13 of the patients have now completed 3 months of this routine, 10 of them four months or longer. One additional patient developed sulphone dermatitis, and had to be withdrawn.

In all cases clinical progress has been most satisfactory, and free from any complications other than the case of sulphone dermatitis. Biopsies repeated in 4 patients have all shown substantial histological evidence of resolution. Bacteriological progress is indicated by Table 4.

These results are eminently satisfactory. In all 15 cases there was a very speedy action on the bacilli, a 50% decline in normally staining bacilli in routine smears taking place within one month in 11 of the 15 patients, while by the end of the fourth month they had disappeared from all sites other than the nose in every patient observed for this length of time, granular bacilli and debris alone being encountered. This was a new phenomenon in our experience in such advanced cases as the second and third in Table 4, both of them diffuse lepromatous cases in whom lepromatous infiltration was

FIG 2. Decline in Bacterial Index during chemotherapy

ETIP in combination with DDS

A Etisul and DDS concurrently from the start.
B Short course of DDS followed by combined treatment.
C Etisul combined with DDS and Ciba 1906.
DDS standard is represented by dotted lines.

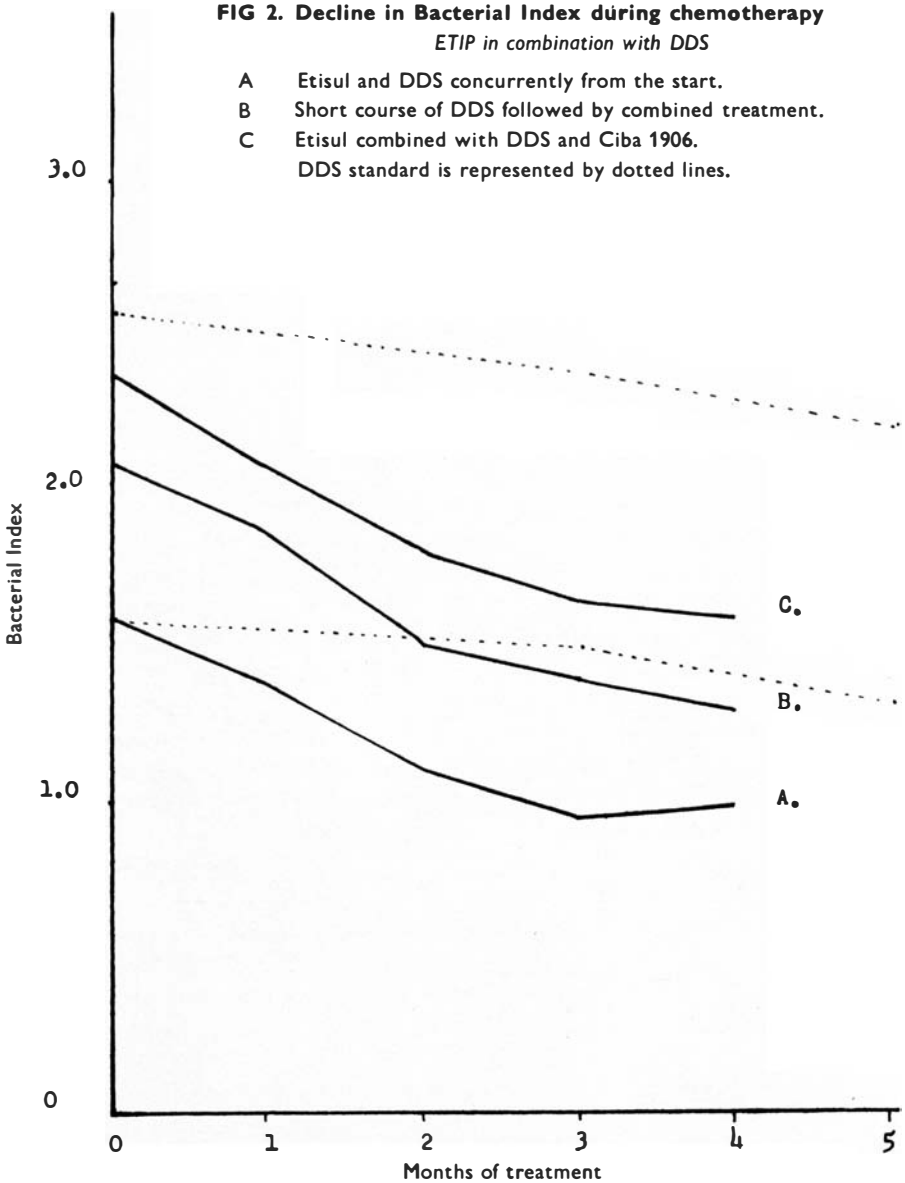

FIG. 2

TABLE 4

Bacteriological status of patients receiving Etisul combined with Ciba 1906 and DDS

	Bacterial Index—Months							*Morphology of Bacilli Months taken for reduction in normal bacilli by*	
	0	1	2	3	4	5	6	50%	100%
G.E.	1.5	1.3	0.7	0.5	0.4	0.2		1	2
N.	3.9	3.2	2.9	2.5	3.0	2.8		1	5
R.	4.0	3.8	3.6	3.0	3.3	3.0		1	> 5 persisting (nose only)
A.E.	1.3	0.9	0.7	0.3	0.3			1	4
N.O.	3.9	3.6	3.0	3.3	3.3			1	> 4 persisting (nose only)
C.O.	2.5	2.3	2.0	2.1	1.4			2	4
A.N.	0.5	0.4	0.1	0	0			2	4
S.N.	3.1	2.4	2.2	2.1	2.2			3	> 4 persisting (nose only)
A.E.	0.6	0.5	0.4	0.4	0.2			1	4
J.	2.6	2.4	2.5	2.2	1.8			2	> 4
N.I.	1.7	0.9	0.8	0.7				1	3
E.A.	0.6	0.7	0.7	0.4				1	3
M.	3.2	3.1	3.1	2.6				1	> 3
V.I.	4.0	3.7						1	> 2
M.	0.25	0.1						1	2
Average (patients completing 4 months treatment).	2.4	2.1	1.8	1.65	1.6				

encountered through the whole thickness of the corium in biopsy material. In this group the decline in Bacterial Index was also notable, though once again some diminution in the rate of progress can be detected between the third and fifth months in some patients.

In Figure 2, the variation in Bacterial Index during the period of observation is shown for the three groups of patients receiving combined treatment.

In Table 5 the change in bacterial morphology in the various groups is compared with that experienced with Ciba 1906. In all groups receiving Etisul it will be noticed that the proportion of normally staining bacilli in routine smears declined more rapidly than in the case of Ciba 1906, and was most marked in the group receiving Etisul in combination with Ciba 1906 and DDS.

Discussion

During the past six months numbers participating in this trial have doubled, and evidence has continued to accumulate that in Etisul we have a drug with a limited but very valuable sphere of action.

Toxicity presents no problems. Careful laboratory control has been exercised in all the 133 patients who have received courses of Etisul, and no toxic action of any kind could be detected. The problem of administration has largely disappeared as patients have

TABLE 5

Speed of change in staining properties of M. leprae during chemotherapy

Assessment	*Decline by 50% in proportion of normally staining bacilli in smears*				*Decline by 100%, Bearing granular bacilli and debris only*			
Drug	*Ciba* 1906	*Etisul for* 10-12 *weeks followed by DDS*	*Etisul in combination with DDS*	*Etisul combined with DDS and Ciba* 1906	*Ciba* 1906	*Etisul for* 10-12 *weeks followed by DDS*	*Etisul in combination with DDS*	*Etisul combined with DDS and Ciba* 1906
No. of patients	17	19	22*	15	17	19	22*	15
Time								
Up to 1 month	1	4	10	11	—	2	—	—
2 months	7	11	10	3	1	3	3	2
3 months	6	1	2	1	1	2	4	2
4 months	3	1	—	—	1	1	2	4
5 months	—	1	—	—	2	—	3	1
Over 5 months	—	1	—	—	12	11	9	1
Uncertain**	—	—	—	—	—	—	1	5

* Excluding 2 patients who had only granular bacilli on admission.

** Patients not yet completing 5 months treatment but still exhibiting some normally staining bacilli in routine smears, particularly in the nose.

witnessed the effects of the drug. It has become a popular form of treatment.

The sphere of usefulness of Etisul is clearly at the onset of treatment. Its activity has two aspects. There is in the first place the shortlived but sometimes powerful chemotherapeutic action which has been observed in every group studied, and which appears to last for about two to three months, but then diminishes and may disappear altogether. In the second place there is the continued accelerated resolution which has repeatedly been witnessed during standard chemotherapy following a short course of Etisul.

The mode of action of Etisul is of great interest. The most striking effects on the bacilli have occurred in those patients in whom the bacilli have been almost or entirely 100% normal in their staining properties, regardless of the severity of the infection. The details given earlier in this paper show how speedily the situation may change in such patients. One of its interesting features is that quite regularly bacilli of normal type have been found to linger longest in the nose. These are not saprophytes, all patients concerned having unmistakable globi in nasal smears. The drug undoubtedly has a speedy action on the staining qualities of the bacillus, and for this and other reasons it has been suggested that its action may be more bacteriocidal than bacteriostatic.

The combinations of Etisul with DDS, and with DDS and Ciba 1906 together, have so far given very encouraging results. In these groups progress has been rapid and uniform, and with most of the patients now past their fourth month of combined treatment, no evidence suggestive of drug resistance has been seen as yet. In deciding whether or not to precede Etisul treatment with a short course of DDS it is well to consider the psychological stimulus provided by Etisul inunction. Most patients need this as early as possible.

One month's treatment with DDS before initiating Etisul has been found satisfactory and logical, Etisul being given when the dose of DDS has reached the therapeutic level of 400 mg. weekly. Although Etisul has been continued in these groups beyond the third month, further study will be needed before it can be determined whether this is therapeutically desirable or not. The good long term results in those patients who had short courses of Etisul suggest that long courses may be unnecessary. It would be logical to continue Etisul until bacilli of normal appearance can no longer be found in routine smears, and two short courses separated by an interval may be preferable to one long course. These matters call for further study.

In conclusion it may be said that further experience has confirmed earlier impressions of the usefulness of Etisul, but the work here reported remains essentially a pilot trial of exploratory nature. The large scale trial of the drug along the lines here suggested is now called for.

Summary

A further stage in the pilot trial of Etisul in leprosy treatment is reported. Earlier impressions are confirmed that this drug lacks toxicity and is of value in the early stages of treatment, inducing a rapid change in the staining properties of the bacilli, and a rapid fall in the Bacterial Index, and leading to accelerated resolution.

It has been found to combine readily with DDS, and with Ciba 1906 in addition. When combined in this way resolution has been rapid and uniform, and after four months no sign of drug resistance has been detected.

Large scale trials are now called for.

Acknowledgements

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INFLUENCE OF VARIOUS PRO-OXIDANT NUTRITIONAL CONDITIONS ON THE GROWTH *IN VIVO* OF *M. LEPRAE*

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Introduction

In an extensive series of papers which we have recently summarized[1, 2, 3], we published theoretical and experimental findings which permitted us to establish a connection between the autoxidation of lipids and the pathogenesis and therapy of leprosy.

Of all these findings, the growth of *M. leprae* in the testes of rats fed pro-oxidant diets[4, 5, 6] (a semisynthetic diet with a very low content of vitamin E and containing 15% of linseed oil) deserves special attention, particularly in conjunction with results reported in this paper.

In rats fed this diet and inoculated intratesticularly with *M. leprae*, reproduction of this bacillus is sufficient to permit its passage in rats in series, as well as the development of integral lepromins. The observation that such lepromins from rats behave similarly to lepromins of human origin confirms the biological specificity of the bacilli obtained from the inoculated animals[7].

Using pro-oxidant diets of various types with the object of trying to find the best experimental conditions for the growth of *M. leprae* in rats, we carried out the experiments which are described below.

Material and Methods

Thirty-six white male rats, raised under the usual nutritional conditions from birth up to the 21st day of age were divided into six groups with six animals per group, and were then submitted to the conditions described below.

The groups were designated by letters A to F; groups A and B were controls, while groups C, D, E and F constituted the experimental groups.

GROUP A. This group remained throughout the entire experiment on a complete diet consisting of fresh vegetables, bread and milk, and water *ad libitum*.

GROUP B. The animals in this group were fed similarly to those in the previous group, plus twice weekly addition of 40 to 50 mg. of d-l alpha tocopherol acetate given to each rat by mouth.

GROUP C. The animals in this group were given the following semi-synthetic diet with a low content of vitamin E and 15% of crude linseed oil:

Dry mix	Casein	23.8 gm.
	Yeast powder	8.9 gm.
	Mineral salts	3.0 gm.
	Corn starch	48.9 gm.
	Crude linseed oil	15.5 gm.

The components of this diet, except for the oil, are common to the rest of the groups and from now on will be referred to as the dry mix.

The mixed mineral salts which were used correspond to the formula of Hubbell, Mendel and Wakeman (J. Nutrition 1937, **14,** 273).

The casein employed in these diets was industrial casein used without previous extraction of lipids. The oils were added daily to the rest of the dry mix.

GROUP D. Animals in this group were maintained on the following diet:

Dry mix	84.6 gm.
Cod liver oil	15.5 gm.

GROUP E. The animals in this group were fed as follows:

Dry mix	84.6 gm.
Crude linseed oil	15.5 gm.

This diet, similar to that of group C, was prepared daily and was kept in open cans for six days before being administered. In addition the diet was aerated daily and was heated gently for two hours. The change in colour and odour during the six days period showed that the diet was becoming rancid and it was in a rancid condition when used to feed the animals.

GROUP F. The rats in this group were fed on the following diet:

Dry mix	84.6 gm.
Cod liver oil	15.5 gm.

During the entire experiment, the drinking water consisted of tap water to which was added 0.5 parts per thousand of silver nitrate.

In addition, after 21 days and for 4 months afterwards we gave a once weekly subcutaneous injection of ½ to 1 cc. of rat blood haemolysate prepared in the following manner. Taking 3 cc. of rat blood and adding 3 cc. of distilled water, the whole was filtered through wet filter paper and the filtrate was used for injection.

On the 36th day, after being placed on the indicated experimental conditions, at which time the rats were 57 days old, an inoculation was given in each testis of all animals of 0.1 cc. of a recently prepared suspension of *M. leprae.* The bacterial suspension was made by grinding a large leproma obtained from an untreated leprosy patient and suspending the ground material in 15 cc. of physiological saline.

Two, five and seven months after the inoculation, two animals were sacrificed from each group, except when animals died, as in the case of group F.

The testes, other organs and the depot fat of each animal were investigated. Bacterioscopic studies were made of one testis of each animal and histopathological studies were made of the other one.

The bacterioscopic examination consisted of counting the bacilli and globi present in 50 microscopic fields of 4 impression smears making a total of 200 fields counted. A qualitative study was also made by examining the morphological and acid-fast characteristics of 50 bacilli. Although all these studies yielded only approximate figures, we believe that the results are sufficiently exact to give a reasonably accurate idea of the quantitative and qualitative bacteriological changes occurring in the testes of the inoculated animals.

The bacteriological study of the testes was made by means of impression smears stained by the usual method of Ziehl-Neelsen, and also by histological sections of tissues embedded in paraffin and stained by the usual methods for acid-fast bacilli in tissues.

Experimental Results

GROUP A. (Complete diet). In this group we noted a progressive decrease in the number of bacilli in both testes from the second through to the seventh month of inoculation, with granulation and loss of acid-fastness of the bacilli.

At the seventh month the histological sections did not show any acid-fast bacilli in the testes, and the impression smears of these organs showed only a small number of granulated bacilli with loss of acid-fast properties.

GROUP B. (Complete diet with vitamin E added by mouth). The bacteriological picture of this group of animals was approximately the same as that of the preceding group A. In fact at the end of the seventh month after inoculation, the histological sections did not show any acid-fast bacilli and impression smears showed only a very small number of bacilli which for the most part were granular with loss of acid-fastness.

GROUP C. (Vitamin E deficient diet with 15% linseed oil). In this group we noted a progressive increase of bacilli in the inoculated testes. At the fifth month there appeared in the inoculated testes a large quantity of thin bacilli which were not very acid-fast, similar to bacilli seen by us in previous work[5] which we have termed "bacilos de regeneración", i.e., new bacilli, of new growth. The sections showed the presence of these bacilli in the intertubular spaces.

The contrast in the bacteriological picture between the second and the fifth month after inoculation was highly significant. In the second month the bacilli were largely acid-fast, granular, and of characteristic diameter, while at the fifth month bacilli of new growth began to appear with characteristics already described.

GROUP D. (Vitamin E deficient diet with 15% cod liver oil).

Bacteriological studies of the inoculated testes of animals in this group showed a progressive increase in the number of bacilli from the second to the seventh month after inoculation. At the seventh month quantities of new bacilli and histological sections showed the presence of these bacilli in the intertubular spaces.

GROUP E. (Vitamin E deficient diet with 15% rancid linseed oil). Bacteriological studies of the inoculated testes showed a very noteworthy increase in the number of bacilli from the second to seventh month after inoculation. Already at the fifth month one would see large numbers of new bacilli which became very frequent at the seventh month when the total number of bacilli was enormous. At this time both new bacilli and bacilli with the usual characteristics were observed. In histological sections both types occurred in the intertubular spaces.

GROUP F. (Vitamin E deficient diet with 15% cod liver oil, with silver nitrate added to the drinking water and with injection of haemolysate). Bacteriological studies of this group, made in almost all of the animals in the fifth month after inoculation, showed at this time an extraordinary number of homogeneous and strongly acid-fast bacilli. New bacilli were also observed. The extreme acid-fastness and homogeneity of these bacilli were very remarkable, as was the number of new bacilli that were present. In addition we observed large red spots composed of thousands of acid-fast bacilli. One animal of this group showed masses of homogeneous and strongly acid-fast bacilli, which formed compact globi in the lungs and spleen, and to a lesser extent in the liver. The bacillary richness of the inoculated testes was extraordinary; histological sections showed enormous numbers of bacilli and globi disseminated throughout the intertubular spaces. The experimental result of this group has been described previously[8].

Discussion

From the results of the experiments described above we can draw the following conclusions:

1. In regard to the formation of ceroid pigment in the fat depots, observation of the colour of the fat indicated the absence of this pigment in groups A, B, C and E; and a great quantity of pigment in groups D and F.

In respect to the atrophic degenerative change in the testes, such changes were absent in the control groups but were manifested in the rest of the groups, especially in animals sacrificed in the fifth and seventh months of inoculation.

2. The weight of the animals of all the groups was essentially the same except in the case of group F in which some of the animals suffered an appreciable dimination in weight as compared with the animals in other groups.

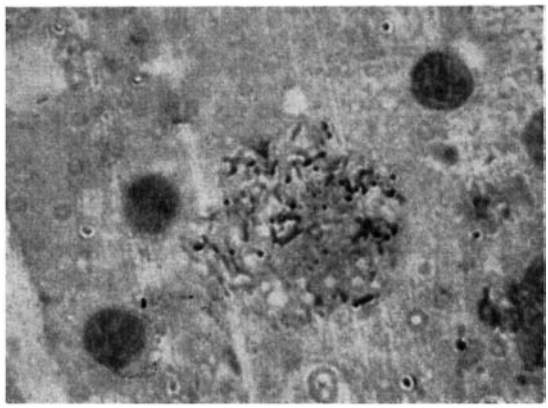

FIG. 1.—*Impression smear of testis of rat Group C sacrificed at the fifth month after inoculation showing group of new bacilli. (1000x)*

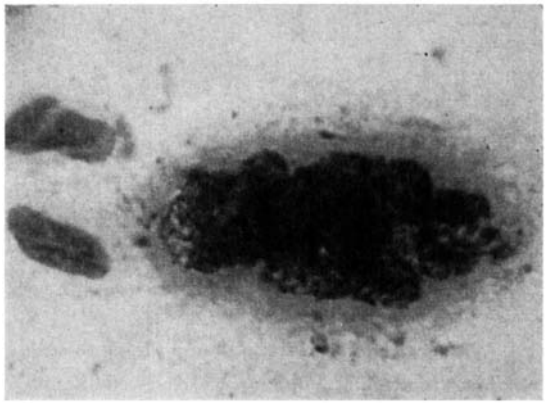

FIG. 2.—*Impression smears of testis of rat of Group F which died in the fifth month after inoculation showing large red spot composed of acid-fast bacilli. (1000x)*

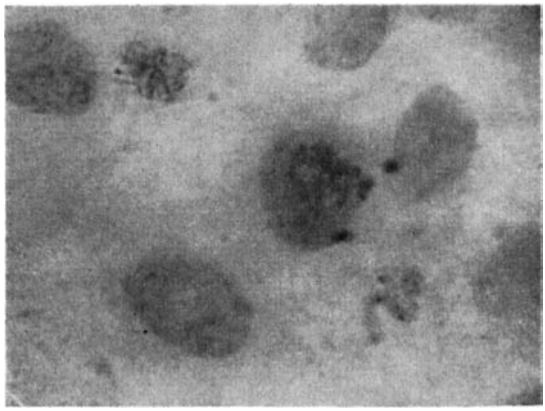

FIG. 3.—*Impression smears of lung of a rat of Group F found dead in the fifth month after inoculation, showing large globi, one of which is intracellular. (1000x)*

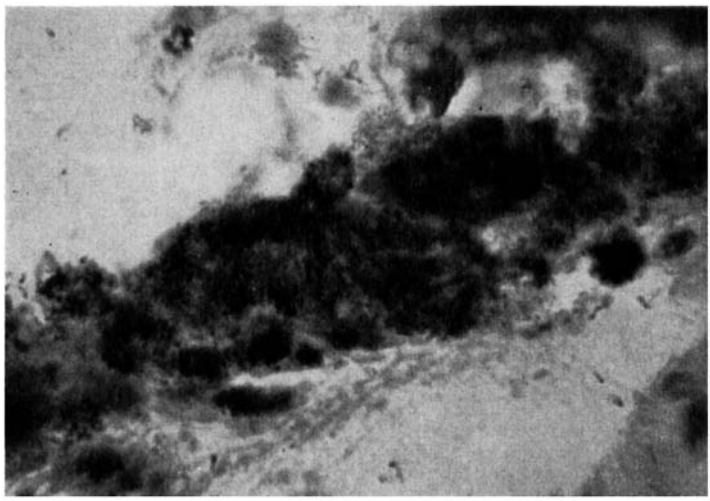

FIG. 4.—*Section of a rat testis of Group F found dead in the fifth month after inoculation showing a great quantity of agglutinated bacilli in the subcapsular zone. (1000x)*

It must be emphasised that in none of the inoculated animals could there be observed any type of macroscopic lesions, nor hypertrophy of any organ attributable to the growth of the Hansen bacilli.

3. The animals of the two control groups showed practically identical bacteriological pictures of progressive diminution in the number of bacilli in the inoculated testes. In addition, the bacilli suffered alterations in morphology and staining ability, consisting in granulation and loss of the acid-fastness.

At the seventh month after inoculation, impression smears showed only a very low number of granulated and non-acid-fast bacilli. This can be taken as evidence that conditions were unfavourable to the growth of *M. leprae.*

4. All the experimental groups showed an evident and progressive increase in the number of bacilli from the second to the seventh month after inoculation; it must be emphasised however that the bacteriological picture in each group was distinct. Groups C and E showed the appearance of new bacilli at the fifth month after inoculation; group D showed them at the seventh month. On the other hand, group F at the fifth month showed an enormous number of strongly acid-fast bacilli, whose degree of acid-fastness was not observed in any of the other groups.

5. In regard to the richness of bacilli, groups E and F showed an enormously increasing growth of *M. leprae.* On the other hand the growth rate of the bacilli was of a lesser degree in groups C and D.

6. From the results of these experiments one deduces that there is no direct relation between ceroidogenesis and the growth of *M. leprae.* Although it is certain that with diets such as diet F which is strongly ceroidogenic there was obtained an enormous development of bacilli, such development also was seen with diet D which is very weakly ceroidogenic.

7. For reasons which escape us, but which may be connected with genetics, not all of the animals reacted in the same way, and although the results in general were more or less uniform, some animals within a given group showed less development of the bacilli than others. Likewise it appeared that in some animals the growth rate of the bacilli slowed soon after reaching a high level, and in these cases the bacilli seemed even to deteriorate in regard to morphology and acid-fastness.

8. The group of animals in which conditions were the most favourable for the growth of *M. leprae* was group F. The diet of this group is highly ceroidogenic and pro-oxidant, and in addition to favouring the growth of the bacilli caused marked renal and hepatic changes which led to the premature death of a large number of the experimental animals.

9. From the point of view of importance in the pathogenesis of human leprosy the diet which can be most plausibly connected with

leprosy in humans under natural conditions is diet E. This diet containing 15% of rancid linseed oil caused an extraordinary growth of *M. leprae*. The relationship between the consumption of this diet by rats in which *M. leprae* would multiply and the ingestion of large quantities of rancid foods by populations living where leprosy is endemic is highly significant and merits future investigation in the field of the prevention, pathogenesis and treatment of leprosy.

Taking into account the high variety of pro-oxidant factors and the possible combinations of two or more of these, such as for example pro-oxidant metallic catalysis, peroxides, oxygen, poly-unsaturated oils, rancid fats, irradiation, absence of anti-oxidant factors, etc., it is easy to realize that there are many possibilities for finding optimal nutritional and pharmacological conditions for the growth *in vivo* of *M. leprae*.

Summary

A comparative study has been made of the growth of *M. leprae* inoculated intratesticularly in white rats submitted to various pro-oxidant nutritional conditions. With the pro-oxidant diet employed (Vitamin E deficient diet with linseed oil, with rancid linseed oil, with cod liver oil, with or without the addition of silver nitrate in the drinking water and injection of haemolysates) there was a notable growth of *M. leprae* in relation to their growth in control animals fed on ordinary diets. The great development of *M. leprae* in the group of animals which received the diet containing the rancid linseed oil may be connected with the pathogenic mechanism of human leprosy. It is indicated that the search for new nutritional and pharmacological pro-oxidant factors may lead to the finding of optimal conditions for growth *in vivo* of *M. leprae*.

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AN ASSESSMENT OF THE EFFECTS OF OUTPATIENT DDS ADMINISTRATION IN KATSINA PROVINCE, NORTHERN NIGERIA

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Introduction

It is generally accepted that the administration of DDS in leprosy considerably alters the course of the disease, but some doubt exists as to its ultimate therapeutic efficacy; Bushby[1], 1958, claimed that most leprologists now expect to cure all early cases of the disease and even when the disease is firmly established, the ultimate outlook is invariably good. However, attention is drawn to the long duration of treatment necessary to procure, firstly, a clinical cure and finally the eradication of the organisms. Wolcott[2], 1956, stated that a patient with lepromatous leprosy had a 40% chance of arrest of his condition after eight years of continuous sulphone treatment. Cochrane[3], 1956, commenting on sulphone therapy in lepromatous subjects, said that many authorities consider that treatment should be continued for life.

At the Sixth International Leprosy Congress held in Madrid in 1953, it was accepted that the new drugs would reduce considerably the infectivity of lepromatous cases, and it was strongly recommended that investigations of the incidence and pattern of leprosy should be carried out in countries where institutional isolation was impracticable and where sulphone therapy was well established. It was decided to carry out an investigation in a number of Leprosy Outpatient Treatment Centres in Katsina Province of Northern Nigeria to assess the effects of DDS administration in leprosy patients in a community of this kind.

Katsina Province was selected for this investigation because extensive outpatient treatment had been practised there since 1953, and the results of DDS administration could be assessed in a community where the majority of established cases of leprosy had been under treatment for some years. All the cases attending a number of randomly selected outpatient leprosy clinics were first examined in July, 1957, and as far as possible, these same cases were re-examined in 1958. From these two surveys the number of cases that have been discharged, the changes which have taken place in the clinical state of the cases still under treatment, the significance which should be attached to absenteeism and the general benefits which have resulted from weekly DDS administration can all be assessed. Details of the quantities of DDS given are to be found in a paper by C. M. Ross[4], 1956.

Katsina Province is a very suitable territory for an investigation of this kind for its administration is in the hands of a most efficient Native Authority, presided over by an enlightened Emir, who

extended every possible facility for the carrying out of these investigations. Katsina is one of the richest provinces of Northern Nigeria, covering 9,000 square miles, and situated between Kano in the south, and French Niger Province in the north. Katsina itself is served by good roads and it is possible to reach all parts of the province even during the rainy season. The rainfall in the northern half of the province is between 20 to 30 inches (50.8 to 76.2 cm.) a year, and in the southern half between 30 to 40 inches (76.2 to 91.6 cm.), almost all of which falls during the months of June, July, August and September. The vegetation may be described generally as Sudan Savannah, which here has been largely disturbed by farming activities, the soil being made up of loose sand which produces the ground nut crop. The population according to the 1952 census was 1,500,000 of whom the great majority are Hausas, living in village communities and engaging in agriculture.

It is important to realise that in a predominantly Moslem territory like Katsina, there is an attitude towards leprosy rooted in tradition. In conversation with the Emir he revealed that there was a widespread belief in Katsina Province that leprosy was hereditary and that traditionally the people considered that it could exist in three forms. The first, called "*judsam*" by the Emir, refers to lepromatous leprosy; the second, "*baras*", describes single or multiple patches, and the third, "*behuk*", describes early very doubtful areas of depigmentation which may develop into either of the first two forms. Although these Arabic words are only understood by the more educated members of the community, the underlying concept of established leprosy existing in lepromatous and non-lepromatous forms is generally accepted by the people of the province as a whole, and I found this simple form of classification could be easily understood by the local Nigerian leprosy attendants with whom I had to work.

In the surveys carried out during the past two years, cases were divided into lepromatous and non-lepromatous groups, and all doubtful early leprosy lesions were classified as non-lepromatous on clinical grounds.

Administration of the Leprosy Outpatient Treatment Service at Katsina

The Leprosy Outpatient Treatment service at Katsina is primarily the responsibility of the Katsina Native Authority, presided over by the Emir. The Native Authority provides the staff and arranges where and when the clinics are to be held, while the Northern Nigerian Government in Kaduna provides periodic medical supervision of these clinics and facilities for the training of leprosy staff employed by the Native Authority. UNICEF provides over 90% of the DDS tablets used for the treatment of leprosy in Northern Nigeria. Details of the administration of this scheme have been set out by Dr. C. M. Ross[5].

Katsina Province is particularly fortunate in having a most experienced leprosy inspector in Malam Shehu Ruma, who has accompanied me on both my surveys, and I never found occasion to disagree with him on the question of diagnosis of leprosy and on the differentiation of lepromatous and non-lepromatous cases. Moreover, subsequent histological exmaination of the skin and nerve biopsies from a selected number of lepromatous and non-lepromatous cases in this series on every occasion showed characteristic changes in conformity with the clinical diagnosis. Because of this it was important to know what clinics had been under his supervision, for here reliance could generally be placed on the original diagnoses.

Selection of clinics, and investigations carried out

Clinics were selected for detailed examination in 1957 in the following way: the province was divided into a northern, middle, and southern section, and three clinics were selected at random from each of these three areas.

At each clinic all the patients attending were examined and the number of lepromatous and non-lepromatous cases recorded, and any signs of toxic reaction to DDS were also noted. From the register it was possible to learn the number of absentees, and, on the evidence of the initial diagnosis made by the leprosy inspectors, to classify them into lepromatous and non-lepromatous groups. Particular attention was paid in the first survey to the clinical state of all the advanced lepromatous cases who were starting treatment at that time. In 1958 it was possible to re-examine the majority of patients attending seven of the nine clinics originally investigated in 1957 and once again to record the number of lepromatous and non-lepromatous cases, the number of absentees, and the number of cases showing signs of toxic reaction to DDS. We recorded the number of new cases attending each of these clinics and the diagnosis in each case.

Observations

These are most conveniently summarized in the form of the following Tables.

TABLE I. NUMBERS OF CASES ON THE REGISTERS IN 1957 AND 1958

Clinic	*Number on Register*, 1957	*Number Discharged* 1957–1958	*Number on Register*, 1958
Jibiya	352	6	426
Katsina	346	0	392
Rimi	424	8	474
Kankiya	328	15	364
Chiranchi	338	7	386
Bindawa	416	28	439
Rimaye	243	0	315

Table I shows the number of cases on the register in 1957 and 1958 and the number discharged during the year. The number of cases on the register has increased while the number of cases discharged is remarkably small.

TABLE II. NUMBER OF NEW CASES ATTENDING, WITH THEIR DIAGNOSES

Clinic	*Number of New Cases* 1957–1958	*Non-lepromatous*	*Lepromatous*	*Lepromatous percentage*
Jibiya	80	64	16	20
Katsina	46	32	14	30.4
Rimi	58	42	16	27.6
Kankiya	51	46	5	10
Chiranchi	55	44	11	20
Bindawa	51	33	18	36
Rimaye	72	53	19	25.6

Total % of Lepromatous Cases 24.2

Table II shows the number of new cases which attended for treatment during 1957–1958 together with the rate of lepromatous and non-lepromatous forms of the disease. The majority of the new cases are seen to be non-lepromatous, only 24% falling into the lepromatous group.

TABLE III. PATIENTS WHOSE NAMES HAVE BEEN REMOVED FROM THE REGISTERS BETWEEN 1957–1958

Clinic	*Total*	*Cured*	*Transferred*	*Wrongly Diagnosed*	*Died*
Jibiya	6	–	–	1	5
Katsina	0	–	–	–	–
Rimi	8	2	–	–	6
Kankiya	15	6	3	–	6
Chiranchi	7	–	4	1	2
Bindawa	28	–	16	2	10
Rimaye	0	–	–	–	–

Table III shows the number of patients whose names have been removed from the registers during 1957–1958. We point out that remarkably few cases were discharged as cured.

TABLE IV. ABSENTEE RATE IN 1957 AND 1958

Clinic	*Number on Register*, 1957	*% Absent* 1957	*Number on Register*, 1958	*% Absent* 1958
Jibiya	352	31.2	426	33.6
Katsina	346	23.5	392	34
Rimi	424	12.3	474	12
Kankiya	328	14.9	364	15.3
Chiranchi	338	23.5	386	25.4
Bindawa	416	21.2	439	28.9
Rimaye	243	17.9	315	20.6
		Mean 20.6%		Mean 27.3%

Table IV shows the rate of absenteeism in 1957 as compared with 1958. It can be seen that the rate has increased appreciably in the last year.

TABLE V. LEPROMATOUS AND NON-LEPROMATOUS ABSENTEES IN 1958

Clinic	*Total number absent*	*Non-lepromatous absent*	*Lepromatous absent*
Jibiya	154	114	40
Katsina	210	168	42
Rimi	57	42	15
Kankiya	55	43	12
Chiranchi	98	79	19
Bindawa	127	101	26
Rimaye	65	54	11
Total	766	601	165

Total absentee rate 27.3% Lepromatous absentee rate 6.0%. In Table V comparison is made between the rate of absenteeism among lepromatous and non-lepromatous cases. Although the total absentee rate is approximately 27%, the absentee rate among the lepromatous group is around 6%.

Table VI shows the number of cases of lepromatous leprosy attending each clinic. The percentage range varies from 30 to 40%, the lowest being found in the long established and well-run clinic at Kankiya.

TABLE VI. LEPROMATOUS AND NON-LEPROMATOUS CASES IN 1958

Clinic	*Number on Register*	*Non-lepromatous*	*Lepromatous*	*Percentage Lepromatous*
Jibiya	426	269	157	36.8
Katsina	392	258	134	34.0
Rimi	474	307	167	34.4
Kankiya	364	354	110	30.2
Chiranchi	386	221	165	35.1
Bindawa	439	278	161	36.6
Rimaye	315	191	124	40.0

Lepromatous Rate: 36.3% mean

TABLE VII. CASES WHICH WERE DIAGNOSED NON-LEPROMATOUS IN 1957 AND WHICH HAVE IN THE PERIOD JULY, 1957, TO JULY, 1958, DEVELOPED MILD LEPROMATOUS CHARACTERISTICS

Clinic	*Number of Cases*	*Percentage*
Jibiya	28	6.0
Katsina	20	5.1
Rimi	44	9.5
Kankiya	33	9.1
Chiranchi	46	14.0
Bindawa	34	7.7
Rimaye	50	15.8

Total 255
9.11% cases on Register

Table VII shows the number of cases which were diagnosed as non-lepromatous in 1957 and which have in the period of one year developed mild lepromatous characteristics. The development of these mild lepromatous manifestations occurred in spite of treatment which there is every reason to believe was regularly administered.

Development of Lepromatous Characteristics in Originally Non-lepromatous Patients

At the Albarka Leprosy Settlement outside Kaduna where there were 130 leprosy patients, 30 leprosy patients who had presented with circumscribed lesions on admission, showed early signs of diffuse lepromatous infiltration of the skin of the whole body, in spite of up to 5 years of regular oral treatment with DDS in the dosages advocated by Dr. C. M. Ross. Miss Lewsey, the Superintendent of the settlement, had been much concerned with these changes

and maintained that such had not occurred under treatment with chaulmoogra oil. These changes consisted of a slight swelling of the skin of the face and ears, and a characteristic diffuse hypopigmentation of the skin over wide areas of the body, usually most easily seen over the back, but also affecting the face and limbs. This diffuse depigmentation is not related in its distribution to the original patches which frequently had disappeared; these cases were indistinguishable clinically from treated diffuse lepromatous patients.

At the S.I.M. Settlement at Katsina I investigated 50 cases of leprosy who had been diagnosed on admission as non-lepromatous, by experienced leprologists. These cases had been receiving DDS and other sulphone drugs for up to 6 years. All these 50 cases gave a negative response to intradermal lepromin injection. On careful clinical examination the same early signs of diffuse lepromatous leprosy that had been seen at Albarka were again present. Smears were taken from the skin of the ears of these patients and in no case were acid-fast bacilli found.

In 1957 I had the opportunity of examining six cases of which five responded positively to lepromin, and these were re-examined after a year of regular treatment with DDS. In 1958, four were still positive to lepromin and showed various degrees of resolution of their lesions, while one case was now lepromin negative and exhibited the same early signs of diffuse lepromatous infiltration that were seen in the patients examined at the Albarka and Katsina Settlements.

In the survey of the Leprosy Outpatient Treatment Centres in Katsina Province in 1957, I was able either to confirm or correct the recorded diagnosis in all the cases that came for treatment, so that in 1958 it was possible to recognise any changes that had taken place during the past year.

From the tables presented above it will be noticed that 255 cases diagnosed as non-lepromatous in 1957 have during the past year developed early signs of diffuse lepromatous infiltration on clinical examination; that is to say, they have developed similar signs to the patients at the Mission at Albarka, at the S.I.M. Settlement at Katsina and the one case I investigated in detail. These cases have been designated lepromatous on clinical signs only.

Advanced Lepromatous Cases

As a result of my own investigations of all the advanced lepromatous cases attending these clinics for the first time in 1957, it would appear that between 1957 and 1958 these cases have shown a very remarkable clinical improvement. In the majority, the nodules of the face and ears had subsided, the nasal and laryngeal symptoms were much less marked, but the most noticeable fact was that the depression and lassitude, so commonly found in untreated

cases of advanced leprosy, had to a large extent disappeared. These findings were further confirmed by the various leprosy attendants in the Province and they also stated that the ulcerations of the hands and feet so commonly found in untreated cases usually disappeared with DDS treatment, which is confirmed by my own observations.

Toxic reactions, consisting mainly of swelling of the face, erythematous changes of the skin, or exudation of fluid at the edges of lesions, were found in 10 cases seen in the 1957 survey. In 1958, 6 of these cases no longer showed signs of toxic reaction, but a further 4 cases with these signs were noticed. In every case the leprosy attendant in charge of the clinic recognised the condition and took appropriate steps to deal with it.

Discussion

It is sometimes argued by the advocates of rigid segregation that the high absentee rate among patients attending outpatient treatment centres indicates a high incidence of toxic reaction to DDS and the existence of a large number of partially treated but infected subjects circulating freely in the community. From the above tables it will be seen that the absentee rate amongst those diagnosed as lepromatous is encouragingly low, and, among those attending, only 4 showed signs of toxic reaction. On enquiry I was always given a plausible explanation of the absence of these lepromatous cases, and from the registers it appeared that the majority of these cases came fairly regularly for treatment. The dangers of lepromatous leprosy are well known in the community and the benefit to be derived from regular treatment is accepted everywhere. It would seem unlikely that the above figures give a false impression of the incidence and attendance rate among a lepromatous group. The higher absentee rate among the non-lepromatous group is, in view of the conversion figures already described, much more alarming. It can be seen that very few cases have been discharged from these clinics as cured during the past year, and removal of names of patients from the registers only occurs when they have transferred to another clinic, or when the original diagnosis of leprosy is found to be incorrect, or when the patient has died. Against this background it is tempting to suggest that a large proportion of the non-lepromatous absentees are now free of symptoms, and this in turn would account for the increased absentee rate in 1958. It is unrealistic to expect patients to walk five or six miles to a clinic in order to receive treatment for a skin lesion which they can see for themselves has disappeared. In a community where the dangers of leprosy are so widely understood it would be reasonable to expect treated patients of this type to seek treatment once again if they noted any deterioration in their general condition.

As stated above, the most encouraging response to DDS is to

be found in the general improvement in the mental and physical state of the patients under treatment. This is not only confined to the nodular lepromatous group, but is found throughout the lepromatous population as a whole. The symptoms of lassitude, deep-seated muscle pain, and fatigue are promptly relieved and in many cases a chronically sick subject is transformed into a reasonably active and useful member of society. The economic effect of DDS treatment in village communities must not be overlooked; in the past leprosy patients sat about the villages all day begging and were exempt from local taxes on the grounds that they could not work. Now they walk to the fields like everyone else, and are able to play a useful part in the community life.

It is tempting at first sight to attribute *all* these benefits to a specific action of DDS on the leprosy organism. Nevertheless, it must be realised that DDS may have a general tonic effect on leprosy patients who are as heavily parasitisized as the people of Katsina; it is known to have some beneficial effect on trachoma (I. Mann[6]), and may produce benefits in leprosy patients which are not directly related to the destruction of the leprosy bacilli. The psychological effect of regular treatment must not be forgotten, and all these factors must be borne in mind in assessing the effect of DDS therapy in a population of this kind. It is hardly justifiable to deny large numbers of chronically sick patients the only effective remedy for their condition in order to assess the effects of treatment. But until this type of experiment is carried out, either by withholding treatment or by comparing the effects of new medicaments with those of DDS, it must be a matter of opinion how much of the benefit DDS is due to a specific action on the organism and how much to other incidental effects.

From the tables, it can be said that the number of cases attending each clinic is increasing and that the new cases are predominantly non-lepromatous. Nevertheless, the development of signs of early lepromatous leprosy in patients originally diagnosed as non-lepromatous indicates that the resolution of circumscribed lesions should not be regarded as a cure, since the evidence from the tables indicates that there is a real possibility of the occurrence of a lepromatous change.

With this danger in mind it would seem that the policy adopted in Northern Nigeria of keeping leprosy patients on treatment at outpatient clinics for as long as they are prepared to come has everything to commend it in our present state of knowledge.

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MOBILE ANTI-LEPROSY TREATMENT CENTRES GHANA

by JOHN H. ELDON

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Until the middle of 1957, anti-leprosy treatment in Ghana was offered at static clinics. Treatment was given by the Ghana Leprosy Service, Government Hospitals, Local Council Dispensaries and by various Missionary organisations. The big disadvantage of this form of treatment was that patients would present themselves for treatment for a number of weeks and then fail to report again. The reasons given for this persistent absenteeism were many but the principal one was economic; the patient did not have the money to pay for the return lorry fare from his home to the clinic. Another reason was that lorries ran so infrequently that the patient had to sacrifice a day away from work to receive treatment.

To overcome these difficulties the Ghana Leprosy Service, through the Ghana Government, asked UNICEF for a number of Land Rovers to start a series of mobile treatment centres throughout Ghana. UNICEF agreed to the request and not only arranged to supply nine Land Rovers but also to supply a two years stock of tablets DDS. Approval of the request came in during the latter part of 1956, with a promise that the Land Rovers would be delivered in Ghana about March, 1957. In order to facilitate the introduction of such a scheme, a pilot mobile treatment centre was inaugurated at Wa in the western region of Northern Ghana. A circular itinerary was arranged and treatment started in areas where previously static treatment centres had been employed. The Leprosy Control Officers in other areas were also asked to give serious thought to the planning of itineraries in their areas. The aim was the treatment of the largest possible number of new and old cases with the most profitable running time. Wherever possible circular itineraries were arranged although in some areas back tracking was necessary due to the road systems.

In March, 1957, the Land Rovers arrived and drivers were engaged at Cape Coast, the largest town near the Ankaful Leprosarium. After an initial period of training, the drivers with their vehicles were posted to the regions where they would be working. Each driver, when engaged, was told that he would be expected to assist the Leprosy Control Assistant in charge of each Land Rover with the distribution of tablets. This they willingly undertook to do and have proved, in the main, to be of great use to the centres. One criticism which was made by the Leprosy Control Officers was that they would have preferred to have engaged drivers from the areas in which they were to work because of the language and housing difficulties. This is a very real criticism as in certain areas of Ghana, particularly in the north, a stranger has great difficulty in making himself understood. Drivers who were engaged locally also had

settled domestic arrangements whereas the drivers engaged at the Ankaful Leprosarium had to uproot their families and transport them to the areas where they would be working.

The Land Rovers are staffed by a Leprosy Control Assistant and a driver with, in one or two cases, a Clinic Attendant. The Leprosy Control Assistant is in charge of the vehicle and responsible for the efficient treatment of all patients suffering from leprosy on his circuit. On appointment to the Ghana Leprosy Service the Leprosy Control Assistant undertook a two-year period of apprenticeship during which time he was trained at the Ankaful Leprosarium and was also in charge of a group of clinics under the close supervision of the Leprosy Control Officer in charge of the region where he was working. The pupil whilst at the Ankaful Leprosarium is given instruction in the diagnosis of leprosy, differential diagnosis, the accurate keeping of records such as would affect him when posted to the field and dealing with the welfare of the patients in residence at Ankaful. In the field he is expected to run efficiently ten or twelve clinics during the course of a week. Periodically reports on the pupils are submitted and their progress assessed. At the end of their training period and subject to satisfactory reports, they are recommended for appointment to the grade of Leprosy Control Assistant.

The Land Rovers travel on circuits which vary from 300 miles to 500 miles each week. As far as possible the period away from base is confined to Monday to Friday which leaves Saturday morning free for maintenance, replenishing supplies, and record work. During the course of the week the Land Rover stops at each village on the route and treatment is given to every patient. The number of patients treated varies greatly from area to area but during 1958 approximately half the total registered patients in Ghana were receiving treatment from the mobile treatment centres. In addition the absentee rate fell considerably. At last the patients did not have to spend money on transport and the Land Rovers arrived regularly each week with their treatment. The keeping of a fixed schedule is one of the most important factors contributing to the popularity of the mobile treatment centres and it is of the utmost importance, if the Land Rover is to be delayed, that the patient should be notified beforehand. One big disadvantage of the mobile treatment centre is that when a Medical Officer visits the circuit to examine the patients the schedule must, of necessity, be delayed. If, however, the patients are warned in advance that the doctor is to visit them they are prepared to wait patiently until the Land Rover arrives.

In order to provide for continuity of treatment one Land Rover was to be held in reserve to enable each Land Rover working on a circuit to be relieved and sent to the main agents for a thorough check over. Circumstances prevented this programme from being put into operation; one circuit was disrupted by a broken bridge, with

the Land Rover on the wrong side of the bridge. As there were no alternative roads the spare vehicle had to stand in for three months until the rains ceased and the bridge was repaired. To replace each vehicle in turn consequently became impossible and to enable much needed maintenance to be done the circuits were closed down for three weeks in August, 1958. The vehicles were sent to the agents, checked over and repaired where necessary. All required fairly extensive repairs, mainly to the engine (new piston rings, etc.), the propeller shafts and brakes.

The close-down of the mobile treatment centres for a three week period also enabled the crews of the vehicles to proceed on leave. In Ghana new leave regulations stipulate that all Ghanaian officers should take leave during the year and that accumulation of leave will not, as a general rule, be permitted. In order to provide an efficient leave roster it has been decided that the mobile treatment centres will close down completely again in 1959 thus enabling all officers working in the field to enjoy their leave at the same time. July has been chosen for the close-down period as the rainy season will be half way through during this month and attendances at the stopping places will be low.

So successful have the mobile treatment centres proved in Ghana that UNICEF have agreed to provide an additional fleet of ten Land Rovers. Eight of these vehicles will be put into circuits and two will be held in reserve. These circuits will come into operation in March or April, 1959, and will make seventeen mobile treatment circuits in Ghana. These seventeen circuits will cover the highly endemic areas of Ghana bringing treatment based on oral DDS to the majority of cases suffering from leprosy.

The following table shows the number of cases under treatment in Ghana at the end of 1958 and the number of cases treated by the mobile treatment centres:

	Number Registered	*Mobile Treatm. Centres*	*Number of Vehicles*
Eastern Region North Ghana	11053	7454	4
Western Region North Ghana	3885	1443	1
Ashanti	4652	1130	1
Eastern Region South Ghana	2991	1269	1
Western Region South Ghana	2014	1118	2
Trans-Volta Togoland	1422	—	
Total	26017	12414	9

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CORTICOSTEROIDS IN THE MANAGEMENT OF FOOT-DROP IN LEPROMATOUS LEPROSY: A CASE REPORT

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In February, 1958, a West Indian aged 21, who had been treated for leprosy in England during the previous 13 months, was referred to the Hospital for Tropical Diseases for further management. On examination he was found to have skin changes of resolving lepromatous leprosy, there was anaesthesia of legs and feet, and both common peroneal (lateral popliteal) nerves felt firm and slightly thickened, the left more than the right. There was no muscular weakness nor wasting. There were moderate numbers of acid-fast bacilli in skin smears, the bacilli showing granular changes, and skin biopsy was typical of lepromatous leprosy.

As the patient refused admission to the Jordan Hospital, treatment had to be planned on an out-patient basis, and this made it impracticable to continue the twice-weekly sulphetrone injections which he had been receiving. Treatment was changed to 50 mg. by mouth of dapsone (DDS) every other day, and a fortnight later the dose was increased to 50 mg. daily. One month later he appeared to be progressing well, and the dosage was increased to 100 mg. alternating daily with 50 mg. Two weeks later he reported to say that, since his last attendance, he had felt unwell, had noticed "red lumps" on his skin, and had developed increasing weakness in his left foot. He was found to have *erythema nodosum leprosum* and a complete dropped foot; he had lost the power to dorsiflex or to evert his left foot, but inversion and plantar flexion were not affected. The left common peroneal nerve, contrary to expectation, was not tender.

He was admitted to the Jordan Hospital as an emergency, and the following treatment was instituted: (1) cessation of sulphone therapy; (2) prednisone 5 mg. four times daily by mouth; (3) a Plaster of Paris back splint supporting his foot at a right-angle. The plaster splint was removed twice daily in order to carry out passive movements; (4) an intraneural injection consisting of 1500 units of hyalase dissolved in 1 ml. of 2% procaine and mixed with 1 ml. of hydrocortisone suspension (25 mg./ml.). This was injected into the left common peroneal nerve at the neck of the fibula.

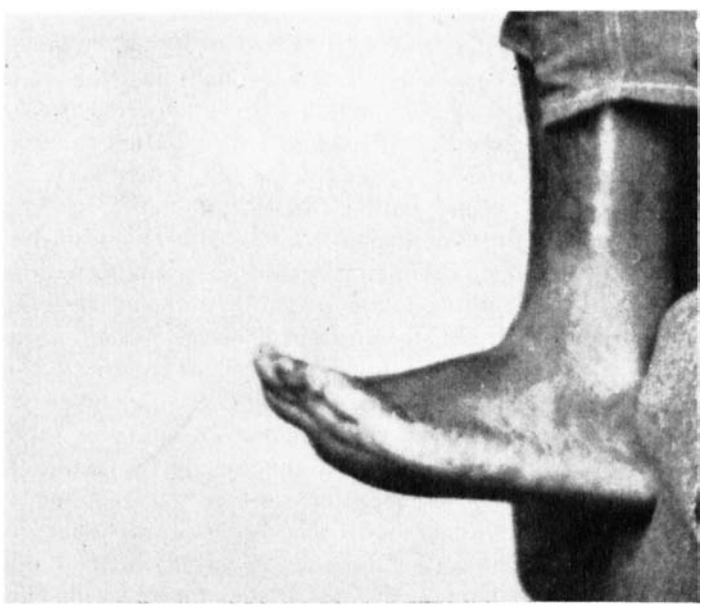
Two days later contraction could be felt in the anterior and lateral crural muscles when he attempted to dorsiflex and evert his foot, and by the end of a week he was able to dorsiflex the foot almost to a right-angle, but moderate pressure with the hand could push the foot down again. At this stage active exercises were increased by getting him to use his foot on a player piano, and he continued to wear the plaster splint when not exercising. Muscle power continued

to improve, and a fortnight later (three weeks after admission) he was able to dorsiflex his foot to a right-angle and all his toes were capable of slight dorsiflexion. The dosage of prednisone was reduced to 15 mg. daily, the splint was worn at night only, and active exercises were continued. One week later the dosage of prednisone was reduced to 10 mg. daily, and this was progressively decreased to nil over the next two weeks.

Dr. W. D. Fletcher, of the Department of Physical Medicine at University College Hospital, saw the patient 5 weeks after admission and reported as follows:

> "I have carried out electrical reactions on his muscles this week and I am pleased to say that these were quite normal. He must have, therefore, a neuropraxia, and I would expect him to get a complete recovery."

One week later he was able to dorsiflex and evert his foot fully, the strength of the affected muscles being about three-quarters that of the muscles on the opposite side. By this time prednisone had



Recovery from foot-drop after treatment as described

been discontinued and the splint discarded. Two weeks later (8 weeks after admission) the muscular power of the left foot was equal to that of the right, the only detectable difference being slight weakness in dorsiflexing the left big toe, but this recovered completely within the next few weeks.

Resumption of anti-leprosy treatment was considered at this stage, and it was decided not to resume sulphone therapy but to

change to Ciba 1906. *There has been no recurrence of neuritis during the subsequent* 12 *months* although there have been several bouts of *erythema nodosum leprosum.*

Discussion

Damage to peripheral nerves in lepromatous leprosy takes the form of fibrous thickening of the connective tissue composing the endoneurium, perineurium and epineurium, and this takes place at sites where the affected nerves are superficial in their course. The basic architecture of the nerves is maintained in the earlier stages, and damage to nerve fibres results from compression. An allergic type of reaction may take place in one or more of the affected nerves during the course of treatment, either as an isolated event or in conjunction with a more generalized reaction, in which oedema is the characteristic feature. This causes a rapid increase in the compression of nerve fibres as the connective tissue thickening prevents expansion taking place, and, if permanent damage to nerve fibres is to be prevented, it is essential to relieve this compression as quickly as possible. Corticosteroid therapy stops further development of oedema by reducing capillary permeability, and an intraneural injection of hyalase, by virtue of its spreading action, causes a dispersal of the oedema which is already present. Wilkinson and Colombo (1955) and Garrett (1956) have described the successful use of hyalase injected into painful nerves in lepromatous leprosy; Jopling and Cochrane (1957) have advocated intraneural injections of hydrocortisone. It is now standard practice at this hospital to give a single intraneural injection consisting of procaine, hyalase and hydrocortisone, as described in this case report, and this gives long-lasting relief of pain without having to stop specific therapy. Results are equally satisfactory when pain is associated with muscle weakness, but in such cases it is necessary to stop specific treatment temporarily and to splint the affected muscles when they are not being exercised.

This routine was followed in the case under discussion, but systemic corticosteroid treatment was given in addition, to control *erythema nodosum* and to ensure that intraneural oedema did not recur during the stage of recovery.

I would like to thank Sir George McRobert for permission to publish this case, and Dr. W. D. Fletcher for his report, and Mr. Frank Barratt for the photography.

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SOME OBSERVATIONS ON THE BACTERIOLOGICAL INDEX IN LEPROSY

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In reviewing a series of cases of "open" leprosy (lepromatous and dimorphous) that had become bacteriologically negative to standard methods of examination and had remained so for several consecutive examinations, the opportunity was taken of analyzing the former persistence of *Myco. leprae* at the various sites from which material had been taken regularly by the scraped incision method. One of the objects in view was to assess the value of routine methods of examination that could be adopted widely in a domiciliary leprosy service treating great numbers of patients and using auxiliary medical personnel.

The sites from which smears were taken were the following:

No. 1. Ear-lobe;
2. Forehead;
3. Cheek;
4. Most clinically active part of the edge of a lesion;
5. Apparently healthy skin;
6. Nasal mucosa;

as advocated by Zanetti (1947) and by Browne (1955).

The dermal smears were stained by Ziehl-Neelsen's method, and the degree of infection at each site recorded on Dharmendra's notation (Cochrane, 1952):

1. *Slight.* Bacilli in occasional fields, not more than 2 or 3 per field; 1 or 2 small globi in 50 fields;

2. *Moderate.* Bacilli in every field, but not more than 10 per field; a few globi here and there;

3. *Heavy.* Numerous bacilli and globi in every field;

4. *Massive.* Innumerable bacilli, and large numbers of globi, in every field.

The "bacteriological index" is the average of the indexes at each of the six sites.

It is conceded that the methods of obtaining the material for staining, and of determining the index at each of the sites, are not of absolute value; but with standard procedures applied uniformly, the method has proved satisfactory (Hanks, 1956).

For the appraisal of the conclusions reached in the course of the present enquiry, the following figures are given of the endemicity of leprosy in the district from which most of the cases under review came:

	Total population	*Cases of leprosy under treatment*	
		Number	%
Men	14,750	2163	14.67
Women	12,255	1921	15.68
Children	18,030	1265	7.02
	45,035	5349	11.88

The clinical forms of leprosy were classified as follows:

Form	*Number of cases*	%
Tuberculoid	3889	72.71
Indeterminate	187	3.49
Lepromatous	1104	20.68
Dimorphous .. .	169	3.16
	5349	100.00

N.B.—These figures take no account of the number of cases of tuberculoid leprosy regarded as quiescent and not needing treatment, either from spontaneous regression or after adequate sulphone therapy; thus the numbers and percentage of tuberculoid cases should be higher than that indicated.

The cases that form the subject of this enquiry were inpatients at the Yalisombo Leprosarium in the Oriental Province of the Belgian Congo, and comprised 156 lepromatous cases and 34 dimorphous cases; they represent a typical cross-section of the members of these groups under treatment throughout the district.

These patients had received treatment as follows:

Lepromatous Cases:

	Cases
1. Dapsone tablets orally, with incorporated protoxalate of iron	106
2. Dapsone by intramuscular injection of a 25% suspension in chaulmoogra oil	3
3. Dapsone orally, interspersed with series of weekly or twice-weekly intramuscular injections of 50% aqueous sulphetrone (with 0.5% phenol)	35
4. Sulphetrone by intramuscular injection, alone	8
5. Sulfon-Cilag orally (a mono-substituted sulphone: Browne, 1955), followed by dapsone orally.. ..	4
	156

Dimorphous cases:

1. Dapsone orally	25
2. Sulphetrone by injection, alternating with dapsone orally	9
	34

In conformity with the general experience of leprosy in the Bantu, the incidence of lepra reaction during the course of treatment was low.

Original bacteriological index on admission

Most cases had received no treatment before admission, and the index represents the findings at the first examination (which coincided with the first clinical examination):

Site	*Bacteriological index*	
	Lepromatous cases	*Dimorphous cases*
(Lobe of ear) No. 1	2.93	1.97
(Forehead) No. 2	2.31	1.47
(Cheek) No. 3	2.17	1.29
(Most clinically active part of the edge of a lesion) No. 4	2.94	2.38
(Apparently healthy skin) No. 5 ..	1.52	0.50
(Nasal mucosa) No. 6	3.54	2.79
Average of all sites:	2.57	1.74

At each site, the average index was lower in the dimorphous group than in the lepromatous; but in both groups the average index showed the same relation between site and site, i.e., the highest index was in site No. 6 and the lowest in site No. 5, and correspondingly. The nasal mucosa was consistently the most highly positive site, containing many globi in each field of the oil-immersion lens in 130 out of 156 lepromatous cases, and in 18 out of the 34 dimorphous cases; and a few globi in 50 fields in a further 14 lepromatous cases, and 10 dimorphous cases.

The material from the earlobes was more highly positive in the lepromatous cases than in the dimorphous cases: 67%, as against 35%, had numerous globi at this site.

Apparently normal skin was highly positive in 43 lepromatous cases (28%), and in 3 dimorphous cases (9%).

Sites first becoming positive

The records furnish no evidence concerning the site that first becomes bacteriologically positive, since most patients had more than one site—usually several—positive at the first examination. In one case site No. 6, and in two cases site No. 4, were initially the only sites positive.

In some cases, the initial indexes for some sites were much higher than those of the other sites. This may or may not imply that these sites were the first to become bacteriologically positive in those patients; other factors, such as intensity of the infection, the disposition of *Myco. leprae* in the nasal mucosa or elsewhere, and the cellular pattern of the epidermis—are all involved.

With this proviso, it is of interest to note that Site No. 1 had the highest initial index in 6 cases; site No. 2 in 1 case; site No. 3 in 1 case; site No. 4 in 8 cases; site No. 5 in no case; and site No. 6 in 14 cases.

Time elapsing before bacterial negativity was achieved

The following figures refer only to those patients whose index had become zero before the date of the present enquiry, and take no account of those who were still bacteriologically positive after at least four years of controlled treatment.

Lepromatous cases

Clinical stage	*Number of cases*	*Average duration of treatment before bacterial negativity*
I	8	2.68 years
II	45	2.10
III	103	2.31
All stages: 156		2.26 years

N.B.—The "clinical stage" indicates in the main the extent of skin involvement in each case.

Another analysis based on the initial bacteriological index, gives the following results:

Initial bacteriological index	*Number of cases*	*Average duration of treatment before bacterial negativity*
3.0 and over	60	2.42 years
2.0 to 2.9	48	2.42
1.0 to 1.9	39	1.83
under 1.0	9	2.15
All cases	156	2.26 years

Dimorphous cases

The classification of dimorphous cases into clinical groupings in accordance with the extent of the involvement of the skin was not considered practicable in view of the nature of the lesions and the

discordance between the extent of the lesions and the gravity of the case. Analysis based on the objective standard of the bacteriological index revealed the following:

Initial bacteriological index	*Number of cases*	*Average duration of treatment before bacterial negativity*
3.0 and over	5	2.05 years
2.0 to 2.9	9	1.87
1.0 to 1.9	12	1.29
under 1.0	8	1.68
All cases	34	1.65 years

Order in which the sites become bacteriologically negative

This order was identical in the lepromatous and dimorphous groups, and was in strictly inverse relation to the degree of initial bacterial positivity of the different sites, i.e., the site with the lowest initial index became bacteriologically negative first, and *vice versa;* this was the order:

Site No. 5. Apparently healthy skin;
3. Cheek;
2. Forehead;
1. Ear-lobe;
4. Active edge of lesion;
6. Nasal mucosa.

Time elapsing before sites become bacteriologically negative

	Lepromatous cases	*Dimorphous cases*
Site No. 5.	0.70 years	0.21 years
3.	1.20	0.64
2.	1.38	0.90
1.	1.85	1.06
4.	1.94	1.60
6.	2.26	1.65

Last site to become bacteriologically negative

It is of clinical interest, practical value, and epidemiological importance to recognize that *Myco. leprae* may be disseminated from various cutaneous surfaces after apparent clinical cure, and, further, to know that a single negative bacteriological examination (by standard methods) of smears from one site does not necessarily indicate that the patient is now non-infectious. Thus, after five sites had become negative, one site remained positive perhaps for many months; similarly, after four sites had become negative, two sites may remain positive for long periods.

	Lepromatous Cases *Sites remaining positive:*			Dimorphous Cases *Sites remaining positive:*			Total
	One site positive	*Two sites positive*	*Total*	*One site positive*	*Two sites positive*	*Total*	
Site No. 1	10	30	40	1	4	5	45
2	4	11	15	1	3	4	19
3	2	10	12	1	2	3	15
4	16	42	58	6	14	20	78
5	1	2	3	0	0	0	3
6	51	47	98	5	17	22	120
Total sites remaining positive	84	142	226	14	40	54	280
Number of patients	84	71	155	14	20	34	189

Of the 10 lepromatous cases in which Site No. 1 was the last site remaining positive, 8 were nodular cases; of the 30 lepromatous cases in which this site was one of the last two remaining positive, 16 were nodular cases.

The nasal mucosa was the site to remain positive longest in 51 out of 84 lepromatous cases—more frequently than the edge of the skin lesion, or the ear-lobe.

These three sites—the nasal mucosa, the edge of the lesion, and the ear-lobe—together account for 243 out of 280 sites last remaining bacteriologically positive.

Infectivity of secretions from trophic ulcers

The patients of these two groups who were suffering from trophic ulceration were included for statistical purposes in a larger group containing tuberculoid cases and "open" cases still bacteriologically positive.

Four lepromatous cases had on five occasions acid-fast bacilli in serious discharges from trophic ulcers; and four tuberculoid cases also had acid-fast bacilli on five occasions. A total of over 1,400 bacteriological examinations were performed in this series of serous discharges from 63 "open" (lepromatous and dimorphous) cases, and 45 tuberculoid cases.

Conclusions

Microscopic examination of material obtained by the scraped incision method from the nasal mucosa, the most active edge of a lesion, and of the ear-lobe (in that order), is of value for purposes of confirmation of the diagnosis of lepromatous and dimorphous leprosy, for assessment of response to treatment, and for ascertainment of freedom from infectivity. The discharge from trophic ulcers is a relatively unimportant source of infection.

Acknowledgements

My grateful thanks are due to Dr. R. G. Cochrane, F.R.C.P., for his helpful criticisms.

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STUDIES IN PLANTAR ULCERS IN LEPROSY
III. THE NATURAL HISTORY OF PLANTAR ULCERS

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The occurrence of a plantar ulcer on the anaesthetic sole is a serious incident in the course of leprosy. The complications which commonly follow may persist long after the disease itself is arrested by modern treatment, and may in fact lead to the permanent disablement of the patient.

The appearance of a plantar ulcer is the climax of a series of changes that have occurred in the mechanics of the foot, leading to the breakdown of devices which protect the normal foot from damage during the stresses of walking. These changes have been described in a previous chapter and are represented clinically by damage in two areas which correspond to the surfaces on which friction-pressures are maximal.

These surfaces are that between the ground and the plantar skin, and that between the plantar skin and the underlying bone at any given moment of the walking roll. Corresponding to these two areas of stress, it is possible to recognise a deep and a superficial type of damage to the plantar tissues which culminate in a deep and a superficial type of ulceration.

It is much to the benefit of the patient that the condition be recognised in the pre-ulcerative stage, so that ulceration itself be avoided. The natural history of plantar damage therefore falls into three parts:

i. The pre-ulcerative stage.
ii. The plantar ulcer.
iii. The complications of ulceration.

(i) The Pre-ulcerative Stage

The regular observation of the feet of leprosy patients makes it possible to recognise a pre-ulcerative stage. When the importance of early treatment is recognised, it is found that patients themselves draw attention to their own foot-damage at an increasingly earlier time.

Symptoms depend to some extent on the intelligence of the individual, but the following description applies to an average case.

When there is profound and prolonged deep anaesthesia of the sole, there may be no pre-ulcerative symptoms, the ulcer being the first complaint if foot inspection is not being maintained. With less deep anaesthesia, there is first a burning sensation at one of the recognised sites of plantar damage, accompanied by tenderness on walking. If walking is continued, the burning sensation becomes accentuated at night in bed, and may disturb sleep. The patient limps, but may continue to walk until a further stage is reached which may include the cracking of a large callosity, or a swelling at the margin of the glabrous skin of the sole. At this stage, he will seek treatment.

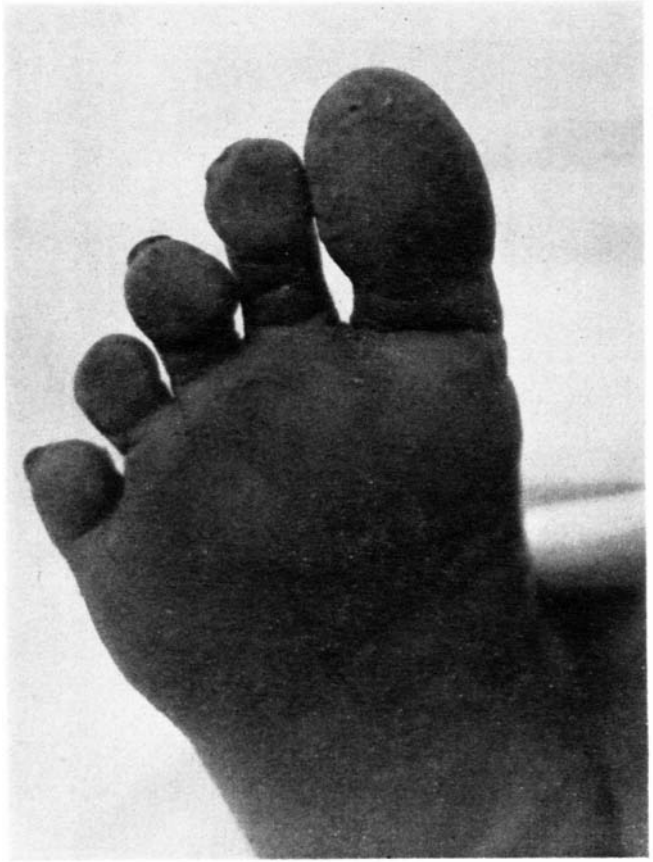

FIG. 1.—*An early sign in the pre-ulcerative stage is a spreading of two or more toes, due to localised oedema of the forefoot. Note the clear spaces between the toes. The local swelling is visible on the sole.*

FIG. 2.—*A necrosis blister indicating damage to the deep tissues between plantar skin and underlying first metatarsal. The fluid is sterile and will be absorbed if the foot is rested and raised.*

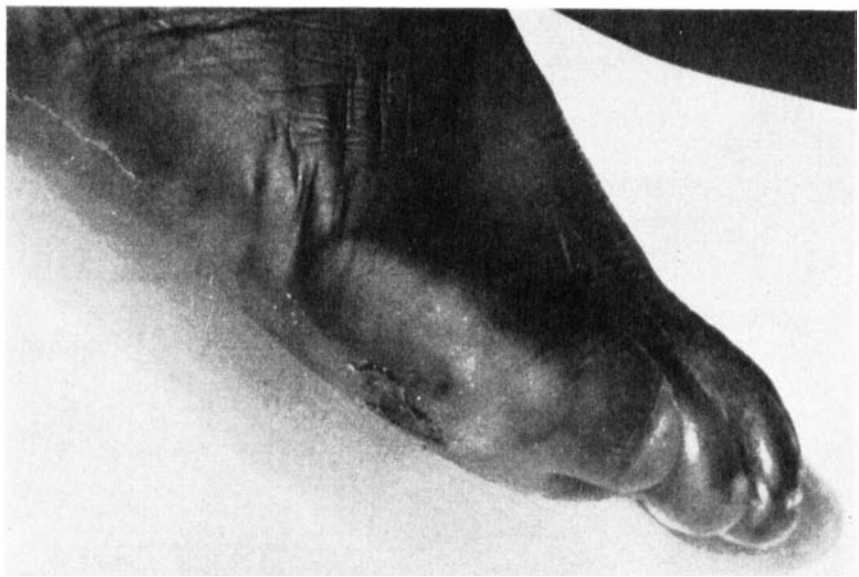

FIG. 3.—*A necrosis blister indicating a threatening plantar ulcer over the 5th metatarsal head. There is also a cracked callosity on the plantar surface of the damaged area.*

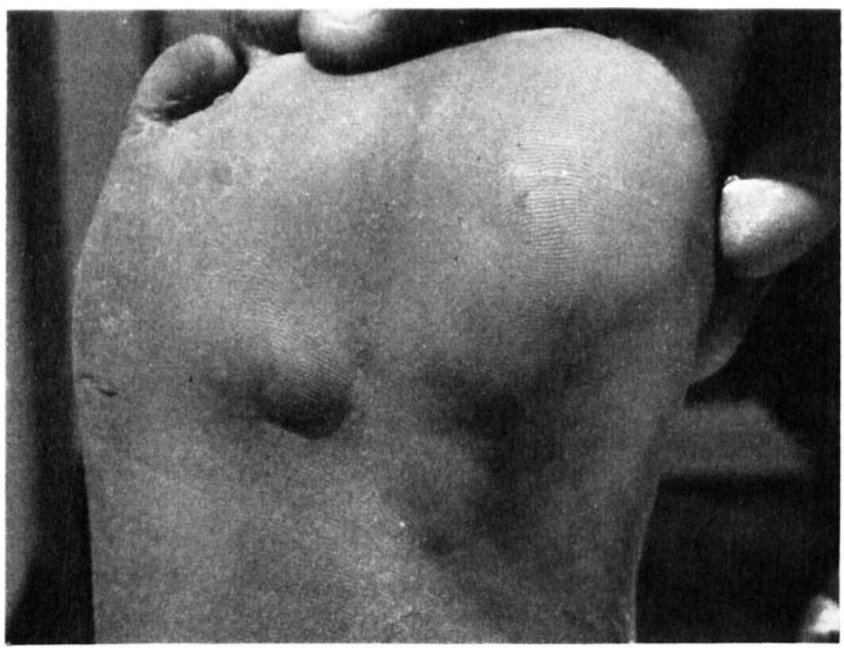

FIG. 4.—*Some necrosis blisters derived from the metatarsal heads point on the medial side of the glabrous skin. This one comes from the 5th metatarsal head. Note the cracked callosity nearby, nevertheless the contained fluid is sterile.*

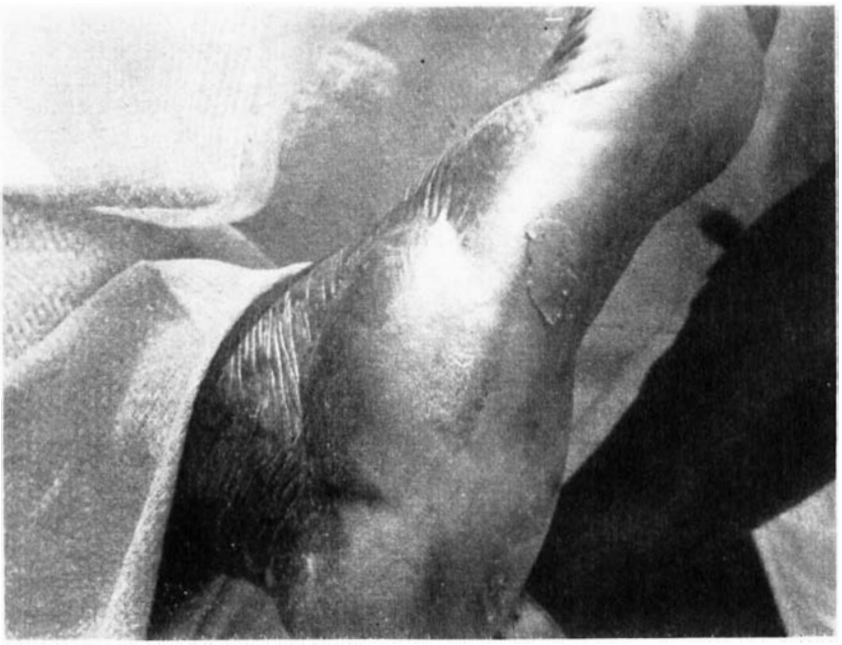

FIG. 5A.—*Necrosis blisters arising from damage between the calcaneal tuberosities and plantar skin often track to one side or the other of the heel and are large.*

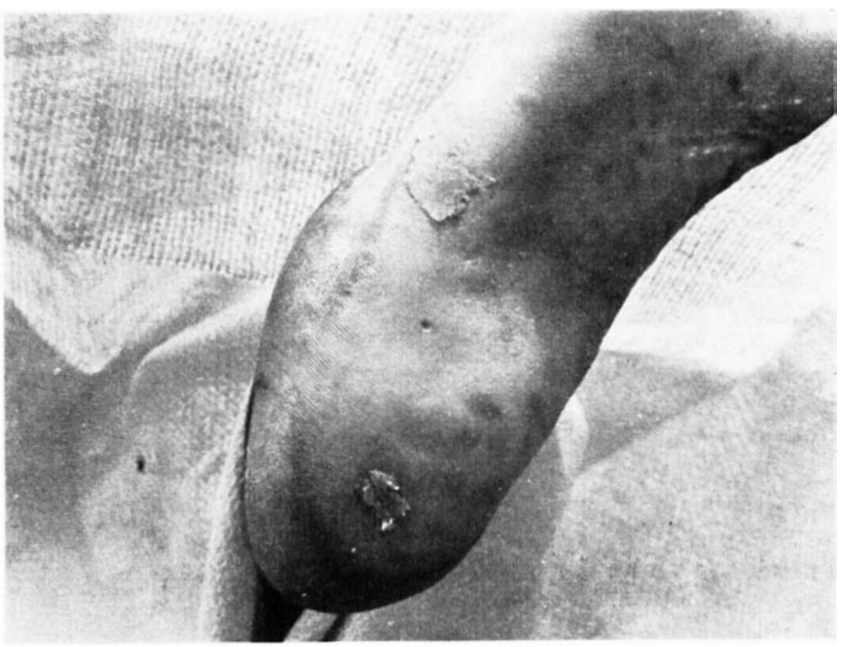

FIG. 5B.—*Note that the origin of the necrosis and the track of the blister is visible under a good light. If allowed to break down, this ulcer will be extensive.*

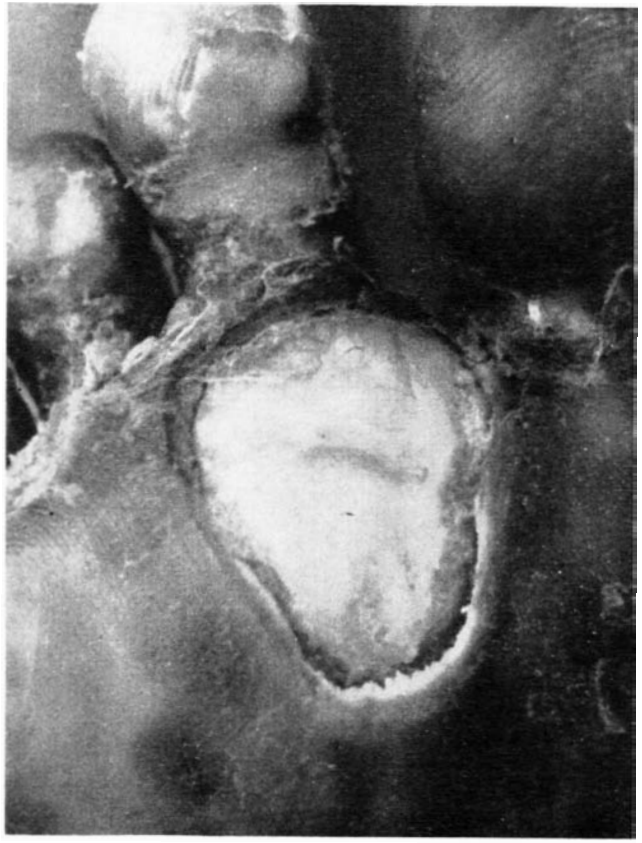

FIG. 7.—*The superficial type of plantar ulcer. This type involves considerable skin-loss and inevitable serious secondary infection.*

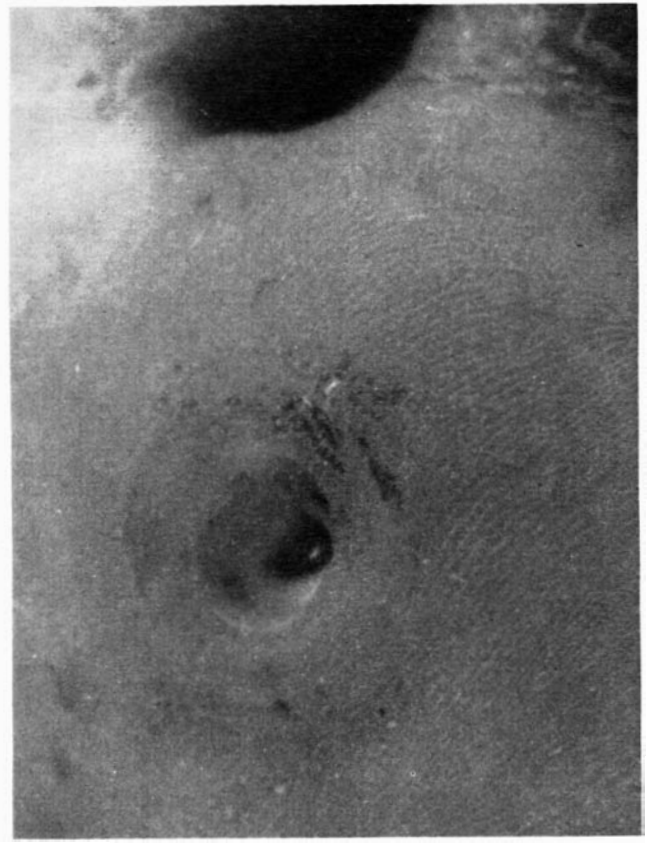

FIG. 6.—*The deep type of plantar ulcer. This is the common plantar ulcer in leprosy. It is really a sinus leading down to a necrotic area adiacent to the head of the metatarsal bone.*

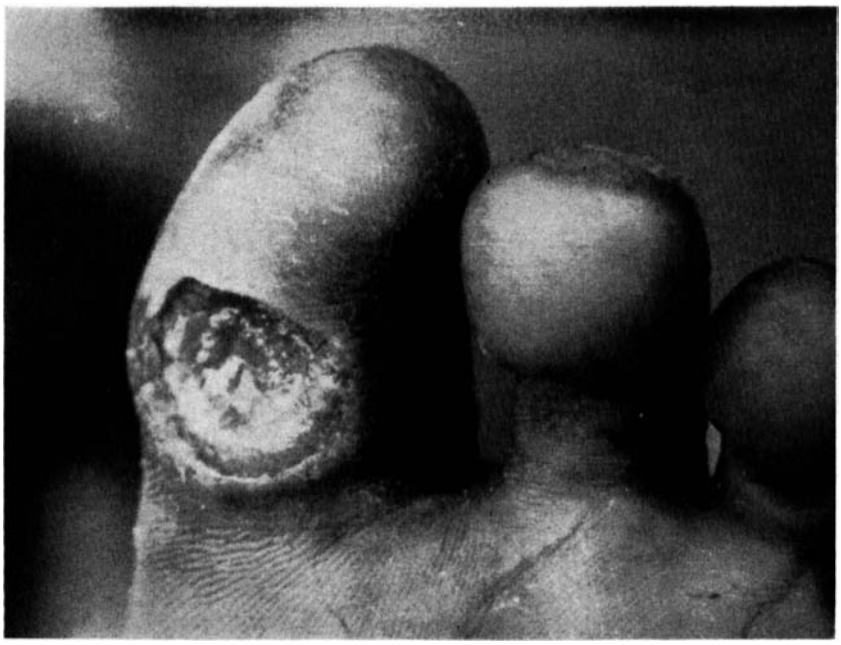

FIG. 8.—*The head of the proximal phalanx of the big-toe is not an infrequent site of plantar ulcer in an anaesthetic foot.*

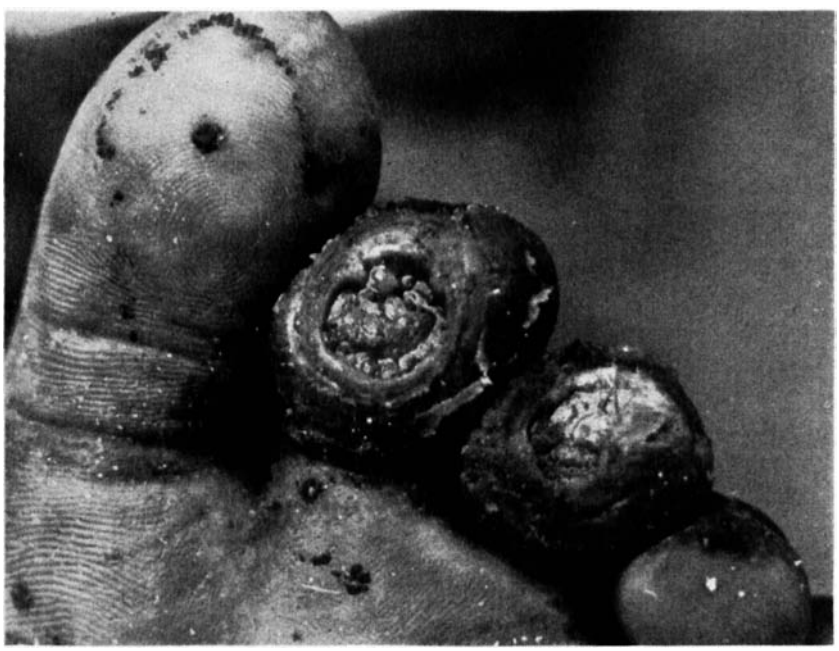

FIG. 9.—*Toe-tip ulceration is often multiple and represents tissue damage due to stresses at the final push-off of the walking step. They must be distinguished from trauma of the toes in drop-foot, in which the damage is on the anterior surface of the tip, or even on the dorsum.*

The *signs* of the pre-ulcerative stage will be noted when the patient first complains, but with increasing experience a careful observer will notice these signs in some cases before symptoms occur. This underlines the importance of the weekly foot inspection at which all feet known to be anaesthetic are observed and palpated. These signs are:

1. *There is a localised swelling of the foot*

In the early stages, this swelling is indefinite and may evade casual inspection; but if the two soles are compared it is possible to notice a difference in the length or width of the affected foot, due to localised oedema. There is a slight rise of local temperature. An affection of the forefoot will be indicated by a spread of the toes, between which a clear space can be seen (Fig. 1); on the unaffected side, the corresponding toes will normally be in contact. In a more advanced stage, the whole forefoot will be oedematous, though the oedema is more marked on the dorsum than on the plantar aspect of the foot because of the deep attachments of the glabrous skin. It is important to distinguish this condition from the general swelling of both feet which occurs in some cases of lepromatous leprosy and which may result in a slight separation of all the toes of both feet. In this latter condition, any tenderness of the sole is generalised and not limited to any one area.

In some cases of pending ulceration, there is a localised and discrete swelling at the edge of the glabrous skin of the sole, indicating the occurrence of deep necrosis, as will be described.

2. *There is localised tenderness, on deep palpation*

At the weekly foot inspection, the danger areas of the foot are systematically palpated with the thumb. In the absence of tenderness and swelling, the foot can be considered undamaged; but the absence of localised tenderness in a foot with localised swelling should lead to further investigation, including an X-ray if possible, to exclude the possibility of a neuropathic joint.

In cases with swelling at the margin of the glabrous skin, the nearest area of plantar ulceration should be carefully palpated and examined in a strong light.

3. *There may be abnormal callosities of the sole*

Callosities of the sole are not uncommon in patients in cases of threatening plantar ulcer. These are distinguished from the generalised thickening of the plantar skin seen in many barefooted people, because the abnormal callosity is limited to special areas, and often to one foot. In addition, the surface of the callosity may be cracked and in severe cases the crack may extend into the dermis.

Although the callosity may itself breakdown into an ulcer, it is not uncommon to find an abnormal callosity in cases where a neighbouring blister indicates necrosis deep to the callosity. (Fig. 3).

In such a case, the ulceration when it occurs may be either at the callosity, at the blister, or include both.

4. *There may be a localised blister at the margin of the glabrous skin*

The existence of an "idiopathic blister" has long been recognised as a precursor of certain types of plantar ulcer.

They have sometimes been mistaken for burns that have occurred without the patient's knowledge, possibly when he was asleep.

This type of blister is described as a *necrosis blister*, because it contains sterile tissue fluid derived from the necrosis of deep tissues at the area of damage. The blister varies in size from 1 cm. (especially under the base of the toes) to 5 cm. (particularly in relation to the heel)—Figs. 2, 3, 4, 5. It is often possible to see, with a powerful light, the deep track from the necrotic area to the presenting blister (Fig. 5b). In the early stage, the swelling is hard and may be dark from the presence of blood; but it progressively softens as liquefaction occurs.

A necrosis blister indicates that deep damage already exists, and that ulceration is imminent. The worst treatment is to precipitate ulceration by opening or pricking the blister and introducing infection. The contained fluid is sterile, and the condition will subside and the fluid be absorbed if the foot is rested in bed in a raised position, and covered with a simple protective dressing. A usual time for absorption is 7-10 days. No antibiotic is necessary, but can be used as a prophylactic.

Summarising the symptoms and signs of the pre-ulcerative stage, it can be said that the complaint by the patient, or the discovery by the foot inspector, of a foot which has an area of localised swelling and tenderness over the known ulcer-bearing areas of the sole is in danger of ulceration. This danger is imminent, if there is also a localised and cracked callosity, or a necrosis blister; but ulceration can be avoided even at this stage by suitable treatment.

(ii) The Plantar Ulcer

The plantar ulcer of the neuropathic foot of leprosy is only too familiar to all workers. It occurs either as a deep and often chronic hole corresponding to damage to tissues close to bone; or as a superficial and often acute ulcer, corresponding to damage at the superficial area of friction-damage.

Although commonly single, plantar ulceration may be multiple and as many as four ulcers may be present on one sole, excluding associated toe-tip damage. The distribution and frequency of these ulcers has been described in a previous chapter.

a. The deep type of plantar ulcer (*Fig.* 6)

This is the common chronic ulcer on the sole of the foot in leprosy, though it may be masked by associated longstanding secondary infection. When this infection is minimal, it is seen to be a collar-stud type of hole leading from the skin surface through a funnel which

opens into the necrotic area adjacent to the underlying bone. Frequently, the patient walks on such a foot without any dressing or other protection. The danger of secondary infection of bone and joint is great, but skin loss is minimal.

Neglected necrosis blisters frequently initiate a deep ulcer. In this case, the ulcer may persist at the site of the blister; but often it extends to include the damaged skin directly overlying the affected bony prominence, and the condition then appears as a long ulcer extending from the hard skin of the sole round to the soft skin on the adjacent non-weight-bearing skin.

In leprosy, as in diabetes, there is a frequent association of this type of plantar ulcer with the neuropathic joint of Charcot. Such a joint may be at a distance from the actual ulcer, and is commonly at a tarso-metatarsal or even at the ankle-joint.

b. The superficial type of plantar ulcer (*Fig.* 7)

This type of ulceration involves a large area of skin and may or may not include deeper tissues. It is fortunate that it is not as common as the deep type, for serious secondary infection is inevitable and the damage to the foot may be considerable. A similar ulcer is also seen under the head of the proximal phalanx of the big-toe (Fig. 8) and at the tips of the toes (Fig. 9) and is not uncommon at the heel.

In this type of ulcer, skin loss is an important factor and some type of skin replacement is necessary to effect an adequate cure of the condition without deformity.

The course of plantar ulceration varies in its outcome. It may lead either to spontaneous and permanent cure, to spontaneous cure with later relapse, to chronicity without complications, or to chronicity with complications.

It is not uncommon to find chronic ulcers on which a patient has walked for years without special treatment. The reasons for the variation in the course of the condition are not fully understood, but undoubtedly include the extent of secondary infection and the degree of deep anaesthesia, as well as the time during which the anaesthesia persists or recovers. The degree and duration of intrinsic palsy of the foot is also a factor. Superficial anaesthesia is always present but may be limited to an area in which the ulcer occurs; however chronic ulcers may persists after partial restoration of plantar sensibility. Chronicity is also related to the use of the foot, for rest and immobilisation will permit healing to occur if maintained long enough.

Summary

In describing the natural history of plantar ulceration in leprosy, stress has been placed on the pre-ulcerative stage, because treatment at this time is relatively easy and effective.

The established ulcer is a problem mainly because of the tendency to relapse and because of the frequency of complications and their gravity. These complications are described in the following section.

THE TRIPLE TREATMENT OF TUBERCULOID LEPROSY

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Westfort Institution, Pretoria

A tuberculoid case is considered to be active as long as elevation persists in the maculae or if erythema remains in the lesions or if the lesions continue to spread. When none of these three conditions is present and only a flat hypopigmented blemish remains we consider the case to be clinically cured provided the skin and nasal smears are negative.

In 1948 I reported[1] on the effect of antimony as an adjuvant treatment to chaulmoogra injections. This expedited the arrest of the disease in certain types of the disease and in some instances the results were dramatic but the average period before arrest was achieved in tuberculoid cases was two years. In 1954 I reported[2] on the effect of Atebrin on various manefestations of leprosy. This followed on the work of Page[3], Woodburne *et al*[4] and Rogers and Finn[5] who were reporting on the effects of antimalarial treatment on Lupus Erythematosis. We found Atebrin to be of use in lepromatous cases in that it expedited the resolution of nodules and lepromatous plaques and macules but as it had no effect on the bacillary index we do not use it now on our lepromatous cases. In our borderline cases we find it causes resolution of lesions and as the sulphones cause the toal elimination of bacilli in an average of two years we consider Atebrin to be of value to them. In tuberculoid cases its effects are most dramatic. Such cases are usually negative and Atebrin greatly expedites the resolution of the lesions.

The sulphones *per se* cause arrest of the tuberculoid process but from our experience and from what I can gather from the literature it takes about two years to bring about a clinical cure.

As we were obtaining results with each of the three drugs used separately we decided in 1957 to use all three drugs together.

Posology. DDS is our routine sulphone given in daily doses not exceeding 200 mgm. per day. We consider it essential that the induction must be slow so start with 300 mgm. per week for the first month. In the second month it is increased to 100 mgm. per day and the maximum dose is started in the third month.

Trivalent antimony in the proprietary forms of Fouadin, Anthiomalin or Stibophen is given intramuscularly in a course which totals 50 cc. We usually start with 2.5 cc. on the first day, then 3.5 cc. on the second day and then 5 cc. daily except Sunday. Some patients are intolerant of this dosage and suffer from nausea and vomiting. We then reduce the dosage to 3 cc. daily or if this is not acceptable we give 3 cc. on alternate days. After 50 cc. has been

given we stop the antimony for 30 days and then resume at the low dosage.

As an antimalarial we have had most experience with Atebrin which we give once a day in a 200 mgm. dose for 6 days per week for three weeks. This is followed by a weeks rest. The signs of toxicity to be looked for are headache, abdominal pain or Atebrin psychosis. All these complications we have found to be extremely rare.

Atebrin at first causes hyperpigmentation in some cases. This is particularly common in spongy succulent tuberculoid maculae. This hyperpigmented skin may be restored to natural colour by painting with a 1 in 1 watery solution of trichloracetic acid. After painting the lesion we neutralise the acid with a solution of bicarbonate of soda.

We studied the type of lesions encountered in 20 females and 20 males admitted between the period May, 1957 to October, 1957. The results show that 2 females and one male still show signs of activity after 13, 10 and 11 months respectively. The other 37 patients have become clinically cured in an average of 5 months.

Relapses are extremely infrequent but as a precautionary measure we continue a maintenance dose (100 mgm. daily) of sulphone for a minimum period of two years after a clinical cure has been obtained.

Summary

1. Clinical activity of tuberculoid maculae is confirmed by the presence of erythema, elevation, or the spread of lesions.

2. It is recommended that tuberculoid leprosy should be treated by the simultaneous administration of sulphones, trivalent antimony and Atebrin. The administration of the sulphone should be continuous but trivalent antimony is given in courses of 50 ccs. separated by a month's rest period. Atebrin is given for three weeks in each month in daily 200 mgm. doses.

3. Forty cases are detailed of whom three have not yet responded to treatment. The other 37 required treatment for an average of only five months.

4. It is recommended that sulphones be continued for a minimum period of two years after clinical cure is obtained.

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MANAGEMENT OF ACUTE PSYCHOSIS IN LEPROMATOUS LEPROSY

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Acute psychosis in lepromatous leprosy is not very common now but still we get a few cases now and then. If not properly treated they go into the chronic stage which is rather a difficult problem for doctors working in leprosy homes.

The symptoms and signs vary according to the severity of the case. This article is based on five cases treated during the course of two years. Four of the five patients were receiving the sulphones at the onset of the symptoms and in one treatment was discontinued because of repeated reactions. In most of the cases some tragic incident in the domestic side precipitated the attack. In three out of the five cases we were able to trace the cause to the family. In one infection may have played a part as the patient had a very bad ulcer. One or two days before the onset of the acute stage the patient becomes non-cooperative, tends to be unruly and abusive. There may be a slight rise in pulse rate and temperature. Careful and patient management at this stage is required. Scolding the patient and trying to discharge him from the ward will only aggravate the condition. The next stage is the acute stage when the patient looks very anxious and confused. There is flight of ideas and thinking is retarded. Sleep is disturbed and the patient becomes violent and angry if not properly managed. He abuses each and everyone and feels he is being persecuted by all. He refuses to take food and water. In four of the five cases there was high temperature and erythema nodosum or subcutaneous nodules.

There are four essential things one has to consider in the management of these cases. They are (1) Isolation; (2) Sedation; (3) Maintainance of fluid and vitamin levels in the body, and (4) Occupational therapy when once the acute stage is passed. In this article only the first three are dealt with.

Isolation in our opinion is absolutely necessary for two reasons. The patient gets excited on seeing people around him and the other reason is that the fellow-patients acting as nurses who help in the wards make fun of the patient without realizing the condition of the patient. He should be assigned nurses who have understanding of the mental condition of the patient.

Sedation was best achieved in all the cases by the parenteral administration of Chlorpromazine (Largactil). We have also tried paraldehyde in combination with barbiturates in previous cases but Largactil has proved to be far superior. Of course this report is based

only on five cases. The parenteral dosage administered was 75 mg. of Largactil four hourly on the first day and then 50 mg. four hourly from the second day onwards. The intervals of administration were lengthened as the symptoms subsided. The symptoms subsided in all the cases from three to six days.

Fluid level at all costs should be maintained. In three cases we administered 2-3 pints of intravenous saline in each case as they persistently refused to take anything. Five to six pints of fluid by mouth should be sufficient. The vitamin level was maintained by giving 200 mg. of vitamin C and 2 cc. of vitamin B complex daily intramuscularly. All the patients recovered from the acute attack.

In one case high doses of penicillin was administered along with Largactil and vitamins as we suspected infection may have played a part.

Summary

1. This article is based on five cases.
2. Some of the symptoms and signs are described above.
3. The four essential things in the mangement of acute psychosis are:
   (*a*) Isolation.
   (*b*) Sedation.
   (*c*) Maintainance of fluid and vitamin levels.
   (*d*) Occupational therapy.
4. Sedation is best achieved by parenteral administration of Largactil.

REPORT ON A VISIT TO AL WALID LEPROSARIUM, DAMASCUS, SYRIA

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1. General

In Syria, when a leprosy case is discovered, the Government requires that the patient be transferred to the leprosarium. This is done under the responsibility of the police and is a very difficult task, because the patient is reluctant. He is generally repudiated by his family, and moreover, if married, his own relatives do not wish to be associated with him. For this reason the difficulty of caring for a leprosy patient is great.

The Al Walid Hospital, Leprosarium Kouseir, is located on the road from Damascus to Aleppo, about 18 km. north of Damascus. There is a big mental hospital facing the leprosarium. The leprosarium is secluded by a wood and a high wall and is surrounded by land, mostly of agricultural nature. I visited there on 18th November, 1958.

Patients come to this leprosarium from Syria: Djebel-el-druze (Kafar laha); Hauran (Sanamain, Mahajjeh, Souda and Housoun); Lattakia (Brumaneht-Mashaekh, Aramo and Tel-Kalakh); Aleppo (Al-Bab); Lebanon: Baalbek (Hurmel); Sidon; Tyre; and Palestine, 4 refugees.

2. Finances

The Government pays all expenses of the patients, but individual patients receive no cash subsidy.

The Wakf, which is an institution handling the allocation or the dedication of lands or other property to some beneficial or pious enterprise, contributes about 125 Syrian pounds, equivalent to about U.S. $32.60

The financial status of the leprosarium at the moment is rather unsound, because of inadequate cash resources and uncertainty of future income. There are very few voluntary contributions either in cash or in kind.

3. Staff and Personnel

The existing staff comprises the Medical Director in charge of the leprosarium, Dr. Izzat Roumani, who is a physician but not a specialist in leprosy. Although his speciality is psychiatry, he approaches his duties seriously. There is also a male nurse, Mr. Adel Rabia, and a female nurse, Wisal Daghoustani, in charge of the nursing staff. They have received no special training in leprosy work but have held their posts for the past 11 years in this leprosarium and also take their responsibilities very seriously.

The auxiliary staff is made up of 16 men and women; one of these is the porter at the gate and he does not have any close contact with the patients.

Training of medical staff could be done; it only needs arrangement and the provision of modern equipment and financial resources. Training of auxiliaries could also be done if qualified social workers and those skilled in rehabilitation and physiotherapy were available.

4. Capacity of the Leprosarium

At present there are 120 patients, but there is adequate space for 20-30 more patients. The possibility for expansion exists but this would involve reducing the recreation ground for the patients.

5. Patients

The patients enter the leprosarium in different stages and all suffer from mixed types of leprosy. Up to date there are in the leprosarium 120 patients divided into:

Sex	*Age*	*Single*	*Married*	*Total*
Females	12–90	28	20	48
Males	15–100	52	20	72
Total:		80	40	120

Only 2 couples have children, one with 2 girls and 2 boys, and the other with 3 girls and 1 boy. Five of these children are in the leprosarium with their parents but are not yet infected. One was adopted by a family and 2 were entrusted to a special institution outside.

6. Treatment

In surgical treatment minor amputations are done for ulcers and deformities of the limbs, and in medical treatment there are several drugs used in this leprosarium: Diasone is sometimes combined with several other drugs such as Nicotibine, Dusolone, Sulphetrone, Cimedone (Specia), and Ciba 1906, which is still under test but the results of which have been successful up to now.

7. Discharge from the Leprosarium

Only 1 patient was discharged from the leprosarium in the past 20 years. The eligibility for discharge from the leprosarium is based only upon bacterial negativity.

8. Living Accommodation for the Patients

There are 4 pavilions for the patients, 1 for male patients, 1 for female patients, 1 for invalid male patients, and 1 for the operating room and for all the members of the staff and employees. Each pavilion accommodates 27 patients and there is a general dining room. Married couples live in wooden cottages built by themselves.

9. Hygienic Condition of the Leprosarium and its Surroundings

Generally speaking the hygienic conditions are good. All the wards and cottages are clean and well-kept. In the grounds are a shop and a store run by the patients themselves and poultry are also kept, the eggs and the birds being sold outside to provide extra money.

The operating room I did not see but was assured that it was in good condition. It is used once every 3 months when a surgeon from a neighbouring hospital comes to perform minor operations, such as correcting limbs, etc.

10. Dietary Regulations and Distribution of Food and Foodstuffs

Every day at a regular time, the patients get their food from a central kitchen. This food is the same as for the people outside, but of much better quality. Patients are allowed to have meals other than the regular meals. They have to prepare these themselves and can have them whenever they like.

11. Social Factors

Social amenities are, generally speaking, very poor and inadequate. When a patient enters the leprosarium he is dead for his own family and nobody pays any more attention to him. Consequently most of them prefer to stay in the leprosarium and this is an economic strain on the institution. This is one of the numerous reasons why people from outside are afraid to consult a physician, because if they happen to be diagnosed as suffering from leprosy, they know what kind of social consequences ensue.

No social worker visits the leprosarium. Consequently the patients are deprived of all outside contact. The leprosarium sometimes receives gifts. For males it is mostly second-hand clothing or obsolete military uniforms.

The social relationship between the patients is tolerable, except during the first three to four months during which they are more or less difficult. This is understandable. They have lost their freedom, their relatives, virtually everything. Sometimes there are some discords between the patients, often due to differences of political character. The patients are not exclusively Syria nationals. It is due to the efforts of the Medical Director and the nurse that these quarrels are mitigated and eliminated. Not only by their authority, but also by their human understanding and approach to the circumstances of the patients, they assist in the resolution of these problems.

Another very important factor is the marriage of the patients and the resulting offspring. Patients are not allowed to marry outside the leprosarium. Once married they can devise their own manner of living, so that it resembles outside life a little. But perhaps one of the most important problems is the question of the children born of these marriages. There is no law to say that these children shall be taken

away from their parents. However, from the medical standpoint, it would be advisable and necessary that the children be segregated from the risk of infection. There is no external creche or preventorium. These children have to stay in the leprosarium as long as their parents are inhabitants, which may be for ever. What is the future then for these children? It looks the same as that for the parents. In this leprosarium there have been three exceptions, two children were sent to a special institute and one child was adopted by the nurse of the leprosarium.

12. Vocational Training

There is no possibility of this, because of the lack of trained staff and the apathy of the people outside the leprosarium.

13. Religious Instruction, Educational Care, Welfare Arrangements

Clergymen come once a year to pay a visit to the patients and to offer them some candy. The patients are without any educational care, and there are no teachers or social workers who could do something for them, so that at least they may learn something to make their lives a little bit more tolerable than is the case at present. The patients have no facilities for sport, mostly because of their invalid status. On the other hand, no one has given them the opportunity to do it or to try it. There is no library, so they cannot even read books.

14. Hospitalisation and Leave for the Patients

Patients entering the leprosarium in an advanced stage are kept permanently in the leprosarium. For the other patients there is a possibility of going on short leave and perhaps even later of being discharged from the leprosarium.

If a patient goes on temporary leave, the name of the patient is given to the district medical officer at the patient's destination. If a patient leaves the leprosarium without permission, the police are called to bring the patient back, if necessary by force. So far as is known, in Syria all leprosy patients are under state control.

15. Problems Mentioned by the Medical Director during my Visit to the Leprosarium

(*a*) the lack of persons well trained in leprosy in the medical staff as well as in the nursing staff:

(*b*) the absence of a scientific library:

(*c*) the lack of interest outside the leprosarium for the needs, sometimes the urgent needs, of the leprosarium. People outside the leprosarium should be informed about leprosy, so that if there is a case of it they know that it is curable and that they are not social outcasts.

(*d*) The leprosarium needs an endowment of money and more donations, so that they can do a lot of most useful things, for example, the building of a recreation room and some special rooms for handicrafts and rehabilitation.

16 Recommendations

Much can be done for this leprosarium, where the medical director and the nurse are doing their utmost to carry out their duties with devotion, sometimes under circumstances which are not so very pleasant. The patients are very grateful for what is given to them and for all that is done for them.

It is of primary importance that there should be a possibility for training the medical staff and the nursing staff. They should be adequately remunerated and be given the chance to visit well run leprosaria, so that they can exchange their views about work.

There should be social workers who could take care of the patients inside the leprosarium and their subsequent rehabilitation.

A scientific library for the medical staff and a recreational and vocational library for the patients is an urgent necessity.

Facilities for handicrafts would be desirable to keep the patients occupied and to provide means for physical training.

Patients should be taught skills, commensurate with their mental and their invalid status, so that when they are due for discharge they have a trade and there would not be so many difficulties later. Even in the leprosarium they could use these skills to produce goods for sale outside.

Once or twice a month, there might be a good cinema show for entertainment of the inhabitants of the leprosarium.

There should be close contact with the several religions involved and possibilities of spiritual ministration should be explored and encouraged by both civil and religious authorities.

Acknowledgements

I wish to express my thanks to Dr. Izzat Roumani, Medical Director of the Al Walid Leprosarium, Damascus, for his courtesy and kindness in helping me to make this report possible; to Dr. Fakir, Director of the Malaria Eradication Service, Damascus, who arranged the opportunity for me of visiting the Al Walid Leprosarium; to Mr. W. F. Beecroft, PH.D., D.P.A., who assisted me in the preparation of this report.

I was warmly welcomed when I visited the leprosarium by the Medical Director, Dr. Izzat Roumani, and also by the nurse. I was given the opportunity to obtain all the information I wanted and to see everything which I considered relevant.

LETTERS TO THE EDITOR

1. Dr. H. C. De Souza-Araujo of Rio de Janeiro has kindly pointed out two printing errors in the Editorial of *Leprosy Review* of January, 1959. The First International Conference of Leprosy was held in Berlin in 1897 (not in 1877) and the Second Conference of Bergen, Norway, was held in 1909 (not in 1900).

2. Dr. H. W. Wade, President of the International Leprosy Association, writes with approval of the *Leprosy Review* of January, 1959, which gave the gist of the proceedings of the VII International Leprosy Congress, and wishes to clarify certain aspects of the record of his own paper on the nomenclature and classification of skin-test antigens (p. 45 of January issue). His thesis was that only such antigens as are of the nature of the Hayashi-Mitsuda preparation should be called lepromin, and this name cannot be applied to all that have been made. He suggested that the analogous preparation made from the lesions of murine leprosy could quite suitably be called "Stefansky lepromin". With regard to the terms "integral lepromin" and "bacillary lepromin", Dr. Wade suggested that "purified bacillus suspension" or PBS should be used in place of "bacillary lepromin", in order to avoid confusion. In those special preparations containing no bacillary bodies but only soluble elements, for which the name "leprolin" was suggested, it is important to note that they evoke only the early or Fernandez reaction, whereas lepromins proper, or even the purified bacillus suspensions, evoke both the early and late reactions in wholly reactive individuals.

3. Dr. A. S. Garrett, Area Superintendent, Onitsha Area, Oji River, Nigeria, writes referring to the article by J. Dreisbach and R. G. Cochrane in *Leprosy Review* of July, 1958, on the subject of Streptohydrazid in lepromatous leprosy as follows:

"By additions and subtractions I find that at the end of 2½ years 62% of patients were not improved with Streptohydrazid alone. When Sulphetrone was added, 48.2% of cases were not improved. With Dapsone (DDS) alone this figure would be in the region of 2%, and with DPT to cover the gaps, much less than 1%. Streptohydrazid is very expensive. I presume that this article is to show that it is of no value in the treatment of leprosy. Perhaps it would be better to state it clearly."

(As Dr. Cochrane was available in London he was asked to comment on the letter of Dr. Garrett.)

Dr. R. G. Cochrane comments as follows:

"The only fair conclusion from our study of streptohydrazid was not that it was entirely useless in anti-leprosy chemotherapy but, in combination with sulphone therapy in the shape of a 50% solution of sulphetrone by injection, was of definite value in clearing nasal and mucosal lesions and of value in cases which had shown intolerance

to DDS. Such information should not be despised, even though since the article was written there has been news of drugs which promise to be superior to DDS. The superiority of DDS to streptohydrazid alone or to the combination of streptohydrazid with DDS was clear enough from the article and hardly needs to be underlined."

4. Dr. W. H. Jopling of the Jordan Hospital, Earlswood, Surrey, has written on *Reactional Leprosy* or *Leprosy in Reaction.*

"I have been prompted to write this letter on reactional leprosy in the hope that it will stimulate clinicians and pathologists to get together and clarify this subject about which there exists much confusion of thought and of terminology. As a clinician I would point out that it is impossible to have a rational approach to therapy, or to expect clinicians in different parts of the world to agree on therapy, until the different types of reactions are better understood and more clearly defined; and as a teacher I have found it necessary to make my own approach to the subject in order to present it in a manner which can be understood by those who have had little or no first-hand experience of leprosy.

I would like to put forward the following outline of reactional states in leprosy as a possible basis for discussion on the subject:

"*Tuberculoid Reaction.*" This is a reaction in tuberculoid leprosy in which one or more skin lesions (not all) become rapidly swollen and erythematous, giving an impression of erysipelas. Desquamation follows, and sometimes ulceration takes place in the reacting lesions or lesions. An aggravation of existing nerve damage may occur, with or without nerve pain and tenderness, leading to functional disturbance. Caseation may sometimes occur in affected nerves, and in the case of cutaneous nerves there may be discharge of caseous material through the skin. The patient remains afebrile and free from constitutional symptoms. In my experience "tuberculoid reaction" has been defensive in character and has resulted in healing of the affected skin lesions, with scarring if ulceration has taken place, but some leprologists consider that it may not always be associated with a good prognosis as bacilli may appear in the reacting lesions and there may be an evolution to a borderline type of leprosy. The only comment I would like to make on this concept is to say that everything depends on establishing that the lesions were truly tuberculoid in the first place and were not those of near-tuberculoid leprosy, i.e., borderline leprosy close to tuberculoid.

"*Borderline Reaction.*" This is a reaction in borderline (dimorphous) leprosy, a type of leprosy which is universally recognized as being immunologically unstable. All the skin lesions become rapidly swollen and erysipeloid, followed by desquamation. In some cases the reaction is defensive in character, the lesions becoming infiltrated with epithelioid and giant cells, acid-fast bacilli (if present previously) disappearing, and the prognosis being good. Some of the lesions may

break down with subsequent scarring. Nerve pain and tenderness may or may not occur; if it does occur, functional disturbance may follow. This type of reaction corresponds to Cochrane's 'reactional tuberculoid'[1]. In other cases the reaction is invasive, rather than defensive in character, with an increase of acid-fast bacilli in the lesions and constitutional disturbance such as fever, malaise and oedema. I have not seen ulceration in this type of reaction, but I have no doubt it may occur. Nerve pain and tenderness are invariably present, followed by functional disturbance, and there is tenderness of the palms and soles.

"*Lepromatous Reaction.*" There are two distinct types of reaction in lepromatous leprosy. In one type, which I would call "Lepromatous Reaction Type I" the reaction occurs early in the course of treatment, when the bacilli are solid rods, and changes take place in some or all of the actual leprosy skin lesions characterized by swelling and erythema. Nodules break down and ulcerate. The other type of reaction, which I would call "Lepromatous Reaction Type 2" is quite distinct as it occurs later in the course of treatment when the bacilli are fragmented and granular, and it does *not* affect the actual leprosy skin lesions which show no changes clinically or histologically. This type of reaction was given the name *erythema nodosum leprosum* by Murata in 1912[2], a name which is disliked by some[3] on histological grounds, and is opposed by others because erythema nodosum is only one aspect of the reaction. It is an allergic reaction which is probably due to the fact that the patient has become sensitized to breakdown products of his bacilli. When erythema nodosum does occur as part of the reaction, it is characterized by crops of brightly erythematous nodules and raised patches varying in size from a few millimetres to 4-5 centimetres in diameter; these may be few or multiple, occur on any part of the body apart from the scalp, palms and soles, and often appear on areas of skin free from leprosy lesions. They appear suddenly, usually in the evenings, the smaller ones disappearing by the following morning and the larger ones taking days or weeks to disappear leaving a blue stain in the skin. The patient often complains of burning discomfort in the erythematous nodules and patches, and pressure on them with the finger may be painful. Their bright red colour disappears immediately slight pressure is exerted on them, but it returns as soon as the pressure is released. When numerous they are accompanied by constitutional symptoms which include intermittent fever, severe nerve pains, arthralgia, bone and periosteal pains, acute iridocyclitis, orchitis, rhinitis, epistaxis, lymphadenitis, insomnia and mental depression. The fever has its fastigium in the evenings and may be accompanied by rigors and drenching perspiration. In some cases the erythematous nodes develop central necrosis and ulceration, leaving atrophic scars. As mentioned earlier, erythema nodosum is not always present.

Nerve pain and tenderness may occur alone, just as any of the other allergic manifestations listed above may occur alone or in combination without erythema nodosum. They are all different aspects of the same type of reaction and they will all respond to treatment with corticosteroids.

I would suggest that 'Lucio's phenomenon' (*erythema necroticans*) is merely a variant of my "Lepromatous Reaction Type 2" and could be included under this heading. I understand that it can be controlled by corticosteroids[4].

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5. *Dr. R. Pepys of the Tuberculosis Research Unit, Medical Research Council, London, N.W.3, writes regarding depot lepromin as follows:*

"Modifications of local retention of the antigen, for example tuberculin, influence delayed type reactions (Pepys, 1955). Depot preparations in liquid paraffin/lanoline vehicles prolong the retention of the antigen, thereby enhancing its potency considerably, and also showing the development of hypersensitivity in negative reactors in response to BCG vaccination by the appearance of reactions at the previously negative test sites.

It is now possible to compare reactions to multiple puncture tests with a depot tuberculin (PPD) cream (Pepys and others, 1959) and with depot lepromin cream (Brown, 1958). With the depot PPD cream, very low degrees of sensitivity have been found in subjects who fail to react to Mantoux tests with 100 tuberculin units. On the other hand, although the lepromin in a depot preparation also appears to be more potent than aqueous lepromin in tuberculoid cases of leprosy, it did not, like the aqueous lepromin, give reactions in lepromatous cases. Prolonged retention of both the depot PPD cream (Pepys and others, 1958) and the depot lepromin cream (Brown and Stone, 1959) has been shown by the appearance of reactions at previously negative tests after BCG vaccination. The depot lepromin test conversion from negative to positive in healthy subjects after BCG vaccination confirms the antigenic relationship of these mycobacteria. Common polysaccharide components in chemical extracts of *M. leprae* and *M. tuberculosis* have been demonstrated serologically (Pepys and others, 1959 (*a*)).

The similarity of the findings with depot PPD and depot lepromin raises problems related to both tuberculosis and leprosy. Since it is known that persons with relatively weak tuberculin sensitivity, detected by 100 TU intracutaneously, have some natural antituberculous immunity (MRC 1959), it is desirable to determine

whether there is any similar immunity associated with the even lower degrees of tuberculin sensitivity demonstrated in many subjects by the depot PPD cream test. These subjects give accelerated reactions to BCG vaccination, but would in the ordinary way have been considered suitable for BCG vaccination because of their failure to react to Mantoux tests. These findings are important if BCG vaccination is to be studied for the prevention of leprosy, and suggest that depot PPD and depot lepromin should be employed together."

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ABSTRACTS

On the Nature of the Kveim Reaction and the Pathogenesis of Sarcoidosis. R. KOOIJ. Dermatologica, Basle. **117,** 5: 1958: pp. 336-354.

The author describes sarcoidosis, also known as the disease of Besnier-Boeck-Schaumann, and emphasizes that the etiology is still obscure and that its relation to tuberculosis is still unsettled. The diagnosis is made on clinical signs, of multiple infiltrations in the skin, lymph glands, tonsils, lungs, spleen, liver, bone marrow, such lesions being of long duration, and the histo-pathological examination. The latter shows well-defined nests of epithelioid cells with absence of necrosis. This so-called sarcoid structure can however be produced by a number of different agents, such as leprosy, silicates, beryllium and zirconium. The Kveim Reaction is used as a diagnostic test for sarcoidosis: it is useful, but by no means infallible. The Kveim antigen is prepared by extracting in saline from sarcoid tissue. After an intradermal injection of 0.1 to 0.2 ml., a positive reading is recorded if a papule of about 5 mm. develops and persists for one month or more, and for this positive reading some workers also insist on a sarcoid structure as shown by the histological examination of the papule.

The Kveim Reaction has a striking similarity to the Mitsuda reaction of the lepromin test in leprosy, where also the reaction is read at 28 days, but there is the difference that the Mitsuda is not diagnostic but prognostic, and used for the classification of leprosy. Kooij and Gerritsen (1956-58) have shown that the late reaction in the lepromin test can be produced by an antigen consisting of suspensions of non-leprosy skin, and of liver. To a large extent for skin tissues this has later been confirmed by Davey (1958) in *Leprosy Review* **29,** 4, 197-203. The typical feature of the Mitsuda reaction, more than its positivity in the tuberculoid type of leprosy, is its negativity in the lepromatous type. When the preparations of normal skin tissue or liver tissue were used in more concentrated suspensions the results corresponded even more closely to those typical of the regular lepromin antigens. Also, just as in healthy people lepromin gives positive late and very late reactions, so do the suspensions of normal tissue. A few of the reaction papules of the healthy people were examined histologically, and a few of them showed a sarcoid structure. The papules of the positives in tuberculoid leprosy also showed a tuberculoid or sarcoid structure, as occurs with the regular lepromin. Some tuberculoid patients responded to the Kveim antigen by late positive reactions. The author thinks that the active principle in the Kveim antigen, the lepromin antigen, and in normal tissue antigen is probably bound to corpuscular elements. He thinks that the Kveim antigen does not contain a specific substance but there is a sarcoid mode of reaction peculiar to certain people. With

concentrated chloroform-ether extracts of normal tissue he has obtained positive Kveim reactions. It may be the number, the chemical composition, and the size of the particles in the Kveim antigen which determines the activity of the preparation. In any case he thinks the disease sarcoidosis is a syndrome which can be caused by many different agents in certain individuals who are able to respond with a sarcoid reaction, and in support of this hypothesis describes conditions similar to sarcoidosis which were caused by silicates, beryllium, zirconium, spirochaetes, tubercle bacilli, and leprosy bacilli, and 4 clinical photographs and 2 histological are given and 2 illustrative cases are described. He draws attention to variation in clinical symptoms according to the agent, e.g., lung changes in leprosy are rare, bone lesions in beryllium intoxication are rare, and recommends the diagnosis of sarcoidosis being stated in all cases where it is found, even if a specific agent is also found, e.g., sarcoidosis--leprosy, sarcoidosis-tuberculosis, sarcoidosis-silicosis. Because of the major importance of leprosy and tuberculosis, *every* case of sarcoidosis should be studied carefully from the point of view of the possibility of these diseases, and the other causes of sarcoidosis not forgotten.

El Sindrome Neural Leprosa (The Neural Leprosy Syndrome): F. BRESANI SILVA. Revista Peruana de Salud Pública, Lima, **5,** 2, 3 and 4: 1956, **6,** 1: 1957 pp. 447.

The author made a systematic study of neural symptoms in 400 leprosy patients resident in San Pablo leprosarium, Loreto, Peru. He found that 95% of patients showed skin and nerve disorders, 3.5% showed exclusively neural primary or secondary lesions, and 1.5% were purely cutaneous in the type of their lesions. He found that the disease began with neural symptoms in 54.7% of the cases, in 36% with cutaneous, and in 9.3% with varied symptoms. Within the neural syndrome, disorders of sensation are the commonest and earliest manifestations. Thermal sensation is first affected, next pain, next tactile sensation. The author differentiates *four stages in the evolution of disorders of sensation in leprosy. The first* is the stage of alteration of thermal sensation. *The second* is the stage of "syringomyelic dissociation", wherein there are alterations in thermal and pain sensation alongside normal tactile sensation. *The third stage* is that of "peripheral dissociation", wherein normal deep sensation is preserved alongside loss in thermal, pain, and tactile sensation. *The fourth stage* is "pseudospinal dissociation" when the three superficial sensations are lost and deep sensation is also impaired. (This loss of deep sensation is denied by most authors.)

Lesions of the terminal branches of the nerve fibres are the cause of the most important of the disorders of sensation in leprosy, which is loss of superficial sensation. It starts distally on the limbs and progresses centrally. The author insists that loss of superficial sensation is slowly and gradually succeeded by loss of deep sensation

in a third of all cases, in muscles, tendons, and bones. Of the cases of impairment of deep sensation, most are affected in vibratory sensitivity, and only a few in that to pressure and weight.

Motor disorders occur in about 76% of patients and are almost exclusive to the hands and feet, though the facial nerve is sometimes involved. Muscle wasting is common as a later result, and tendon retractions.

Reflexes are diminished or absent, either superficial or deep, due to impairment of superficial or deep sensibility. Accentuated reflexes can occur in stages of great activity of the disease or in lepromatous reaction.

Peripheral neuritis results from an invasion of the nerves by the bacilli. This leads to changes in thickness, form, and consistency which are very typical and almost exclusive of leprosy. In order of frequency, the nerves affected are the ulnar, lateral popliteal, supraorbital, radial, and superficial cervical. In lepromatous leprosy the nerve increases in thickness and becomes hard and fibrous and uneven of surface. In tuberculoid leprosy the increase in thickness takes the form of a spindle or string of beads, and there may be caseation and calcification. There is no relation between the grade of thickening and the grade of impairment of nerve function. The nerve undergoes a specific infiltration of the perineurium, the endoneurium, and the interstitial tissue, followed by fibrosis and constriction and destruction of the nerve fibres. The original invasion of the nerve trunks may be by way of metastasis through the blood or lymph, or by way of the terminal branches at the point of the peripheral cutaneous vascular plexuses.

Vasomotor disorders were found in 27% of the patients under study, mainly on the distal parts of the limbs. Cyanosis and oedema and elephantiasis are associated. The basic lesion is of the nerve branches of the autonomic system, which leads to vasomotor paralysis.

Disorders of sweating in the form of segmental anhydrosis occurred in 92% of cases. The limbs are most often affected, sometimes the chest, and in rare cases almost the whole of the body. A compensating phenomenon of excessive sweating occurs in intermediate zones. There is also a local anhydrosis connected with local changes directly due to the mechanical action of pressure by local infiltration of lesions in the skin.

Trophic lesions include perforating ulcers, changes in the skin itself, alopecia, and changes in the bones. Perforating ulcer is a very frequent lesion, occurring almost exclusively in the feet (47.5% of all cases), whereas only 0.5% had palmar perforating ulcer. In the feet it is usually at the heads of the metatarsals or in the toes, rarely in the heel. It is caused and maintained by a combination of factors, the nerve factor causing loss of sensation and destruction of autonomic and trophic fibres, the mechanical factor due to standing and

walking, and the traumatic factor plus the secondary factor of infection. Trophic disorders of the skin include glossy skin, colour changes, desquamation, scleroderma, and ichthyosis. These are symmetrical, commonest in the lower limbs, and more frequent and serious in the lepromatous type. Alopecia was found in 64% of the patients, commonest in the eyebrows, also occurring in eyelids, forearms, legs, thighs, axillae, pubes, but very rare in the scalp. There are three factors in this alopecia, pressure of the specific granuloma on the hair follicle, endocrine disorder, trophic damage to the skin. Trophic disorders in bones occurred in 43% of patients, mostly in hands and feet. Osteoporosis and absorption of bone occur, owing to the neurotrophic factor, the direct action of the bacilli on bone tissue, and secondary pyogenic infection.

Evolution of the Neural Disorders

In almost all cases the disorders of sensation appear before the motor and trophic. Muscle wasting and tendon retractions come a little after the motor disorders. Thickening of the peripheral nerves appears as early as the disorders of sensation, and the degree of thickening is not related to the time. Anhydrosis is an early disorder. The impairment of superficial sensation is noted first in the lower limbs, then upper limbs, next the head, and finally the chest and abdomen. Impairment of deep sensation follows that of superficial sensation. Among vasomotor troubles, cyanosis is common at the beginning of the illness but as time goes on it occurs less. Oedema is almost more frequent as the years elapse, and elephantiasis is the last to appear. Trophic bone changes occur very late, but appear first in the phalanges and metatarsals of the feet.

Notation of Neural Disorders

It is possible to describe 4 grades in all types, which though arbitrary do express the clinical findings fairly closely.

Tuberculostatiques et Sels de Métaux Lourds: Complexes Métalliques de la D-cyclosérine (Tuberculostatics and Salts of Heavy Metals: Metallic Complexes of D-Cycloserine); E. NEUZIL and J. C. BRETON; Bulletin Medical de l'A.O.F. **3**, 9: Apr.-June, 1958, pp. 149-172.

After explanation of the nature of metallic complexes and chelates, the authors review the connection between tuberculostatic activity and salts of heavy metals. Most of the chemical compounds active in the treatment of tuberculosis have an affinity for the salts of heavy metals which results in the formation of chelates. The copper chelates seem to be particularly stable. Like other tuberculostatics of high activity, D-cycloserine gives metallic chelates, especially with copper, as proved by spectrophotometric and potentiometric methods. The existence of these metallic complexes poses numerous problems regarding the mode of action of tuberculostatics and the appearance of microbial resistance. This new line of research may lead to a more

efficient chemotherapy of tuberculosis (and also of leprosy).

Activisima y Acelerada Reproduccion del Bacilo de Hansen Inoculado a Ratas en Severas Condiciones de Prooxidacion (Very Active and Accelerated Multiplication of M. Leprae Inoculated into Rats Subjected to Severe Conditions of Pro-oxidation) M. BERGEL La Semána Médica, **113,** 25: Dec. 1958, pp. 1119-1124.

The author's severe conditions of pro-oxidation for the experimental rats comprised his special pro-oxidant diet for them (casein 23.8, brewers' yeast 8.9, mineral salts 3.0, maize starch 48.9, and codliver oil 15.5), plus the ingestion of silver nitrate 0.5 per 1000 in the drinking water, and the injection subcutaneously of 1 ml. of a haemolysate (obtained by taking 3 ml. of rat blood from veins which was washed with 3 to 4 ml. of twice distilled water, and filtered). The experimental rats were inoculated in both testicles with 0.1 ml. of a fresh suspension of *M. leprae* derived from the trituration of human lepromatous tissue. The control group of rats were placed on standard diet. At 5 months of the inoculation of *M. leprae* into the pro-oxidant group the testes showed an active and rapid reproduction of the germs, even reaching the point of the formation of globi in the lungs, spleen, and liver. The control animals showed only a scanty occurrence of bacilli in the testes. The author thinks that the conditions of pro-oxidation notably favour the growth of *M. leprae* in inoculated rats. In this experiment the pro-oxidant conditions were made purposely severe and caused the death of the animals and produced a series of lesions attributable to the argyria, the hypovitaminosis E, and the large amounts of polysaturated fats ingested. It would be possible to scale down these features by lessening the concentrations in the diet and arrive at a diet very suitable for the transmission of *M. leprae* to rats. (For further information of the lines of thought of M. Bergel see the abstract in *Leprosy Review*, **30,** 2: April, 1959, p. 126 "Consideraciones sobre Quimioterapia de la Lepra")

Contribution to the Study of the Lepromin Reaction. M. FUKUDA. The Reports of the Research Institute for Tuberculosis and Leprosy, Tohoku University, Sendai, Japan. **8,** 2: June, 1958, pp. 137-160.

The author has studied the significance of a brownish red spot which accompanies the papule at the site of the late or Mitsuda reaction of the lepromin test and adduces strong evidence for taking the measurement of this spot as an accurate index of the reaction. He indicates the 8th and 15th day as the best times to measure this spot.

Experimental Transmission of Human Leprosy Infection to a Selected, Laboratory-Bred Hybrid Black Mouse: K. R. CHATTERJEE, Internat. J. of Lep., **26,** 3; July-Sept. 1958, pp. 195-202.

K. R. Chatterjee, working in Calcutta School of Tropical Medicine, began an investigation in 1956 to transmit *M. leprae.*

He reports the successful transmission of tissue-free *M. leprae* to a new type of selected hybrid black mouse bred in the laboratory. He used 100 animals and also 48 hamsters, in which also a certain degree of success was obtained. Hybrid mice were derived from crossing male Indian house-mice with female Swiss white-mice. The black mice from this cross were selected to form a special colony. Inoculations were given only to those between the ages of 10 to 15 days. The inoculum was derived from untreated cases of active lepromatous leprosy. Successful transmission was demonstrated so far up to the third serial passage, and the animals had a progressively heavier infection. The onset of the infection in the animals occurred from the end of the sixth or seventh month after inoculation, and the heaviest infections were observed a year or more after inoculation. Intracellular and extracellular acid-fast bacilli were demonstrated in the spleen, lymph glands, liver, kidney, omentum, testis, ovum, skin and peripheral nerves. The possibility of contamination with the tubercle bacillus or other acid-fast bacilli was excluded by test cultures. When an antigen was made from the infected mouse tissues and compared with Dharmendra's antigen in the lepromin test, typical reactions were obtained.

The inoculum used throughout was practically tissue-free after differential centrifugalisation and dilution in normal saline to contain a known number of bacilli per c/c. of suspension. The dose of the first inoculum was adjusted to contain a thousand million bacilli. For passage from animal to animal, this dose was reduced to lie between one and twenty million bacilli. Each animal was inoculated only once.

The author thinks that the success of this transmission probably depends on the tissue-free nature of the inoculum and perhaps on the hybridity of the mice. He refers to Bergel's work from which he reports transmission to white rats who are kept on a special pro-oxidant diet.

Communicable Diseases in Africa: Leprosy. WHO Chronicle, **13,** 2: February, 1959, p. 81.

Very interesting information is given about leprosy in Africa and the campaigns against it. Some 2,300,000 cases of leprosy—or about a quarter of the world-wide total—are to be found in Africa south of the Sahara. Half of these cases are already being treated with sulphones, and it is expected that treatment will be extended to all leprosy cases in the region within the next few years. The percentage of "neutralized" patients, i.e., those who have been rendered non-contagious—is already very high and, although the treatment takes some time, the risks of reinfection are relatively low. It is therefore reasonable to hope that the present generation of Africans will be the last to suffer from the disease to any large extent.

Mass antileprosy campaigns in French Equatorial Africa started in 1953, and have been assisted by WHO and UNICEF since January, 1956. The weekly or fortnightly administration of sulphones,

either orally or by injections, is carried out by mobile units. Those who cannot be reached by the units are treated in fixed centres or leprosy villages. Of the 145,000 cases recorded in the area up to July, 1958, 91,700 are receiving regular treatment; more than 20,300 cases are now considered as neutralized. As the lepromatous form of the disease—the most malignant—is rare in French Equatorial Africa, where it affects only 7% of patients, the outlook for the eradication of leprosy from the area is most promising.

The campaign in French Equatorial Africa has served as a pattern for activities in French West Africa, where some 290 mobile units have been formed for the detection and treatment of leprosy. About 300,000 cases, out of a probable total of 400,000, had been recorded by September, 1957. Early in 1958 UNICEF donated 46 million sulphone tablets and supplied 90 motor vehicles and 200 bicycles for use in the campaign.

Case-finding surveys in the French Cameroons have revealed some 26,600 cases of leprosy, of which 18,000 have been or are being treated, 13,700 of them regularly. The total number of cases is estimated at 50,000. Of the 36 motorized treatment units which have been set up, 19 are equipped by UNICEF.

The leprosy control campaign in Gambia started in August, 1957. The total number of cases is estimated at 10,000, of which a quarter were under treatment in June, 1958. The small area of the territory permits treatment to be carried out in existing fixed health centres.

In Ghana, 36,000 cases of leprosy were treated and 300 neutralized between March and December, 1957. Fixed treatment centres are supplemented by 12 mobile teams, 9 of which have been equipped with Land Rovers by UNICEF.

Nigeria was the first African country to use sulphones in the treatment of leprosy. When the antileprosy campaign began in 1951, the number of leprosy cases in the country was estimated at 500,000, but recent surveys indicate that 700,000 would be nearer the mark. WHO and UNICEF assistance to the campaign started in 1954, and about 219,000 cases had been treated by the end of 1957. Treatment is given mostly in fixed centres, to some of which mobile teams are attached, and in leprosy villages.

Sulphones have also been widely used in the treatment of leprosy in the Belgian Congo, Spanish Guinea, and the Union of South Africa, for several years. In Uganda, a campaign to set up leprosy villages near dispensaries or hospitals began in 1957, while an antileprosy campaign is to be started in Sierra Leone this year.

UNICEF has already promised more than $2½ million in material assistance to antileprosy campaigns in Africa for the period 1958-1960. WHO will continue to give technical advice and supply consultants for these campaigns, as well as granting fellowships to antileprosy workers from the African Region.