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CONTENTS

Edited by DR. J. ROSS INNES, Medical Secretary of the British Leprosy Relief Association, 8 Portman Street. London, W.1, to whom all communications should be sent. The Association does not accept responsibility for views expressed by writers.

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From 'Leprosy: A Changing Situation in Eastern Nigeria,' Brit. med. J., 1956, ii. 65.

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EDITORIAL

Advances in the lepromin test

In this issue J. A. Kinnear Brown reports on his studies in Uganda in practical modifications of the method of testing. He has shown that the multipuncture method of application, borrowed from the method of Heaf for tuberculin, is as informative in its results as the customary method of intradermal injection, and allows of diluted lepromin being used at 1/100 in isotonic saline. The method is simple and quick and economical and therefore is suitable for use in widespread campaigns, such as in controlled field trials of BCG as a prophylactic against leprosy, wherein it will be necessary to distinguish large numbers of lepromin-negative individuals. T. F. Davey of Uzuakoli reports in this issue on another aspect of lepromin, that of the antigenic activity of normal skin tissue, thus confirming the work of Kooij and Gerritsen. Davey studied the effect on 50 leprosy patients of the intradermal injection of a preparation of normal skin, i.e., skin obtained surgically at a general hospital and processed as it if were the usual material for lepromin, and checks were made to show that acidfast bacilli were absent. Davey found that it had not much effect in inducing the early Fernandez reaction of the lepromin test, but it did induce the later Mitsuda reactions in tuberculoid leprosy, and these reactions, though smaller in extent, followed the same pattern of reactions as induced by the standard lepromin and refined lepromin, which were used in comparison. By suitable adjustment of the standards for the various grades of positivity, the preparation of normal skin used in this experiment could have been used instead of lepromin to distinguish positive from negative Mitsuda reactors.

In our issue of July 1958 (p. 135) we referred to this subject brought forward by the work of Kooij and Gerritsen as *vital*, and it is apparent that Davey thinks so too. It is essential to find out what principle is involved, and further study is likely to be rewarding. The testing of normal skin preparations in non-leprosy subjects, and the histological study of all reactions, are important next steps.

The Seventh International Congress of Leprology

This will be held at Tokyo this year from 12th to 19th November, by kind invitation of the Japanese Leprosy Foundation, who with the Japanese Leprosy Association will be hosts. The Organizing Secretary of the Congress is Dr. K. Hamano, 2–5 Uchisaiwaicho, Chiyodaku, Tokyo, Japan. From 20th to 24th November the WHO Inter-Regional Conference on leprosy will be held in Tokyo.

A MODIFICATION OF THE LEPROMIN TEST

by J. A. KINNEAR BROWN, B.SC., M.D., M.R.C.S., D.T.M.
Specialist Leprologist, Uganda

Lepromin is an antigen prepared by grinding 1 gm. of autoclaved bacteriologically positive tissue in 20 ml. of normal saline, a concentration of 1:20. The test is made by injecting 0.1 ml. intradermally. At the end of 24 to 48 hours, there is a tuberculin like response which rapidly fades, to be succeeded in most instances by a nodular infiltration which reaches its maximum size in three to four weeks. The early reaction is allergic, less constant, and may include a non-specific element due to tissue debris; the late result, the Mitsuda reaction, is thought to depend on the presence of whole bacilli and to indicate resistance to infection, because those with a negative Mitsuda develop the more serious forms of leprosy, and those with a strongly positive reaction, the milder forms. The late reaction is measured as follows:—

Infiltrations of 1 and 2 mm. are designated ± doubtful

Infiltrations of 3 and 4 mm. are designated + weakly positive

Infiltrations of 5 mm. and over are designated ++ positive

Ulceration is designated +++ strongly positive.

It is this late reaction which is referred to as the lepromin test in this report.

In the absence of a culture, the only satisfactory source of lepromin is the tissue of lepromatous patients. The supply of antigen is limited by their number and may not be equal to the demand. Attempts have therefore been made particularly by Floch, Diniz and Neto, and Schujman to discover the extent to which lepromin can be diluted and give results which can be correlated with those produced by the standard antigen.

In the majority of adults, the results of the lepromin and tuberculin tests coincide and it would simplify matters if tuberculin could be used to detect those who respond weakly to lepromin. The parallelism is not sufficiently close, however, and the measure of agreement depends to some extent on the test dose of tuberculin. In any case, the two tests are fundamentally different. The response to PPD reflects a definite experience with the tubercle bacillus but says little about the future; that to lepromin says little about the past (positive reactions occur quite commonly outside endemic areas) but more about the future, because it indicates reasonably well what will happen if the individual encounters infection. Until a successful culture is made or a new test evolved, experiments must continue until the present one has been so modified that its use on a large scale becomes practicable.

Preliminary Work. 269 patients in the Buluba Leprosarium were lepromin tested by the ordinary intradermal method using dilutions of 1:20, 1:300 and 1:750. The percentage that gave positive reactions dropped from 86% with 1:20, to 53% with 1:300 and to 37% with 1:750. The percentage that gave doubtful reactions increased from 12% with 1:20 to 23% with 1:300 and persisted at this level at 1:750. The percentage of negative results increased from 2% with 1:20 to 23% with 1:300 and 41% with 1:750. In some of those who remained positive throughout there was a reduction in the size of the infiltration with the more dilute antigens but this was less noticeable in those who were initially strongly positive. In those who were tested with 1:100, there was little difference from the result with normal antigen.

I. A MULTIPUNCTURE LEPROMIN TEST

It was decided to investigate the possibility of using a multipuncture apparatus to carry out a modified lepromin test, using normal lepromin and a dilution of 1:100. The Heaf apparatus provides a convenient method of tuberculin testing, particularly where children are involved. It produces six tiny punctures arranged in a circle and these are made through antigen smeared on the skin. The reaction which follows is read after 72 hours.

A positive reading is indicated by a palpable induration of at least four puncture points, and is graded as follows:—

Grade 1. Discrete palpable induration at the puncture points.

Grade 2. A coalescing of the indurated points to form an oedematous ring.

Grade 3. More extensive induration forming a coin pattern approximately 10 mm. in diameter.

Grade 4. More extensive induration with possible sloughing of the centre.

The lepromin used was made up to strengths of 1:20 and 1:100 to which 10% glycerine was added (as in PPD). A small quantity was placed on the flexor surface of the forearm. The plate of the multipuncture apparatus, sterilised by flaming was pressed evenly on the moistened area and the plunger driven home, when the six needles penetrated the plate and made the punctures. The tests with the weaker antigen were made at a higher level on the arm and the patients were made to sit after testing with their forearms supported horizontally until the antigen had dried. Where an ordinary intradermal test was done at the same time, it was placed at a lower level, so that there was no chance of more concentrated antigen running

down by gravity and contaminating a test made with a weaker dilution.

One hundred and ninety-two patients at the Kumi-Ongino Leprosarium were chosen of all ages and at various stages of treatment, none of whom was clinically lepromatous, and none of whom had been previously tested. 27 were tested with standard lepromin in the ordinary way (referred to for simplicity as 'the intradermal method'). These and the 165 others were tested at the same time percutaneously with the Heaf apparatus with lepromin in the two strengths.

In all the multipuncture tests, there was an immediate traumatic response which rapidly faded. This was followed by another similar in appearance which was differentiated as visible, palpable or prominent. At the apices of some of the latter, a pinpoint vesicle and crust eventually formed. In contrast with PPD, the swelling at each puncture remained discrete, there was fusion only in a very small minority and in no case did the whole area become involved. There was no distinctive early and late reaction. The response appeared at a different time in each individual but once it appeared, it persisted and was usually progressive. Of the 192 patients, the numbers with a palpable reaction at various time intervals were:—

Time interval	*Number reacting*
24–48 hours	24
72 hours	53
5 days	106
1 week	115
2 weeks	149
3 weeks	146
4 weeks	136

In some of the others, and in many of those who had a palpable reaction, there remained eventually a pinhead circle of hyperpigmentation at the site of each puncture. This was discounted. The chief difficulty at first was in deciding *whether a response was palpable*, this having been chosen as the arbitrary standard of positivity. This difficulty lessened with experience.

All the 27 patients tested intradermally had clinical tuberculoid leprosy and were Mitsuda positive, with a late infiltration of 5 mm. or more. Only 12 of these produced a ring of papules with the multipuncture tests; the other 15 showed either no visible change or none that was palpable. This work was repeated at the Buluba Leprosarium on 23 patients who had been Mitsuda positive one to three years previously, and who had been tested with the multipuncture apparatus three months earlier, with positive results. They were retested

simultaneously by both methods on the same arms. Of the Mitsuda results 9 were now stronger, 10 were the same, and 4 were weaker; by the percutaneous method, none were stronger, 7 were the same and 16 weaker. The positive Mitsuda response appeared, therefore, to depress that to the percutaneous method in some patients if done at the same time, thus nullifying this method of calibrating one test in terms of the other.

In the patients who showed a palpable reaction to the percutaneous method, that to the 1:100 dilution was often stronger. This was an anomaly difficult to explain. All the lepromin was from the same batch. All the tests with the normal antigen were done first before any dilution was made. A different and previously unused apparatus was used for the two series.

Subsequently, this was repeated on a small group at the Buluba Leprosarium with glycerinated lepromin, when 6 out of 11 patients showed a stronger reaction to 1:100, but weaker to 1:300, or 1:750. When unglycerinated lepromin was used, and the dilution 1;100 made with normal saline, there was little difference, except that the normal lepromin gave a slightly stronger reaction.

At the Buluba and Nyenga Leprosaria, 216 patients whose lepromin status had been determined intradermally one to three years earlier were now examined by the percutaneous method, using lepromin 1:20 without glycerine. The agreement between the original and the new tests was very close. If anything, there were slightly more positives by the later tests among the tuberculoid patients but this was what one would expect as the previous dose of antigen would have had a stimulating effect. Where there was a change in the opposite direction, it was among the indeterminate and dimorphous patients who are always the more unstable.

II. CORRELATION OF THE TWO METHODS OF LEPROMIN TESTING

When the intradermal and multipuncture tests were done on the arm side by side, the multipuncture test was frequently suppressed, making it difficult to establish any correlation. Twenty-one lepromin positive patients were now tested simultaneously on the forearm and back, using 1:20 lepromin intradermally. All gave a late positive response of more than 5 mm. The reactions in each individual were not always the same but any difference was small and it was not in favour of either site. *The site of injection did not, therefore, affect the response. If there was any suppression of one test by the other it was not considerable.*

Twenty adults were then tested simultaneously by the intradermal method, using 1:20 lepromin on the arm and 1:100 lepromin on the back. All gave a late positive response of 4 mm. or more.

The addition of 25% to the size of the infiltration caused by the

weaker antigen gave the grade of positivity produced by the stronger. It did not always give the exact measurement, but it did give the grading.

The addition of 25% to smaller infiltrations of 1, 2 and 3 mm. (ignoring fractions of a millimetre) would not alter their grade. With this method of correlation, an infiltration of 4 mm. is the only one that would be put into a higher grade, and this is what happened—an infiltration of 4 mm. to 1:100 lepromin was accompanied by a 5 mm. response to the 1:20 antigen.

In another series, in which the reaction to intradermal 1:20 lepromin had been determined three months earlier, the response to 1:100 lepromin had a similar relationship. Adding 25% did not put any patient into the wrong grade. As a practical measure, therefore, where it is desired to know more than whether the reaction is positive or negative 1:100 lepromin can be substituted.

Alternatively the same result in degrees of positivity would be achieved by adjusting the Standards for 1:100 lepromin as follows:—

Infiltrations of 1 and 2 mm. ± doubtful.

Infiltrations of 3 mm. + weakly positive.

Infiltrations of 4 mm. or more ++ positive

Ulceration +++ strongly positive.

If there is ulceration, it usually occurs with both antigens but it is less severe with the 1:100 dilution.

Forty children were now lepromin tested by the intradermal method in the interscapular area, and by the multipuncture method on the forearm using 1:20 lepromin in isotonic saline in both instances. Between the third and fourth week, 37 were positive to both tests and the responses in each patient were proportional. In the earlier work *the suppression of the multipuncture test by the intradermal must have been due more to local than central action.*

Three failed to give a reaction to the multipuncture method nor did they do so when it was repeated while the ordinary Mitsuda response was still present. *This could only mean that suppression is not entirely a local phenomenon.*

The following arbitrary grading was now adopted:

Grade I Four or more palpable and discrete papules

Grade II Four or more prominent and discrete papules

Grade III Four or more prominent papules with pinpoint ulceration at one of them, or all tending to coalesce.

Table I compares the results obtained with both tests.

TABLE I

	Intradermal in mms.	*Multipuncture by Grade*		*Intradermal in mms.*	*Multipuncture by Grade*
1	9	I-II	21	5	I
2	30	III	22	15	I
3	8	I-II	23	7	I
4	7	I	24	6	II
5	7	I	25	6	—
6	7	II	26	6	I
7	9	I-II	27	6	I
8	8	II	28	16	II
9	6	I	29	5	I
10	7	I	30	10	II
11	6	II	31	8	II
12	7	I-II	32	6	I
13	6	I	33	6	I
14	13	II	34	6	I
15	7	II	35	6	I
16	15	II	36	7	I
17	7	I	37	14	III
18	7	I	38	9	I
19	6	I	39	8	II
20	6	—	40	5	—

With a little experience, estimating the relative size of the papules is not difficult. It may not appear to be as accurate as measuring with a ruler but that carries a disproportionate margin of error when the infiltration is small. The chief feature of the results is that they broadly corresponded, the larger the infiltration by the intradermal method the more prominent the reaction to the multipuncture tests. The correlation in the majority was sufficient almost to make the three arbitrary grades of positivity equivalent to those of the International Standard.

III. SIMULTANEOUS LEPROMIN AND TUBERCULIN TESTING BY THE MULTIPUNCTURE METHOD

Having demonstrated that lepromin testing by the multipuncture apparatus was feasible and gave results not very different from those by the more orthodox intradermal injection, it was decided to attempt simultaneous lepromin and tuberculin testing by this method. 368 patients in the Buluba and Nyenga Leprosaria were chosen and the lepromin test applied on one forearm and the tuberculin test on the other. The lepromin used was the normal crude 1:20 suspension in isotonic saline. The Tuberculin was PPD (Weybridge) as used in the Heaf Tuberculin Test. The apparatus was the Heaf multipuncture instrument. Separate and new instruments were used for each antigen so that there could be no contamination.

For purposes of comparison only the late lepromin reaction was used although the early reaction was observed. The results varied with the type and group to which the patients belonged. Where there had been any doubt about the classification, a biopsy had been taken for confirmation.

(a) The Early and Late Lepromin Reactions

	Number Positive at 48 hours	*Number Positive at 3 to 4 weeks*
Lepromatous ...	17	11
Dimorphous ...	8	10
Indeterminate ...	34	53
Tuberculoid ...	83	157
Total ...	142	231

(The early lepromin response differs from that due to tuberculin in that it reaches its maximum at 48 hours not 72).

An interesting feature was that 15 of the lepromatous patients had a Grade IV response to PPD with blistering and of these 13 had an exaggerated response to the lepromin in which the papules coalesced and there was diffuse infiltration. This did not occur when the lepromin test was done alone. It was regarded as allergic in origin precipitated by the tuberculin. In 8 of these patients the lepromin was still positive four weeks later although very much subsided. X-Ray of the chests showed active tuberculosis in one, a healed focus in five and no change in the others. No reactivation at the site of old lepromin tests was observed.

Sixty three per cent more gave late positive reactions at three to four weeks. A small number of the early positives faded completely which was in line with earlier experience. The fewer positives with the earlier reading and the possibility of allergic interference make the late reading more valuable for estimating the immunological status and particularly the resistance of the individual .

TABLE II

(b) Comparison of Tuberculin and Late Lepromin Results

	Tuberculin Positive	*Tuberculin Negative*	*Lepromin Positive*	*Lepromin Negative*	*Total*
Lepromatous	36	23	11	48	59
Dimorphous	11	11	10	12	22
Indeterminate	50	25	53	22	75
Tuberculoid	132	48	157	23	180
Total	229	107	231	105	336

	Tuberculin Positive Lepromin Positive	*Tuberculin Negative Lepromin Negative*	*Tuberculin Positive Lepromin Negative*	*Tuberculin Negative Lepromin Positive*	*Total*
Lepromatous	11	23	25	0	59
Dimorphous	7	8	4	3	22
Indeterminate	38	10	12	15	75
Tuberculoid	120	11	12	37	180
Total	176	52	53	55	336

The proportion of Lepromin positives increased in the order Lepromatous (20%) Dimorphous (45%) Indeterminate (70%) Tuberculoid (93%). There was less variation among the Tuberculin positives. It was not possible in this series to correlate with the age groups.

The relationship of one test to the other varied with the type and group. This variation is seen in the increasing proportion that were positive to both as one passed from the lepromatous to the tuberculoid type (Lepromatous 20%, Dimorphous 32%, Indeterminate 50%, Tuberculoid 67%) and the decreasing proportion that were negative to both (Lepromatous 40%, Dimorphous 36%, Indeterminate 13%, Tuberculoid 6%). In the same direction, there was a decrease in the proportions that were Tuberculin positive and Lepromin negative (Lepromatous 42%, Dimorphous 18%, Indeterminate 17%, Tuberculoid 7%) and an increase in those that were Tuberculin negative Lepromin positive (Lepromatous 0, Dimorphous 14%, Indeterminate 20%, Tuberculoid 20%). It is recognised that the dimorphous group was much smaller than the others and percentages are only used to make comparison easier.

In 228 patients, two thirds of the series, the tests coincided, both being positive or both negative. The remaining third was divided equally between those that were positive to one and negative to the other, or negative to one and positive to the other. The agreement was at least as great as could have been expected, in some groups it was greater. The measure of agreement was generally less than that reported for groups of healthy individuals.

The parallelism in two thirds again suggests a relationship between the two diseases. The important groups, however, are the one sixth (52) who were negative to both tests and the other sixth (53) who were tuberculin positive but lepromin negative. These two groups outline the problem of detecting those whose resistance is weak. Among the general population, the individual who is negative both to tuberculin and lepromin can be vaccinated without risk with the assurance that the majority will convert to lepromin positive. A few

will not, however, despite tuberculin conversion. On the other hand, the individuals who are positive to tuberculin and negative to lepromin have failed to become lepromin positive in the presence of a natural infection with tubercle bacilli. It is hardly to be expected, therefore, that they will convert with BCG. The attempt to vaccinate them will produce a Koch reaction. There would also be the danger of breaking down a quiescent focus, a danger which may be more theoretical than real. Either occurrence would not enhance the popularity of the procedure. This group might be dealt with by repeated oral vaccination or by an antigen of killed Stefansky bacilli combined with a smaller dose of BCG on the lines of that suggested by Hanks.

In any case, it is advisable to discover those at risk at a much earlier age before there has been a primary infection with tubercle. For this, tests are required which are simple to apply and without inconvenience to the individuals who, in most cases, will be the uninfected children in the families of patients. The multipuncture tests appear to fulfil these criteria. Both can be done together or the Heaf tuberculin test can be done when the result of the lepromin test is known. For this purpose grading into degrees of positivity is not necessary. All that is required is to pick out the individuals who are likely to benefit by vaccination and who can be vaccinated without risk.

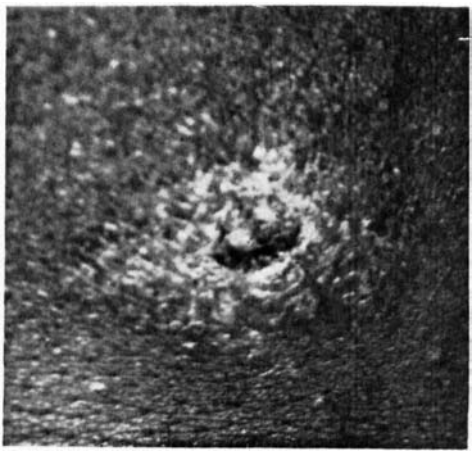
IV. The Use of Dilute and Depot Lepromins

Using the multipuncture method, one batch of lepromin diluted to 1:100 to which 10% of glycerine had been added gave more pronounced reactions than the ordinary 1:20 saline suspension. There was no obvious explanation but there are at least three possibilities:—

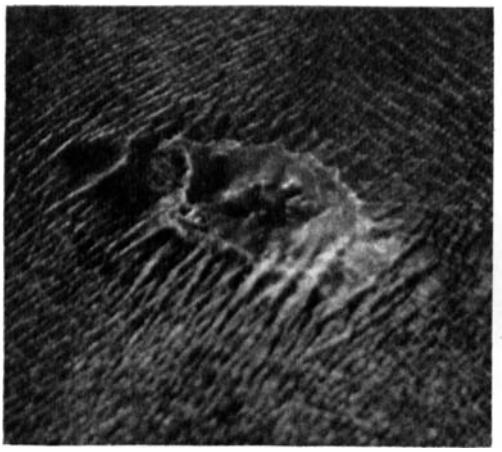
(*a*) the added glycerine released more bacilli from the tissue debris and bacillary clumps;
(*b*) the glycerine had a vasoconstrictor effect and thus kept the antigen longer in contact with the tissues of the patient;
(*c*) the glycerine in some other way had a depot effect.

It was also found that when intradermal and percutaneous tests were done side by side, the reaction to the former frequently suppressed any reaction to the latter, as though in some patients all available antibodies were attracted to and used up by the larger dose. This was much less obvious when the tests were done in different parts of the body although there was some evidence that the *suppression phenomenon* was not entirely local in origin.

Twenty-seven patients were chosen at random and tested percutaneously on the back with normal 1:20 lepromin and on the arm with a dilution of 1:100 in isotonic saline. 17 were positive to the 1:20 antigen, 9 were also positive to the 1:100 dilution. 10 were negative to both. Three weeks later the same patients were tested on the back



The late Mitsuda with ulceration



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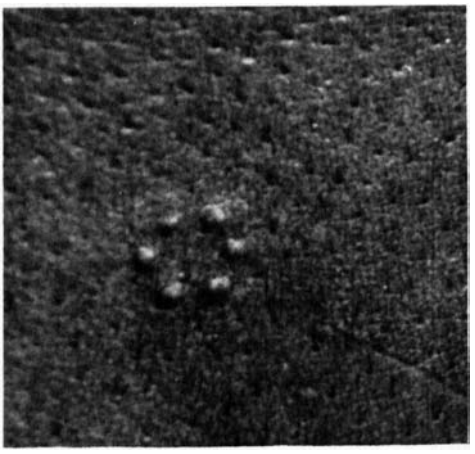
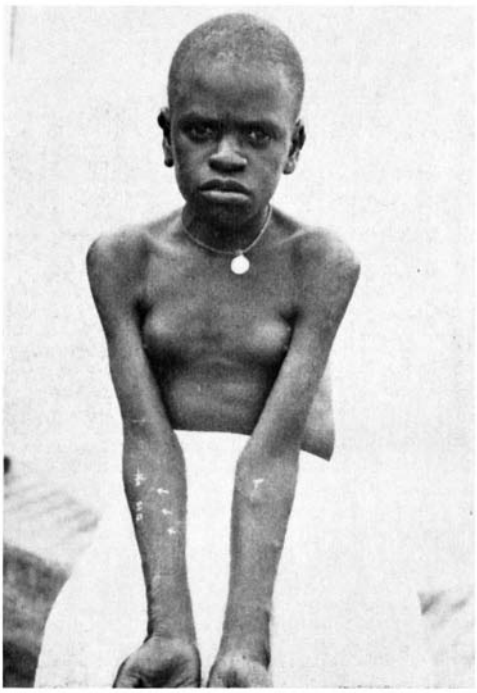
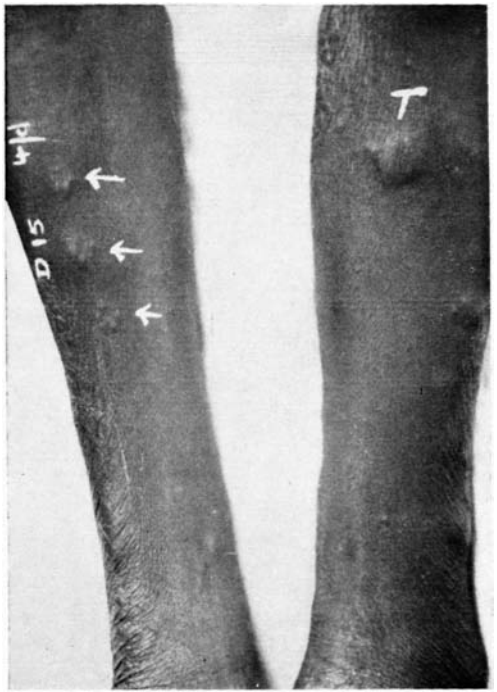


Multipuncture Response Grade II

Multipuncture Response Grade III
Papules coalescing and pinpoint elevation



Boy who had a Group IV response to the Heaf tuberculin at 72 hours, and an exaggerated response to the multipuncture lepromin in dilutions of 1:20, 1:100 and 1:300, at the same time. He was normally lepromin negative at 4 weeks and as can be seen he was obviously lepromatous with bilateral gynaecomastia. His x-ray showed active tuberculosis. The exaggerated lepromin response was allergic, due to coincident tuberculosis and the P.P.D.



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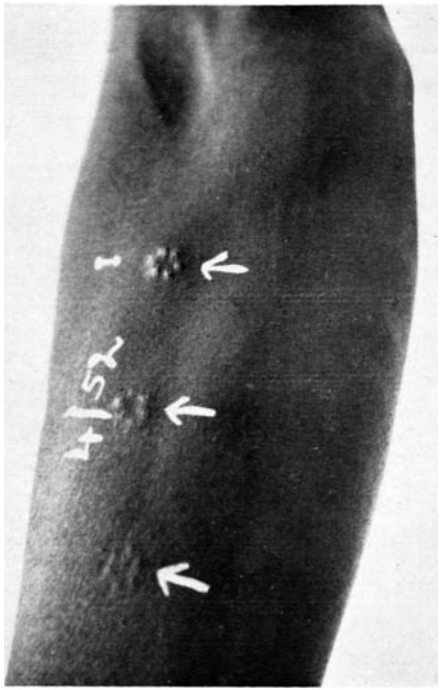

Pilot Tests. Grades I, II, III with different dilutions at 4 weeks. Pin point elevation in 1:20

with glycerinated lepromin in dilutions of 1:20 and 1:100. The same 17 were positive to the stronger antigen but the number positive to the 1:100 dilution had increased to 13. The lepromin used in all the tests was from the same batch.

More positives were obtained when glycerine was included in the diluted antigen than when it was left out, although on this occasion the response to 1:100 glycerinated lepromin was less pronounced than that to the stronger preparations.

In this work the glycerine had been added some weeks previously when the lepromin was made; in the earlier series it was added just before applying the test. Without being able to say precisely what the role of the glycerine is, it would appear that if a dilute lepromin is to be used by the percutaneous route 10% of glycerine should be added at some stage.

It was now decided to try to depot lepromin made similarly to the depot tuberculin described by James and Pepys (1956) on the grounds that if the antigen could be kept in close contact with the epidermal tissues for a longer period, an enhanced response might be obtained with less concentrated preparations. It was also thought that if the absorption of the antigen could be delayed, only one test would be necessary in a mass preventive campaign, because it would first pick out the poor responder and after BCG vaccination, it would indicate whether there was conversion to positive or an improvement in response.

The depot medium consisted of 8 parts of light liquid paraffin B.P. and 1 part of anhydrous lanoline B.P. to 4 ml. of which 1 ml. of isotonic saline was added. Control multipuncture injections were made with this emulsion in 20 patients of various types, but at the end of six weeks, there had been no trace of any reaction whatever. A 1:20 depot lepromin was then made by grinding 0.25 gm. of autoclaved lepromatous tissue in 5 ml. of the saline constituted depot medium. Further dilutions were made of 1:100 and 1:500.

Thirty-nine patients, 36 of whom were positive and 3 negative by the intradermal and percutaneous route and who had also been tested percutaneously with a 1:100 saline diluted lepromin were now injected with the three depot lepromins using the multipuncture apparatus.

The agreement in the responses of 37 of the 39 patients to the saline and depot lepromins in concentrations of 1:20 was complete, 34 were positive to both and 3 negative. The lack of correspondence in the other two—positive originally but negative now to the depot lepromins—was most probably the result of the *suppression phenomenon* as the tests were made fairly close together and the earlier intradermal and percutaneous 1:20 saline reactions were at their height.

Of the 34 who were positive to the 1:20 depot lepromin, 26 were

positive to 1:100 and 19 to 1:500. The results are summarized below.

TABLE IIIa

	Saline Lepromins		*Glycerinated Lepromins*	
	1:20	1:100	1:20	1:100
No. of Positive Reactors	17	9	17	13

TABLE IIIb

	Depot Lepromins		
	1:20	1:100	1:500
No. of Positive Reactors	34	26	19

(The 17 patients in both parts of IIIa are the same and are not included in the 34 in Table IIIb.)

It is not possible at this stage to say whether the response to percutaneous depot lepromin will persist longer than that to ordinary saline lepromin. In many cases, however, the 1:100 depot reaction was more definite than that to 1:100 saline, and the response to 1:500 depot lepromin in the second series was certainly as good as that to 1:100 saline lepromin in the first.

Depot lepromin has thus certain advantages. It is also less difficult to prepare. It spreads more easily on the skin and is, therefore, more economical. Using a tuberculin syringe and needle as a dropper and applying the lepromin to the skin direct, 250 tests were obtained from 1 ml. of the 1:20 preparation, 25 times the number when the intradermal route is used.

It is probable that a depot lepromin in a concentration of about 1:50 will give the same results as 1:20 and such a strength would be less viscous and somewhat easier to use. On the other hand, if it is desired to employ BCG in a mass campaign for the prevention of leprosy the use of a 1:100 depot test preparation has much in its favour. It is necessary to protect not only the negative responders, but those who react weakly and a 1:100 strength will pick out those who fall into either group. The disadvantage of a stronger antigen is that its scope is not wide enough. It will only identify those who do not react at all. A 1:100 depot lepromin is also even more economical for 1 ml. of 1:20 preparation diluted down will provide sufficient material for over 1,000 tests. The great advantage of this test is that it makes practicable a pilot scheme for using BCG prophylactically against leprosy in countries like Uganda.

The problem of the individual who is negative to lepromin and positive to tuberculin, and the individual who is negative to both lepromin and tuberculin and does not convert with BCG has been already referred to. Nevertheless, if only 50% of negative lepromin

reactors can be converted to positive, a big step forward will have been taken. There is evidence that those who do convert are much less likely to contract leprosy and if they do, it will be in its less infectious form. The BCG prophylaxis of leprosy linked with the provision of regular and continuous treatment for all who need it should vastly reduce the number of potential patients and the number from whom the disease can be contracted. Hanks described himself as being in the cruel dilemma of knowing how to protect the poor responder but of not knowing how to discover him. It is believed that this modification of the lepromin test will, to a large extent, provide the answer.

SUMMARY

1. A Series of investigations is described using various lepromins by the intradermal and multipuncture (percutaneous) routes.

2. When the two methods were used simultaneously, the reaction to the bigger dose appeared to suppress any to the smaller. This was more marked when the tests were placed near together.

3. In some patients 10% glycerine added to 1:100 isotonic saline solution enhanced the response to the percutaneous injection.

4. A 1:100 lepromin in isotonic saline can be used as effectively by the intradermal method as the 1:20 concentration and correlation can be established quite simply.

5. The multipuncture (percutaneous) test with 1:20 saline lepromin correlates completely with the 1:20 intradermal test. The multipuncture (percutaneous) test with the 1:20 depot lepromin correlates completely with the 1:20 isotonic saline lepromin by the same route.

6. The multipuncture (percutaneous) test with 1:100 depot lepromin is adequate to detect all the negative reactors and the majority of those who respond weakly: that is, those who most need protection.

7. This modification of the traditional Mitsuda is advocated for field work and where lepromin is in short supply. It is extremely economical of antigen and can, therefore, be used on a very wide scale. It is simple and quick to apply and read. It gives no inconvenience to the individual in the form of a painful and indolent ulcer and is, therefore, not likely to antagonise public opinion in a preventive campaign. It can be used side by side with the Heaf tuberculin test.

8. It is believed that this test opens the door to pilot schemes for trying BCG in the prevention of leprosy and watching the results in both groups of lepromin negatives, i.e. in those who convert and those who persist.

9. The problem of the individual persistently negative to lepromin and positive to tuberculin is discussed.

ACKNOWLEDGMENTS

This work has occupied a period of nearly four years. It was intended originally to present it in a series of papers in which reference could more easily be made to those who had contributed. For simplicity in reading, however, it was decided to compress the papers into one. Parts I and III were carried out in conjunction with Dr. W. M. Blenska of the Buluba and Nyenga Leprosaria and could not have been done without her help. Dr. J. M. Lea and Sister M. M. Stone of the Kumi-Ongino Leprosarium assisted with some of the work in Part I. Dr. J. M. Lea gave access to his patients for the work recorded in Parts II and IV and Sister M. M. Stone carried out the day to day routine with patience and thoroughness. To all these, I wish to express my gratitude. I am grateful also to Dr. G. Murray Short, Medical Officer Tuberculosis (Uganda) for his advice at various stages and to Dr. J. Pepys of the Medical Research Council, Tuberculosis Laboratories, for his interest and for providing the depot medium.

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LEPROMIN-LIKE ACTIVITY OF NORMAL SKIN TISSUE

T. F. DAVEY, O.B.E., M.D., M.S.C., and
S. E. DREWETT, F.I.M.L.T.

Leprosy Service Research Unit, Uzuakoli, E. Nigeria

Kooij and Gerritsen (1956, 1958) have reported a number of experiments in which skin reactions apparently identical with lepromin reactions were obtained by the use of extracts and suspensions of normal tissue. Many leprologists would consider their early findings inconclusive, suggestive more of personal idiosyncrasy than of typical lepromin reactivity, and would consider the comments of Kinnear Brown, Murray Short and Blenska (1957) very much to the point. In some of the later experiments however, reactions were described which were as pronounced as those to be expected with a standard lepromin preparation, though here again the occurrence of macroscopic reactions among lepromatous cases introduced an atypical element into the reactions obtained.

Among the sources of material used in these experiments, normal skin is of particular interest. Floch (1956) has also reported the occurrence of similar reactions using suspensions of normal skin, and the possibility arises that the tissue components in standard lepromin are not as inert as has been supposed. The subject obviously calls for further study, for these findings if generally confirmed could be of profound significance in more than one direction. We have repeated the first experiment reported by Kooij and Gerritsen, using additional controls, and as it has been suggested to us that the findings may provide an incentive to others to undertake similar work, we present them here.

Patients

Fifty leprosy patients took part in the experiment. Particular care was taken to classify them accurately, and on a basis of clinical bacteriological and histological findings, they were classified as, lepromatous 10, indeterminate 3, borderline 10, minor tuberculoid 17, major tuberculoid 10. All were segregated under close observation and were receiving chemotherapy.

Materials

(*a*) *Normal skin preparation*

In order to merit the description "normal" it was felt desirable that the skin used should be obtained only by biopsy. Specimens of skin removed during the course of surgical operations at a general hospital were autoclaved immediately after excision, sealed and despatched to us, and kept in a refrigerator until needed. The method of preparation was identical with that recommended for standard lepromin, following Wade's modification of the original Hayashi-

Mitsuda method. Subcutaneous fat was scraped from the specimens, which were then pooled, cut up and ground fine in a mortar with the addition of saline up to 20 ccs per gramme of skin. The suspension was filtered through nylon cloth. The residue was not used again. 0.5% phenol was added to the filtrate, which was transferred to rubber capped bottles, and these were again autoclaved and labelled. Smears of this preparation made for checking purposes after its use for inoculation showed no acid fast bacilli.

(*b*) *Lepromin*

It was felt desirable to provide additional controls in this experiment by using both standard and refined lepromin, prepared from the same material. A fresh sample of each was prepared from the same specimens of lepromatous skin. These were cut into two after autoclaving, and standard Mitsuda-Wade lepromin prepared from one half by the method stated above, while the other half was used for the preparation of a refined antigen by Lowe's simplification of the Dharmendra technique. This has been described elsewhere by Lowe (1953), but is described again here for convenience as follows.

After autoclaving, fat was scraped off the specimens of leproma, which were then cut in very small pieces and ground in a mortar with small amounts of chloroform, the chloroform extract being pipetted off from time to time and replaced with fresh chloroform. This process was repeated, until the chloroform extract being pipetted off contained very few bacilli. The residue in the mortar was then discarded, and the chloroform removed from the extract by evaporation. The syrupy residue was then ground with carbol saline, 0.5%, and the aqueous layer pipetted off into a separating funnel, where it could be separated again more perfectly from the fatty material present. The substrate was run through nylon cloth into rubber capped bottles, autoclaved, labelled, and kept in the refrigerator until required.

Lepromin refined by this method has been in standard use in this laboratory for several years. Its significance from the standpoint of this experiment lies in its almost complete freedom from tissue components, while at the same time the bacilli are not denatured to any marked extent.

The new batch was standardised both directly and biologically against the standard in regular use, and found to possess an activity fully up to this standard.

Method

The three preparations used in this experiment were thus, (*a*) Standard Mitsuda-Wade lepromin, (*b*) Refined Dharmendra-Lowe lepromin, (*c*) Normal skin preparation.

0.1 cc. of each of these was inoculated into the skin on the inner side of the upper arm in each of the 50 volunteers at sites one below the other. 0.1 cc. of 0.5% carbol saline was injected at the same time

as a control into the skin of the other arm. Reactions were measured after 24 and 48 hours, on the seventh day, and then weekly up to the thirty-fifth day, and readings were checked before being recorded.

Results

(*a*) *Fernandez Reaction*

Forty-eight hour readings are presented in Table I, classified both according to the accepted degrees of positivity in the Fernandez Reaction, and according to the type of leprosy displayed by those concerned.

The carbol saline control inoculations provided sufficient irritation to produce areas of oedema in a considerable number of patients, small but still measurable after 48 hours. Due regard is paid to this by indicating the excess over the control readings exhibited by the test inoculations. Totals for this excess in millimetres are given in Table II in the various groups of patients.

Both Tables bring out the close similarity between the two lepromins in the Fernandez reactions they elicited, both in size of reactions and their pattern in the various types of leprosy. Both were active and behaved normally, with reactions increasing in intensity towards the major tuberculoid group.

There is an obvious contrast between them and the normal skin preparation in this respect, made particularly clear in Table II. The normal skin preparation had only a very slight capacity to evoke the Fernandez response, with an insignificant increase in activity in tuberculoid cases.

These findings differ from those of Kooij and Gerritsen, though in a later publication in which details are given by these authors (1957), there appears to have been little difference between their lepromatous and tuberculoid case in the Fernandez reactions they produced to a concentrated skin preparation.

(*b*) *Mitsuda Reaction*

Readings for the Mitsuda reaction are given in Table III, classified in the same way as those in Table I. As is usually the case, the date when the peak reaction was attained varied from one patient to another, in some at 21 days, in others at 28 days. The peak readings are recorded here. This gives a more accurate picture of the reactions obtained than would have resulted from 28 days readings only. No readings are given for controls, for they were negative in every case.

A comparison between the three preparations can also be made by recording the total of the reactions produced in the various classes of patients. This is given in Table IV.

The standard lepromin was obviously a highly active preparation, giving intensely positive readings in major tuberculoid cases, strongly positive readings in minor tuberculoid cases, and positive findings in both borderline and indeterminate cases.

TABLE I
FERNANDEZ REACTIONS IN MILLIMETRES

	Below 5	5–9	10–14	15–19	20 plus
LEPROMATOUS CASES 10 Patients					
1. Standard Lepromin	6	4	0	0	0
2. Refined Lepromin	6	4	0	0	0
3. Normal skin preparation	9	1	0	0	0
4. Controls	10	0	0	0	0
INDETERMINATE CASES 3 Patients					
1. Standard Lepromin	1	1	1	0	0
2. Refined Lepromin	1	1	1	0	0
3. Normal skin preparation	2	1	0	0	0
4. Controls	3	0	0	0	0
BORDERLINE CASES 10 Patients					
1. Standard Lepromin	2	6	2	0	0
2. Refined Lepromin	2	7	1	0	0
3. Normal skin preparation	7	3	0	0	0
4. Controls	10	0	0	0	0
MINOR TUBERCULOID CASES 17 Patients					
1. Standard Lepromin	1	9	6	1	0
2. Refined Lepromin	1	12	4	0	0
3. Normal skin preparation	10	6	1	0	0
4. Controls	12	4	1	0	0
MAJOR TUBERCULOID CASES 10 Patients					
1. Standard Lepromin	0	4	4	2	0
2. Refined Lepromin	0	4	4	2	0
3. Normal skin preparation	6	4	0	0	0
4. Controls	10	0	0	0	0

TABLE II
FERNANDEZ REACTION: EXCESS IN MILLIMETRES OVER CONTROL READINGS

	LEPROMATOUS 10 cases			INDETERMINATE 3 cases			BORDERLINE 10 cases			MINOR TUBERC. 17 cases			MAJOR TUBERC. 10 cases		
	STD	REF	NSP	STD	REF	NSP	STD	REF	NSP	STD	REF	NSP	STD	REF	NSP
Total	15	14	5	10	8	4	33	29	1	77	82	12	79	81	16
Average	1.5	1.4	0.5	3.3	2.7	1.3	3.3	2.9	0.1	4.5	4.8	0.7	7.9	8.1	1.6

STD Standard Lepromin REF Refined Lepromin NSP Normal skin preparation.

The refined lepromin produced reactions following the same pattern but at a lower level of activity. This was as expected, though the loss of activity was emphasised by the unusually high activity of the standard lepromin. With the refined preparation reactions were generally smaller in size, and in a proportion of the indeterminate and borderline groups of patients they were reduced to a negative level.

Reactions were also produced by the normal skin preparation, and these undoubtedly followed the same pattern, though at a still

TABLE III

MITSUDA REACTIONS IN MILLIMETRES

	Below 3	3-4	5-7	8-9	10 plus
LEPROMATOUS CASES 10 Patients					
1. Standard Lepromin	10	0	0	0	0
2. Refined Lepromin	10	0	0	0	0
3. Normal skin preparation	10	0	0	0	0
INDETERMINATE CASES 3 Patients					
1. Standard Lepromin	0	0	1	0	2
2. Refined Lepromin	3	0	0	0	0
3. Normal skin preparation	3	0	0	0	0
BORDERLINE CASES 10 Patients					
1. Standard Lepromin	0	1	6	0	3
2. Refined Lepromin	4	3	3	0	0
3. Normal skin preparation	8	2	0	0	0
MINOR TUBERCULOID CASES 17 Patients					
1. Standard Lepromin	0	1	0	2	14
2. Refined Lepromin	4	0	8	4	1
3. Normal skin preparation	4	1	12	0	0
MAJOR TUBERCULOID CASES 10 Patients					
1. Standard Lepromin	0	0	0	0	10
2. Refined Lepromin	0	0	7	1	2
3. Normal skin preparation	0	1	6	3	0

TABLE IV

MITSUDA REACTION: TOTAL READINGS IN MILLIMETRES

	LEPROMATOUS 10 cases			INDETERMINATE 3 cases			BORDER LINE 10 cases			MINOR TUBERC. 17 cases			MAJOR TUBERC. 10 cases		
	STD	REF	NSP	STD	REF	NSP	STD	REF	NSP	STD	REF	NSP	STD	REF	NSP
Total	6	2	0	33	4	0	66	24	5	207	101	73	183	68	63
Average	0.6	0.2	0	11.0	1.3	0	6.6	2.4	0.5	12.2	6.0	4.3	18.3	6.8	6.3

STD Standard Lepromin REF Refined Lepromin NSP Normal skin preparation.

lower level of activity. Without exception lepromatous cases gave negative reactions. Major tuberculoid cases gave a definite macroscopic reaction in every case. Minor tuberculoid cases also gave macroscopic reactions, though some of these were very small, less than 3 mm. in diameter in 24% of cases, though here identical findings were obtained with the refined lepromin. For the most part indeterminate and borderline cases gave negative reactions.

As the refined lepromin often produced reactions similar in size to those evoked by the normal skin preparation, a comparison of features of the reactions other than that of size could easily be made. It was impossible to detect any difference in appearance or texture. In their development the reactions usually ran parallel with one another, an early peak in the lepromin reaction being associated with an early peak in the reaction to normal skin, late peak reactions also

being similarly associated. Where their decline was concerned, the reactions to refined lepromin showed some tendency to subside earlier than the reactions to normal skin and standard lepromin. Clinically the reactions were thus closely similar, and this similarity was also found in histological preparations of the reactions in four individuals at the fortieth day.

Discussion

There can be no doubt that the preparation of normal skin used in this experiment possessed a capacity to induce skin reactions which was distinctive, resembling a weak lepromin in its capacity to induce the Mitsuda type of response, but lacking the capacity of lepromin to induce the Fernandez type of response to any significant extent.

The question immediately arose as to whether there had been any opportunity for the contamination of the normal skin preparation with lepromin or lepromatous tissue in the laboratory. A careful review of the method of preparation, labelling and preservation made this exceedingly unlikely. Attention was paid to the glassware used, as it is known that tuberculin can adhere to glass and contaminate a preparation made subsequently in the same vessel.

The mortar used for the normal skin preparation had been used in the past for preparing lepromin, but it had been thoroughly scrubbed and autoclaved before being used, and the extreme unlikelihood of any contamination from this source is evidenced both by the failure of the preparation to induce Fernandez reactions and the absence of acid fast bacilli in smears made from it. The utmost care was taken in labelling and preservation. New syringes and needles were used for the inoculations. By all reasonable standards contamination can be ruled out as a practical possibility.

It follows that we can at any rate in part confirm the findings of Kooij and Gerritsen that lepromatous tissue is not essential for the production of the Mitsuda reaction. By suitable adjustment of the standards for the various grades of positivity, the preparation of normal skin used in this experiment could have been used instead of lepromin to distinguish positive from negative Mitsuda reactors.

It would be interesting to observe the effects of concentrating such a preparation. We may note here that although at first Kooij and Gerritsen observed no increase in activity by concentrating their preparation, (though different subjects appear to have been used for testing the concentrated material), the marked reactions they obtained later resulted from the inoculation of concentrated material.

The resemblance of the normal skin preparation to refined lepromin in the Mitsuda reactions it produced is also worthy of note. Where the Mitsuda reaction alone is concerned, it is questionable whether the refined lepromin had any real advantage over it. It was in Fernandez reactivity that the difference between the two was apparent.

It remains to be seen whether the activity displayed by the specimens of normal skin used in this experiment is a freak finding, or illustrates a general principle. The possibility cannot be ruled out that even if contamination with lepromatous tissue can be ignored apparently skin may contain unsuspected antigens such as microfilariae and fungi which are capable in appropriate conditions of inducing a tuberculoid type of reaction. The likelihood that such things could have induced the reactions observed is of course exceedingly remote, but it would be useful in future studies to have histological evidence for the exclusion of such possibilities.

It is not proposed here to discuss the pathological processes which may underlie these reactions. The data available are not sufficient for the drawing of conclusions. More experiment is needed with histological control. Kooij and Gerritsen have rendered useful service in drawing attention to the existence of these interesting reactions. Their thorough investigation is now called for.

Summary

An experiment is described in which standard lepromin, refined lepromin and a normal skin preparation were inoculated into the skin of 50 leprosy patients of various types in an attempt to confirm the findings of Kooij and Gerritsen that a normal skin preparation could induce both Fernandez and Mitsuda reactions. It was found that the normal skin preparation used had no appreciable capacity to induce Fernandez reactions, but did induce reactions indistinguishable from Mitsuda reactions in tuberculoid cases of leprosy. These were decidedly smaller than those induced by standard lepromin, a little smaller than those produced by refined lepromin, but followed the same pattern. The Kooij and Gerritsen observations were thus in part confirmed, and the subject needs further study.

Acknowledgments

Grateful thanks are due to Dr. J. Gower of the Queen Elizabeth Hospital, Umuahia, who kindly supplied the material from which the normal skin preparation was made, and to the patients who volunteered to take part in this experiment. Thanks are also due to Dr. K. Seal, Leprosy Adviser, and Dr. Onwu, C.V.O., Director of Medical Services, Eastern Region, Nigeria, for permission to publish.

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LEPROSY and LUNG LESIONS

A REPORT ON INVESTIGATION OF THREE CASES BY A DIFFERENTIATING STAIN: "SUDAN BLACK"

by DR. B. B. GOKHALE,
MISS USHA OAK,
DR. S. M. WABLE.

of Sassoon Hospitals, Poona, Bombay State, India

Diversity of opinion exists on the subject of the etiology of lesions of the lung in leprosy. Some workers think that the lesions are due to *M. leprae;* others feel that they are due to *M. tuberculosis.*

Sticker (1905) expressed his opinion thus: Leprosy may affect the lung in any form, from that of chronic peri-bronchitis to caseous pneumonia, in which case it may resemble tuberculosis. There may be no minute changes though bacilli may abound.

Babes (1906) put forward the theory that varying degrees of lung lesions may be present in leprosy patients. His evidence in favour of these lesions and their differentiation from tuberculous lesions depended on the arrangement and the morphological characteristics of the two organisms.

Sagai-Masaki (1917) stated that, in leprous patients, tuberculosis is a primary and leprosy a secondary lesion of the lungs. Yet, he mentioned finding leprous nodules in the pleura.

The observations of Kobayashi (1929) were based on the autopsies of the lungs of leprous patients. "In 32 out of 60 cases he found tubercle bacilli and pathological changes of a tubercular nature. He found lepra bacilli in 19 out of these 60 cases. In 8 out of the 32 tubercular lungs and in 11 out of the 28 non-tubercular lungs he found lepra bacilli".

E. Muir (1933) drew his conclusions from his experiments on guinea pigs who were inoculated with A.F.B. positive sputum. He also depended on the clinical signs in the lungs. He opined that the lung lesions in the 9 cases he recorded were due to leprosy.

Ranade and Gokhale (1954) published a report on 8 cases of leprosy with lung lesions. They concluded that in 7 of these cases the lung lesions were due to leprosy and in one case due to tuberculosis.

Hansen and Looft (1895) denied the existence of leprosy of the lungs. They stated: "There exists a sharp anatomical distinction between leprosy and tuberculosis and there is no such thing as leprosy of the lungs". To establish a differential diagnosis, they recommended a thorough examination of the bronchial glands.

Wise (1912) tried to clarify the facts by experiments made on guinea pigs. A small portion of the lung tissue of patients with A.F.B positive sputum was removed and pocketed in the thigh of the guinea pig. He based his comments on the post-mortem findings—macroscopic and microscopic:— "The disease was well advanced

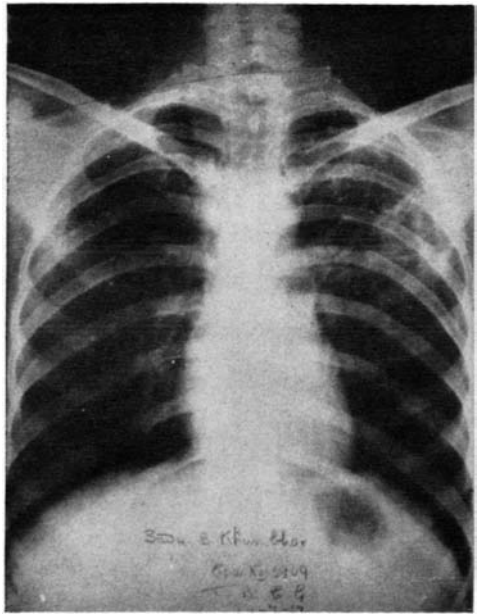

PLATE NO. 1 (1954)

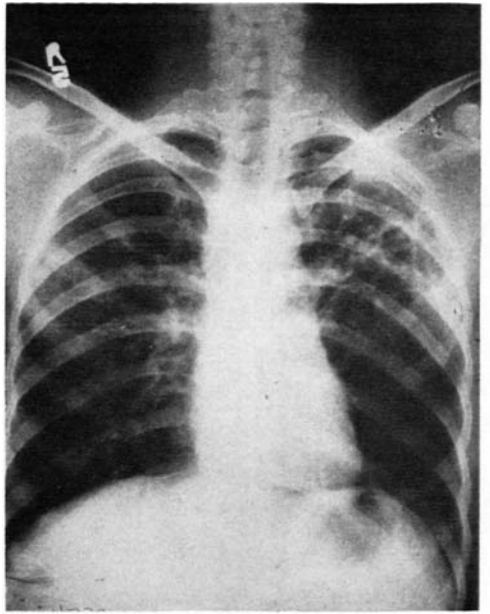

PLATE NO. 2 (4.7.58)

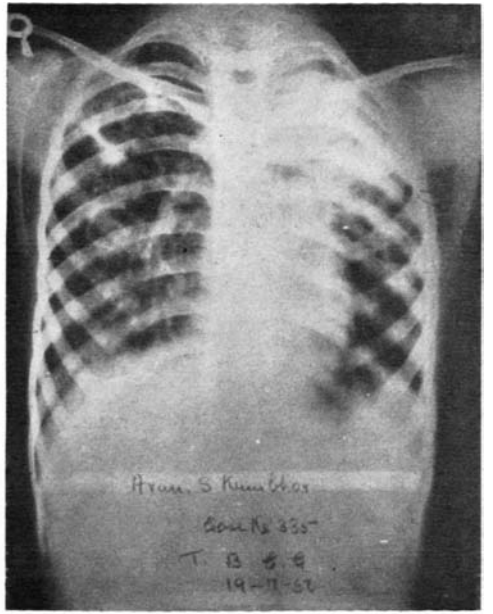

PLATE NO. 3. (S.S.K.'s son)

CASE NO. 1 (S.S.K.) *Compared to first skiagram (pl. No. 1—1954) there are now, 4.7.58 (pl. No. 2). increased number of nodular lesions in left upper lobe, with presence of streaky fibrotic strands. A definite cavitation is seen near the anterior end of eleventh rib. A few nodular lesions are seen in right upper lobe, with some thickening of minor inter-lobar fissure.*

Findings are consistent with pulmonary tuberculosis.

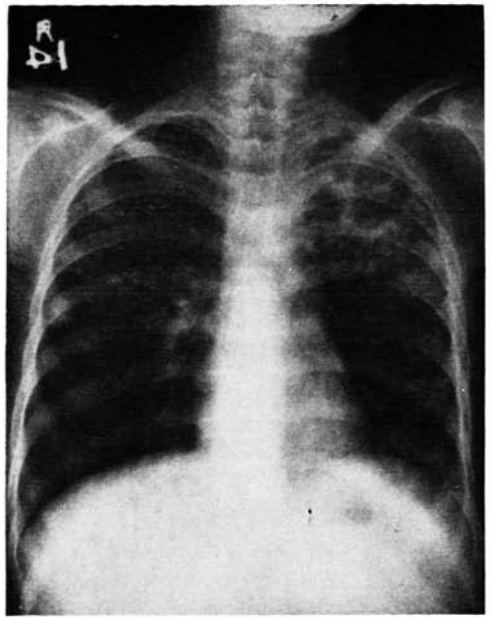

PLATE NO. 4

(S.G.) CASE NO. 2 (4.7.58)

Nodular infiltration of the entire left lung and right mid-zone, with cavitations in left infra-clavicular region. A few nodular lesions are also seen in right upper lobe.

Findings are consistent with pulmo-

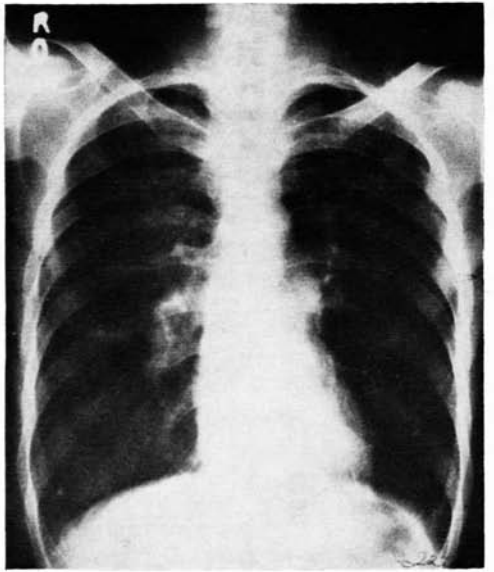

PLATE NO. 5

(L.B.K.) CASE NO. 3 (4.7.58)

Both lungs are markedly emphysematous. Pulmonary segment is prominent with engorged pulmonary hilar vessels Cardiac apex is slightly elevated, suggesting right ventricular enlargement.

Findings indicate pulmonary emphysema with cor pulmonale.

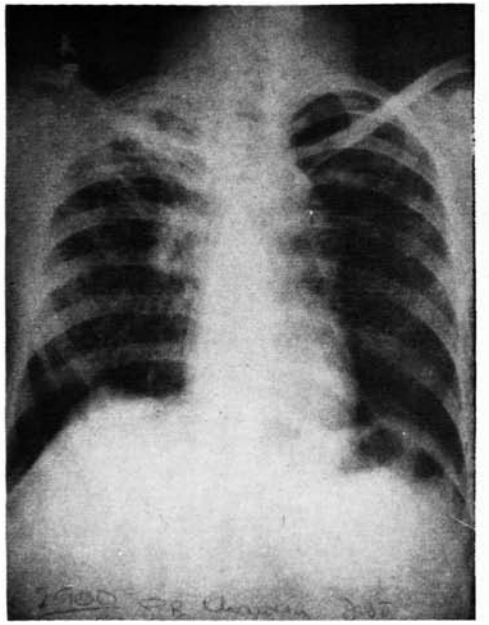

PLATE NO. 6

(G.B.K.) CASE NO. 4

Infiltration of the lungs with cavitation at the apex of the right lung.

Findings are consistent with pulmoary tuberculosis.

when death occurred and the lung lesions, which were certainly recent in origin, resembled more of a final general dissemination than of a natural sequence of leprosy".

Wade (1927) denied the presence of lung lesions in leprosy. His observations were from numerous post-mortems he had done on patients who died of leprosy.

In the absence of a definite positive proof, the observations were more or less speculative.

Chaussinand and Viette have described a method of staining, enabling the differentiation between *M. tuberculosis* and *M. leprae.*

We decided to take advantage of this method in our work on lung lesions in leprosy:

Material and Method

A 24 hours collection of sputum of patients was made in a clean glass container.

A specimen for preparation of a slide was picked from this collection and a smear made as usual.

A portion of the sputum was concentrated as for *M. tuberculosis* by Petroffe's method, and smears were made from this concentrated material.

The slides were then fixed by heat. One set was stained as usual by Ziehl Neelsen method, and the other by Sudan Black as below:

Seventy per cent alcoholic solution of Sudan Black was poured on the slide and the stain was burnt till emitting a blue flame.

The slide was then washed on both sides first with water, and next with acetone for 2 to 5 minutes.

It was counterstained with safranin and finally washed with water again.

By this method, *M. tuberculosis* takes up the stain, but *M. leprae* remains unstained.

Material aspirated at the time of bronchoscopy was also examined microscopically.

CASE REPORTS

Case No. 1:

A male S.S.K. (a pottery maker) aged 36 years, was first seen 4 years ago when he complained of tingling and numbness in the extremities and cough with expectoration. At that time his sputum was examined and an X-ray plate (Plate No. 1) taken. The sputum showed A.F.B. He was treated with diamino-diphenyl-sulphone.

Clinically, he is a case of tuberculoid type of leprosy. Two months ago, he was admitted as in-patient in the hospital on account of an attack of haemoptysis.

His family history showed that his son, aged 12 years, had a hypopigmented anaesthetic patch on the right cheek. The boy was under treatment for leprosy for one year. He also had lung lesions (X-ray plate No. 3). Last year, he was admitted in the hospital for profuse haemoptysis and he expired.

Present condition of the patient: Facial and palmar erythema with two hypopigmented anaesthetic patches in the lumbar region. The supratrochlear glands are palpable. (X-ray plate No. 2) shows a cavity at the left apex.

Investigations

(*a*) *Blood:*

1. Hb — 9 gms. %
2. R.B.C.'s — 3.1 mill./cu.mm.
3. W.B.C's — 6200/cu.mm.
4. Diff. P — 64%
   L — 27%
   E — 2%
   M — 7%
   B — nil
5. E.S.R. — 45 after 1 hour } corrected to 38
   — 43 after 2 hours }
6. P.C.V. — 42 parts %
7. V.D.R.L. — negative.

(*b*) *Urine:* nothing abnormal detected.
(*c*) *Local smears:* negative for *M. Leprae.*
(*d*) *Laryngoscopy* (done on 3/6/58): larynx and pharynx normal.
(*e*) *Radiogram of the chest:* A.P. view (X-ray plate No. 2).
(*f*) *Sputum:* smears positive by Ziehl Neelsen and Sudan Black stains.
Culture reports of both these cases are positive for *M. tuberculosis.*

Case No. 2:

A male S.G. aged 20 years started developing hypopigmented and erythematous patches on his body eight years back. Since one year, he also has got cough with expectoration.

Clinically, he is diagnosed as a case of dimorphous type of leprosy.

He was admitted as an in-patient 1½ years ago, and is under treatment since then for leprosy.

On clinical examination, the patient shows hypopigmented anaesthetic and erythematous patches all over. There is loss of hair of the eyebrows. The ulnar nerves are thickened. The ear lobules show thickening. (X-ray plate No. 4).

Investigations

(*a*) *Blood*

1. Hb — 8 gms. %.
2. R.B.C.'s — 2.75 mill./cu.mm.
3. W.B.C.'s — 6400/cu.mm.
4. Diff. P — 56%
   L — 36%
   E — 1%
   M — 7%
   B — nil.
5. E.S.R. — 55 after 1 hour. Corrected to 34
6. V.D.R.L. — weakly positive

(*b*) *Urine:* Nothing abnormal detected.
(*c*) *Smears from the patches:* negative for *M. leprae.*
(*d*) *Laryngoscopy* (done on 3/6/58): nothing abnormal detected.
(*e*) *Radiogram of the chest:* A.P. view (X-ray plate No. 4)..
(*f*) *Sputum:* smears positive by Ziehl Neelsen and Sudan Black stains.
Result of culture for *M. tuberculosis* is negative. (Loffler's egg medium).
Repetition of culture has been requested.

Case No. 3:

A male L.B.K. aged 32 years is a tailor. He first noticed signs of the disease ten years back. He has widely distributed lepromatous lesions.

He was admitted as an in-patient one month ago, for breathlessness.

Clinically, he is a case of lepromatous type. He complains of tingling and numbness in the extremities, as well as cough with expectoration. The ulnar nerves are thickened on both sides.

This patient has been taking anti-leprosy treatment off and on.

Investigations

(*a*) *Blood:*
1. Hb — 12 gms. %
2. R.B.C.'s — 4.1 mill./cu.mm.
3. W.B.C.'s — 7800/cu.mm.
4. Diff. P — 30%
   L — 62%
   E — 4%
   B — 1%
   M — 3%
5. E.S.R. — 28 mm. after 1 hour corrected to 25 mm.
6. P.C.V. — 45 parts %
7. V.D.R.L. — strongly positive.

(*b*) *Urine:* nothing abnormal detected.
(*c*) *Smears for the lesions:* positive for *M. leprae.*
(*d*) *Laryngoscopy:* (done on 20/6/58) larynx and pharynx normal.
(*e*) *Radiogram of the chest:* A. P. view (X-ray plate No. 5).
(*f*) *Sputum:* smears positive by Ziehl Neelsen and Sudan Black stains.
Culture reports of both these cases are positive for *M. tuberculosis*

Case No. 4:

A male G.B.C. aged 37 years, was admitted as in-patient for haemoptysis for four days.

This patient was irregularly attending the out-patients department of these hospitals for the last few years. He was being treated with diamino-diphenyl-sulphone.

His sputum was examined and an X-ray plate taken (plate No. 6).

Clinically he is a case of tuberculoid type of leprosy. He has got hypopigmented anaesthetic patches on the body. Ulnar nerves on both the sides are thickened

Investigations

The patient left the hospital against advice, a short while after admission, and therefore the laboratory investigations are not complete.
(*a*) *Local smears:* negative for *M. leprae.*
(*b*) *Sputum smears:* positive by Ziehl Neelsen and Sudan Black stains.
(*c*) *Radiogram of the Chest:* A.P. view (X-ray plate No. 6).

Summary

In the three cases described here, *M. tuberculosis* has been demonstrated in the sputum.

With this small report, it is hoped that other workers would report similarly, so that sufficient material may be available for proper elucidation.

Acknowledgments

Our thanks are due to: Dr. M. S. Dikshit, Department of Radiology, Sassoon Hospitals, Poona; to Mr. V. N. Joshi, artist, B.J. Medical College, Poona; and the Department of Pathology, Poona, for the co-operation they have given us.

Thanks for the encouragement and help received all along from colleagues and friends.

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A TRIAL OF ANTIGEN MARIANUM AS AN ADJUNCT OF D.D.S. IN THE TREATMENT OF LEPROMATOUS LEPROSY

D. W. BECKETT, M.A., M.D., D.T.M. AND H.

Medical Superintendent Fiji Leprosy Hospital, Makogai.

Antigen marianum was originally prepared in Lyons at the Leprosy Research Laboratory of the Propagation of the Faith by the late Sister Mary Suzanne, S.M.S.M. According to Blanc, it is a culture of acido-alcohol resistant bacilli from a human leproma which is later killed to prepare the antigen. As there is no certainty that the organism in culture is indeed *Mycobacterium leprae*, Sister Mary Suzanne proposed for it the name of *Mycobacterium marianum* in honour of the Blessed Virgin to whom her Religious Congregation is dedicated. The antigen prepared from this strain, originally known as Chauvire antigen, has also become known as *Antigen marianum.*

The antigen was first used experimentally by Blanc, Prost Lemaire, Kuna and Nkoa in the Cameroons in 1952 and their first report was published in 1953. In this they report that 73.3% of lepromin-negative lepromatous patients and 61% of similar indeterminate cases became lepromin positive after a six to twelve months' course of the antigen.

From these results, Blanc and his colleagues decided to experiment with the antigen as a form of treatment based on an immunological line of attack rather than a chemotherapeutic one. They reported their results in 1955. In their series of 457 patients, there were ten deaths which were not attributable to the antigen. Of the remainder, 21.7% showed no improvement, 79.9% improved and 56.4% showed considerable improvement.

We in Makogai were most interested in these reports as the Fiji Leprosy Hospital is staffed by the Missionary Sisters of the Society of Mary and Sister Mary Suzanne was, in fact, one of the first two Sisters to arrive here on the foundation of the hospital in 1911. She worked in Makogai from 1911 until 1932 when she departed after a short stay in Rotuma, to France. It was in Makogai, we like to think, that she learned the facts about leprosy and developed that interest in the disease that led her into research in the subject. My predecessor, Dr. W. H. McDonald, therefore wrote to her in 1954 and obtained from her sufficient *Antigen marianum* to treat 84 patients. Sister Mary Suzanne displayed throughout the course of the trial a great interest in it and its progress, and the news of her sudden death in November 1957, just as the results were being correlated, was a sad blow to all at Makogai, both staff and patients.

The Trial

The present trial of *Antigen marianum* was commenced towards the end of 1954 by my predecessor in this post, Dr. W. H. McDonald, M.B.E. His object at the time was to see if the postulated immunological effect of the antigen could be made use of synergistically to enhance the value of DDS in treatment of lepromatous leprosy. Eighty-four cases were picked because they were examples of that class which is such a problem to workers in leprosy. All were lepromatous cases whose disease appeared inactive or only very slightly active but whose skin smears remained persistently positive. Out of these 84 cases, 61 were picked by random selection for treatment with the antigen and DDS, while the remaining 23 cases were given DDS alone so as to act as controls.

Most unfortunately, when the time came to start the second six-month course (see 'method' below), Dr. McDonald was on leave and the Medical Officer who was relieving him mistakenly started all 84 patients on to the antigen. It thus results that cases numbers 62 to 84 received only two courses of treatment.

When the time came to correlate results, therefore, there were no accurate controls. In order to obtain some idea of the value of the antigen, all those cases of lepromatous leprosy who were not very active at the start of the experiment but who had not been given the antigen were picked as retrospective controls. These numbered 21 and were generally rather more active than the 84 patients who had been included in the trial.

Method

Every patient had a lepromin test performed and was then given 0.1 ml. of *Antigen marianum* by intradermal injection at monthly intervals for six months. The injections were given into the skin of the palmar aspect of the forearm and the two arms were used alternately. A month after the last injection, the lepromin test was repeated. Three of these six-monthly courses were given with six months interval between each.

Reaction

After each injection, every patient ran a temperature. In the majority of cases, this was not high (below 100°F. or 37.7°C.) and lasted for only one day. However, about one-fifth of the patients ran a high temperature for two or three days and this was particularly noticeable after the earlier injections.

At the site of the injection, a raised, red and angry-looking nodule was formed in every case. As the trial proceeded, these became more severe and broke down to form very chronic and unsightly ulcers. Several patients who bear no other deformity from

their leprosy will carry the scars of these ulcers as most unwelcome stigmata for the rest of their days.

It appeared then that the general reaction to the antigen was greater in the earlier doses but the local protective reaction was greater as the trial advanced and the patients' resistance built up.

Lepromin Reaction

Before the trial, out of the 84 cases, 13 (15.5%) were lepromin positive and 71 (84.5%) were lepromin negative. After three courses of antigen, 69 (82.1%) were positive and only 15 (17.9%) were negative.

Of the 61 patients who underwent the first six months period, 52 were lepromin negative. After one six month's course, 30 of these were positive, 21 were still negative and one had been discharged. This represents a conversion rate of 57.7% after six injections of the antigen and compares unfavourably with Blanc's figure of 73.3% but is better than Relvich's one of 30%.

Crude lepromin was used throughout the trial. It was prepared in the laboratory of the Medical Department in Suva by Dr. Gosden for whose help in this connection we are greatly indebted. The material used was taken from patients in Makogai.

Progress of Patients

Skin smears were examined every three months but for convenience only those taken after each six-monthly course are recorded. A simple classification of bacteriological activity is used in Makogai and the records of each smear are recorded as follows:

— = No mycobacterium leprae found.

\+ = Up to 10 single bacilli in the whole slide.

\+\+ = Single bacilli in over 10 fields or more than 10 bacilli in the whole slide.

\+\+\+ = Small globi present and/or the bacilli being clumped.

\+\+\+\+ = The fields look red.

It is my experience that a more precise classification than this is both cumbersome and unnecessary. Improvement can be seen at a glance on this scale. Admittedly, a change from, say, 8 bacilli to 3 bacilli cannot be shown but this seems to me to be well within the limits of normal human error.

Clinical improvement was calculated by three-monthly physical examination though, again, only those remarks recorded after each course of antigen are shown.

The examination was entirely objective and included inspection of the whole body for skin lesions, palpation of all peripheral sensory and mixed nerves for thickening and tenderness and examination

for deformities or sensory or trophic changes. The patients were not asked whether they felt better and the findings recorded are entirely the examiner's opinion and not that of the examined.

After the trial was over, an assessment of the clinical and bacteriological state of the patients was made. Out of the 84 patients, 31% had been discharged, 43% were judged to have been improved and 26% were stationary or worse. The corresponding figures for the 21 controls were 19% discharged, 57% improved and 24% no better. If the discharged and improvements are combined, then 74% of those given the antigen were better in condition by the end of the trial. But the respective figure for the controls is 76%.

As the controls were rather worse than the test cases before the trial started, one would expect fewer of them to be discharged in the ordinary course of events and 19% of them to be discharged in proportion to 31% of the test cases seems, in my opinion, to be statistically unimportant.

Details of bacteriological and clinical progress of all 84 cases and 21 controls were recorded and are available.

Discussion

It is a matter open to some doubt as to whether it is possible to treat leprosy by the induction of an antibody response to a vaccine or an allergic response to an antigen.

As Muir (1948) says: "*M. leprae* meets with such tolerance in its host that it can multiply to astronomic numbers without producing recognisable symptoms. It would be surprising, therefore, if injection of a comparatively small additional number of such organisms could immunise a patient in whom the disease has already been firmly established," and the position does not appear to have changed during the ten years that have elapsed since these words were written.

Relvich, however, states that, in his opinion, on theoretical grounds, the idea behind the use of antigen for the treatment of lepromatous leprosy appears to be sound. Blanc merely assumes it to be self-evident that immunological treatment is not only effective but is to be preferred to chemotherapy.

The results we have obtained with *Antigen marianum* appear to me to leave no doubt that some immunological response has been obtained. The question then arises as to whether this response has done the patients any good and the only honest answer that can be given is in the negative.

Does merely converting a negative lepromin reaction into a positive one convert a case of lepromatous leprosy into a tuberculoid one? Muir says, "The difference between the tuberculoid and the lepromatous case is not just one of immunity. Nor can it be correct to say it is one of allergy alone. It appears rather that there

is an unknown factor. . . ." I contend that that factor is still unknown. I do not believe that we have converted lepromatous leprosy to tuberculoid and I do not know for how long these converted lepromin reactions are going to stay positive.

Even if it were possible to produce this change, it seems extremely doubtful as to whether it would be beneficial to the patient. In the pre-sulphone era it would, perhaps, have been justifiable to attempt artificially to convert lepromatous to tuberculoid. Nowadays, however, it is the experience of almost all leprologists that the lepromatous type of the disease responds more easily, more quickly and more completely to treatment. I think, therefore, that such antigens are probably not only not beneficial but may even be harmful.

The acid test is, of course, whether such immunised patients have, in fact, benefited from treatment and I think that this trial shows that they have not. It is too early to say whether the antigen has had any adverse effect on them and it is proposed to follow up this report with a further comparison after a year of their progress with that of the controls. Many of them carry unsightly scars as a result of the antigen which they would not otherwise have had.

SUMMARY

1. A three-year trial of *Antigen marianum* in the treatment of lepromatous leprosy was carried out on 84 patients. There were 21 controls who were picked retrospectively as the designated group of controls were given the antigen in error. All 105 patients were also on routine DDS.

2. Three six-monthly courses of one injection of antigen a month were given to 61 cases and two such courses to the other 23. There was a six-months' rest period between each course.

3. Before the trial 13% of the cases were lepromin positive. After the trial, the figure was 82.1%, and 57.7% of negative cases became positive after the first six months.

4. After the trial 31% of patients had been discharged, 43% were improved and 26% were stationary or worse. Corresponding figures for the controls were 19%, 57% and 24%. It is concluded that antigen marianum was of no value when given as an adjunct to DDS in the treatment of lepromatous leprosy.

ACKNOWLEDGMENTS

My thanks are due to the patients who took part so enthusiastically in the trial and also to the Sisters of the Staff of the Fiji Leprosy Hospital who were at all times of the utmost assistance. In particular, I should like to record my gratitude to Sister Mary Prisca, S.M.S.M., who conducted the trial and kept the records and to Sister Mary Kieran, S.M.S.M., and Sister Mary Alberta, S.M.S.M., who did all the tedious laboratory work so devotedly and so accurately.

I should also like to record our gratitude to the late Sister Mary Suzanne, S.M.S.M., who supplied us with generous quantities of the antigen and wrote us several long letters of advice as to procedure.

My thanks are also due to Dr. P. W. Dill-Russell, C.B.E., Director of Medical Services, Fiji, and Inspector-General, South Pacific Health Service, for permission to publish.

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THE INNERVATION OF THE HAND IN RELATION TO LEPROSY

E. W. PRICE, F.R.C.S.

Orthopaedic Surgeon to Leprosy Service, Eastern Nigeria.

An increasing number of workers in leprosy are studying the paralysis and anaesthesia of the hands with a view to rehabilitation. It is evident that the functional loss follows definite patterns, which reflect the lesion in the nerves; but the relation between functional loss and nerve lesion is less easy to define. It is common experience that two patients may present similar clinical abnormalities of the nerve on palpation (enlargement, hardness, tenderness) while one has notable, and the other minimal, functional disability.

Studies directed to elucidate this problem are important in so far as they enable us to form a prognosis of the functional loss, and whether or not surgical intervention is likely to be of benefit. The known facts are few concerning the natural history of nerve damage and its related functional loss (with, or without, adequate treatment), and the indications for surgical intervention to replace lost function are still indistinct.

Understanding of the natural history of nerve damage in leprosy depends on careful clinical observations of the extent and progress of muscle weakness and anaesthesia, and the relation to anatomical observations at operation or on biopsy. Such deductions depend on the anatomical link between muscle (or skin) and the nerve trunk, and in investigating this, it is important to keep in mind the common variations from the normal pattern or sensory and motor nerve supply. Only thus can false deductions be avoided.

Standard works of anatomy (Gray, Cunningham, Grant) do not give details of variations in nerve supply; and this paper summarises the recognised 'anomalies of innervation' for the convenience of workers in this relatively unexplored field.

Interest in the variations of nerve supply was aroused when it was noted (in military and civil accidents) that clinical deductions from damaged hands and forearms did not always correspond with the anatomical lesions seen at operation. It has been observed, for example, that full activity of all the intrinsic muscles of the hand can exist when the median nerve is known to be completely divided (Seddon 1954). Cases are reported (Murphy 1946) where a patient with a complete division of the ulnar nerve is able to extend his fingers completely.

Sensory variations appear to be less complete than motor, but also vary within noteworthy limits.

The practical importance of these variations is that loss of muscle power or anaesthesia of a given patch of skin, may represent a lesion in a nerve, different to that which 'normally' supplies it.

It is assumed that the investigator is aware of the various compensatory trick movements which replace loss of power in a given muscle or muscle group.

Anomalous Innervation and Nerve Shunting

The term *anomalous innervation* is used to describe the innervation of muscle or skin by a nerve bundle other than that described in standard text books of anatomy, and which remains associated with the parent nerve throughout its course; thus, the muscle Opponens pollicis may be supplied by a twig of the deep branch of the ulnar nerve.

The term *nerve shunting* is employed when the nerve bundle destined to innervate a given muscle or skin area is associated with one nerve above the elbow, but leaves that nerve below the elbow to travel down the forearm to its destination in association with another nerve. In this case, the innervation of a given structure will appear to be derived from the former nerve, if the lesion is above the elbow, or from the latter nerve if the lesion is below the elbow, e.g. at the wrist.

In view of the predilection of the leprosy lesion for the part of the ulnar nerve proximal to the elbow, and of the median nerve proximal to the wrist (Brand 1954), *the important nerve-shunt in leprosy* is that in which the nerve bundle leaves the ulnar nerve immediately below the elbow, and joins the median nerve in order to reach its destination; or leaves the median to join the ulnar nerve in the same region (Fig. 1). Cases of this type are described by Murphy (1946).

Shunting above the level of the upper arm is not under consideration, because leprous lesions causing clinical signs are rare above this level.

Murphy states that the only anatomical work found to describe branches between ulnar and median nerves is Poirier and Charpy's "Traite d'Anatomie Humaine", where anastomoses are described crossing from one nerve to the other between the superficial and deep layers of the flexor muscles in the upper forearm. Brash (1955) draws attention to various nerve shunts.

Therefore, the observation of weakness in a given muscle, or of anaesthesia in a given patch of skin may indicate one of the following possibilities:

(*a*) A lesion of the nerve which 'normally' supplies that structure.

(*b*) A lesion of a nerve, other than the 'normal' which is giving an anomalous supply.

(*c*) A lesion of a nerve bundle of the 'normal' nerve which has become involved in the lesion of a second nerve along which it is being shunted.

It must be borne in mind that continual overstretching will also cause weakness of a muscle.

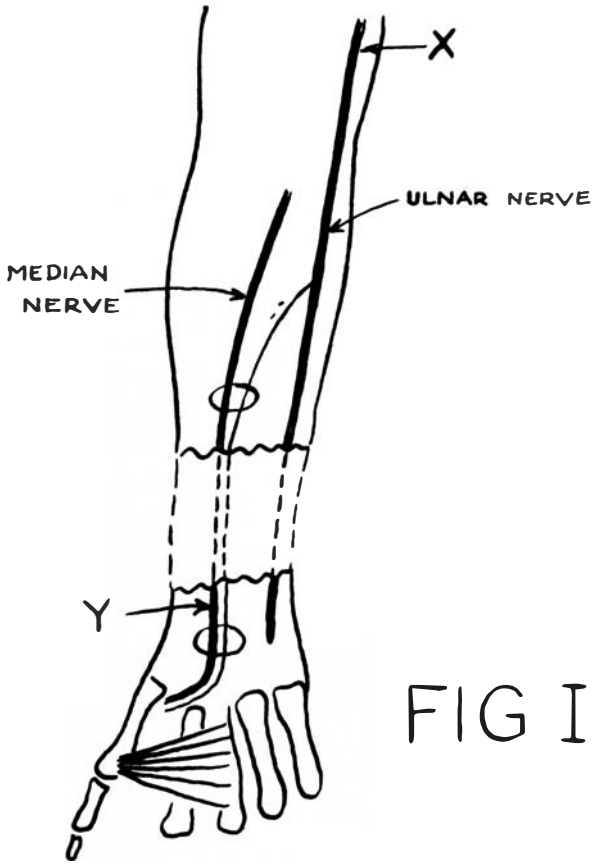


Fig. 1. *Nerve shunting in the Forearm.*

A nerve bundle leaves the ulnar nerve in the upper forearm to join the median nerve, which it accompanies to supply the thenar musculature. Paresis of the innervated muscle will be interpreted as due to a lesion of the ulnar nerve (if the lesion is at X) or of the median nerve (if at Y). In both places the nerve is commonly enlarged and tender in leprosy, but this abnormality does not necessarily imply any functional disability.

The 'Normal' Motor Innervation of the Hand and Forearm

If Flexor pollicis brevis is excluded, the classical innervation of the small muscles of the hand is such that the median nerve innervates the Abductor pollicis brevis, Opponens pollicis and the lateral two Lumbricals, and the ulnar nerve supplies the other intrinsic muscles of the hand. Flexor pollicis brevis is variably supplied by the ulnar nerve, or median nerve, or both (Fig. 2). This classical innervation is true in 80% of cases, but it must be realised that in a leprosarium of 1,000 patients, this means that no fewer than 400 hands will have a different innervation.

In the forearm, the ulnar nerve 'normally' supplies Flexor carpi ulnaris and the medial two bellies of Flexor digitorum profundus.

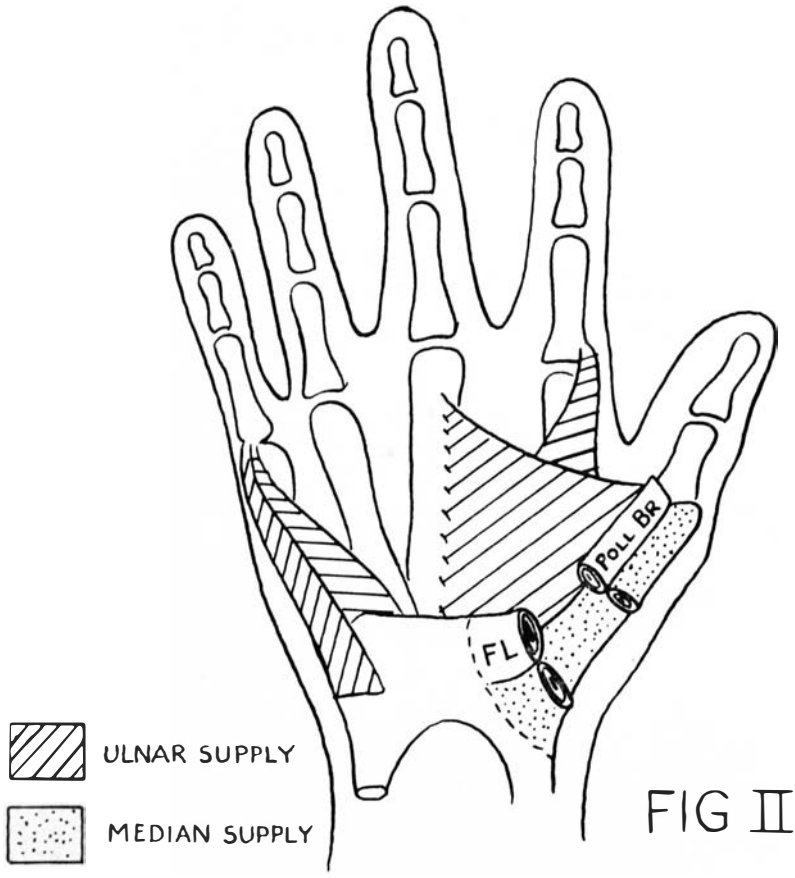


Fig. 2. The 'Normal' Innervation of the Muscles of the Hand.

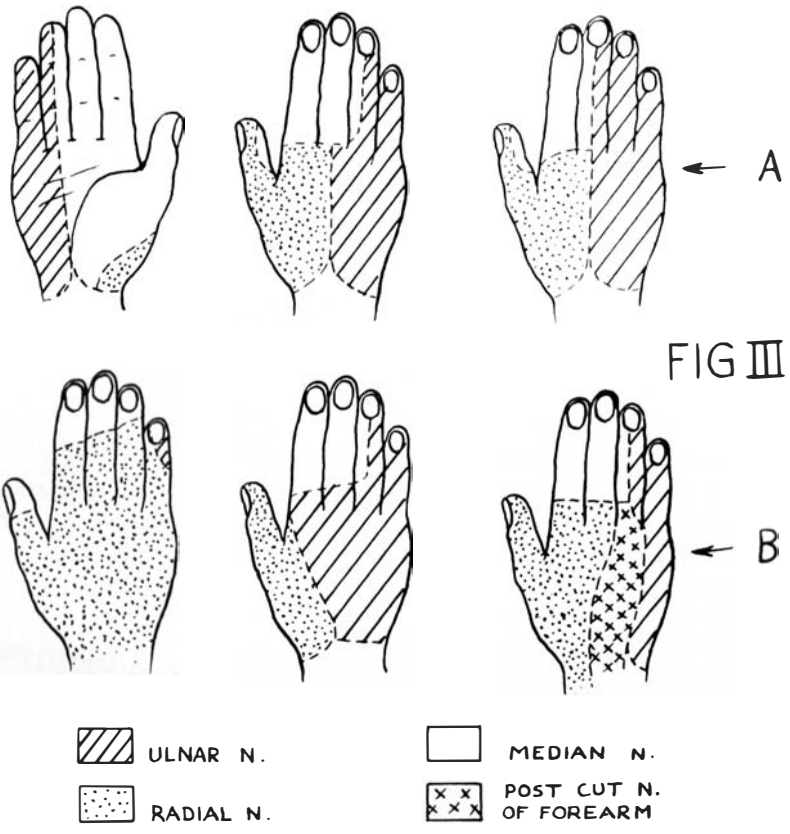
Excluding Flexor Pollicis Brevis, this is the innervation on 80% of hands. Of this group, Flexor Pollicis Brevis is supplied by the ulnar nerve in two-fifths of the the cases, by the median in two-fifths, and by both in the remaining one-fifth.

Anomalous Motor Innervations of Hand and Forearm

The anomalous motor innervations of the hand range from complete ulnar innervation to complete median innervation.

In the cases reported by the Medical Research Council (Seddon 1954), the thenar group were entirely supplied by the ulnar nerve in 2% of all cases (i.e. in 40 hands in a leprosarium of 1,000 patients), and entirely by the median in 3% (60 hands). In the latter group, a third of the cases (1%) showed median innervation of the first dorsal interosseus as well. In view of the frequency of wasting of this latter muscle in leprosy, it should be recalled that in only 20 hands in a leprosarium of 1,000 patients does wasting of this muscle represent other than an ulnar nerve lesion.

In the forearm, the innervation of Flexor digitorum profundus must be kept in mind, in view of its involvement in leprosy in one



(A) The 'normal' cutaneous innervation of the hand. Clinical experience indicates two patterns of innervation on the dorsum, as shown.

(B) Less common cutaneous innervations of the hand. It will be noted that the only area on the dorsum which is invariably supplied by the ulnar nerve is the medial half of the distal phalanx of the fifth finger; also, that the only area always supplied by the median nerve on the dorsum is the distal phalanx of the index and the lateral half of the distal phalanx of the long finger.

out of four or five cases of nerve damage in leprosy (Thomas 1954). There are several variations to the standard description, in which the portion of muscle which is motor to the fourth and fifth finger is supplied by the ulnar nerve. Ulnar innervation may extend to the belly for the long finger, especially when Flexor pollicis brevis is entirely supplied by the ulnar; but it has never been recorded as supplying the belly to the index finger. Median innervation has extended as far as the belly to the fifth finger, supplying in this case the whole muscle. Murphy claims that this is so common that it can hardly be claimed to be anomalous (see also Brash 1955).

The bellies to the third and fourth fingers often have a double median-ulnar innervation. It is evident that the only movement of Flexor digitorum profundus that can safely be taken to implicate a definite nerve is that of the index, of which weakness or loss of

distal interphalangeal flexion certainly indicates a median nerve lesion.

The 'Normal' Sensory Innervation of the Hand

There are two accounts of the 'normal' sensory innervation of the hand. In one account (Grant 1947), the ulnar nerve supplies the skin of the palmar and dorsal surfaces of the fifth finger, and the medial half of the fourth finger. In the other (Cunningham 1931), the ulnar nerve supplies the medial one and a half fingers on their palmar surface, but the medial two and a half on their dorsal surface. It is claimed that the latter is the commoner observation in clinical cases.

Anomalous Sensory Innervations of the Hand

In view of the significance of the sensory loss as an indication of nerve damage, it is unfortunate that no systematic account exists of the variations in sensory supply. Notable variations have been observed (Fig. 3) and it will be seen that the only area on the dorsum of the hand that is consistently supplied by the ulnar nerve is the medial half of the distal phalanx of the little finger. Similarly, the only dorsal area consistently supplied by the median nerve is the distal phalanx of the index and of the long finger.

The skin of the dorsal part of the hand has been reported (Grant 1947) as innervated by the dorsal cutaneous nerve of the forearm as far as the base of the fingers in one case.

Correlation of Sensory and Motor Innervation

No studies have been found in the literature correlating motor and sensory innervation of the hand.

The Return of Sensation to Denervated Skin

It is well known that skin which has become anaesthetic in the course of leprosy may wholly or partially recover sensation under treatment. It is assumed that function is restored in nerve fibres and end-organs that have not been irreparably damaged or atrophied in the course of the disease. While this will certainly be the case where recovery is fairly rapid, it is less likely to occur in cases where the loss has lasted for a long time. In these cases, the end-organs are likely to be atrophied beyond recovery. However, the fibrils serving the pain sense are not normally associated with end-organs, and return of pain sensation can be hoped for even where other functions are lost. The gain of pain sense will be important in the protection of the part against injury.

The only studies found in the literature concerning the regeneration of nerves in denervated skin concern that of the re-innervation of free skin-grafts. This is summarised by Padgett (1948) with

references. Although re-innervation is usually along the track of the original nerve fibrils, it has also been observed along the line of the original small blood and lymph vessels. This possibility must be kept in mind in cases of leprosy where the track of the original nerve fibrils is likely to be inhospitable to new fibrils.

The restoration of sensation will be due to one, or both, of two factors. Re-innervation or renewed function of the original nerve may be occurring; alternatively, diminution of the area of anaesthesia is possible by spread from surrounding areas where the nerves are still relatively healthy. In small areas, this latter phenomenon can completely re-innervate the skin. It is noted that renewed function due to renewal of the original nerve is likely to be observed by diminution of the area of sensory loss proximally and laterally. Spread from surrounding functioning nerves is more likely to be in progress if the gain in sensation occurs all round the area simultaneously.

SUMMARY

1. More information is urgently needed concerning the natural history of nerve-damage in leprosy, particularly under modern treatment.

2. Careful observation of loss of muscle power and skin sensation must take into consideration the recognised variations in nerve supply.

3. The commonly recognised variations of muscle and skin innervation in the hand are summarised.

* * * * *

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THE LEPROSY ENDEMIC IN NORTHERN RHODESIA WITH SPECIAL REFERENCE TO SEX INCIDENCE

DR. J. T. WORSFOLD

Chitokoloki, Balovale, Northern Rhodesia

The author's recent survey, 1957, in 'Lovaleland', which is the Balovale District of Northern Rhodesia,[1] revealed the progress of the leprosy endemic and some interesting data of sex incidence. This area long has been considered as of high leprosy prevalence. By analogy with other areas, this is not surprising, for it is an undeveloped area in the Zambesi basin and public health measures have not developed far: its general leprosy incidence is 11.85 per thousand. This was the first intensive leprosy survey in Northern Rhodesia. In 1950, Ross Innes did a sampling survey of certain areas which did not include the Western Province nor Balovale.[2] In 1932, Cochrane[3] had stated that the country had 10 per thousand of leprosy in parts of it. The Northern Rhodesian Medical Report for 1934 stated that 169 cases of leprosy were notified during the year and that Balovale was the most infected area, with 82 cases notified out of the 10 places mentioned. Muir[4] visited the country in 1939 and singled out Barotseland and Balovale, in particular, as having the highest incidence, and commented that the work of the small leprosy institutions which existed were of little value for the ultimate control of the disease, though noble relief work was done in them. In the 19 years elapsed since this opinion was given, its accuracy does not appear to have changed, for in 1949, the medical officer at Balovale described the very high incidence in that district (personal communication). The survey by Ross Innes[2] showed an average prevalence of 12.6 per thousand for the areas he visited in the Eastern, Southern, and Northern Provinces: the greatest prevalence was 25.6 per thousand on the Luapula River in the Northern Province. In comparison with the present author's findings in the Balovale District, he found a sex rate of 62.2, a childhood rate of 18.4, and a lepromatous case rate of 20.4 per cent (Balovale figures were 44.6, 2.5, and 23.75 per cent respectively). He concluded that: "Northern Rhodesian Leprosy is very much alive, and is slowly and surely increasing."

The present author's Balovale survey of 1957 indicates that a decline in prevalence may have set in, and he agrees with the opinion of Cochrane[5] that predisposing diseases and a lowered state of health have been overrated as epidemiological factors. There was also nothing to suggest any high contagion in leprosy and there was only one case of possible conjugal contagion. It was found that out of 234 adult leprosy cases, 119 were living with an uninfected

husband or wife, even though 21 cases were lepromatous, which hints at low grade infectivity even of lepromatous leprosy and brings in the importance of infection in childhood. The familial source of the infection was indicated in that 66.25 per cent of all cases admitted having a near relative with the disease; prolonged and close contact was probable and most acquired the infection before puberty. After puberty, every person marries and leaves the original house and often the village. Though a case presenting with leprosy may have had no contact with the infected relative for 10 to 20 years, there is a strong presumption that the relative was the essential source of the infection. Each successive age group shows a steadily rising prevalence. Therefore, it does seem as if in many cases leprosy is acquired in early life but does not become clinical until later life, i.e., there is a long *latent period*. The form of resistance in the patient which keeps the disease subclinical for years may be part of the immunological state of the population, but we do not know what causes the breakdown in resistance which leads to the clinical appearance of the disease. There is markedly less leprosy in the lower age groups, parallel with the absence of any decline in population in those age groups, which further suggests that the general incidence of leprosy may be tending to fall in this region. Further support for this is the finding in the Balovale survey of an increase in the average age of onset, which as Doull[6] pointed out occurs when the disease declines, even though leprosy is commonly contracted in childhood.

The *sex prevalence* of leprosy is accepted in most text books as 2 : 1 in favour of males. In 1934, Lowe ([7, 8]) made an exhaustive survey of the literature and found that so it was reported for most countries of high prevalence, though in countries of low prevalence, the females exceeded the males. Since Lowe made this review, Doull,[6] Hopkins,[9] Chaussinand,[10] Strong,[11] Romero,[12] Gehr,[13] and Arnold,[14] and others arrived at the same broad conclusion and most of them attributed the sex difference to inherent female characteristics rather than to environmental influences.

Institutional sex rate figures for neighbouring territories are 63.19 for *South Africa*, based on 1,020 males and 594 females in the four institutions, as given by Davison, A. R. in a personal communication; 64.40 for *Southern Rhodesia*, based on 713 males and 393 females in Ngomahuru, as given by Mostert in a personal communication; 58.60 for *Nyasaland*, based on 2,029 males and 1,433 females in five institutions, as given by Currie in a personal communication. For *Northern Rhodesia*, Ross Innes gave 62.2 sex rate for the three provinces of the East, South, and North: this rate does not have an institutional basis. The present author's Balovale survey in the Western section of Northern Rhodesia revealed the low sex rate of 44.6.

In this region it is likely that we see a fairly true picture of the prevalence of the disease, as leprosy work has been going on a long time and there is no evidence of a tendency to concealment of cases. Certain special factors operate in the other areas, such as compulsory segregation in South Africa, migration of males for labour from the north to Southern Rhodesia, and to the south from Northern Rhodesia and Nyasaland. There may not be much significance in this migration of males as a medical certificate must be obtained before they leave for work.

Cochrane[3] on the basis of the observations of Sharma thought that sex incidence may be more important than any other factor for the purpose of estimating the state of a leprosy endemic, but said that the endemic may be on the increase when the preponderance of males is reduced. Our findings suggest that the endemic may be declining when females preponderate. Both these propositions may have validity in the sense that an early reduction in the preponderance of males may indicate a temporary increase in the endemic which ushers in a general decline. This may be just what we are observing here in this region. Our figures from Chitokoloki Leprosarium are also of interest since it receives patients from a wider field than Lovaleland, and some patients come from over 1,000 miles away.

SEX PREVALENCE OF ALL RECORDED PATIENTS 1930–1958 AT CHITOKOLOKI LEPROSARIUM

	Males	*Females*
Present inpatients	86	98
Present outpatients	104	150
Former patients	1,189	1,325
Rehabilitation villages ...	128	143
Outpatients in districts ...	238	565
	1,745	2,281
Total patients: 4,026.	Sex Rate: 43.3	

The high female leprosy prevalence rate, therefore, damages the concept of a universal male preponderance, though it may be true for most countries. We think that in Africa the movement of peoples from primitive conditions towards civilization brings them through a stage of susceptibility to leprosy and possibly an early male preponderance in incidence because the males make the first steps. With the later inevitable dissolution of tribal disciplines, the more conservative females enter more into the prevalence of leprosy, and changes in domestic and economic conditions are more potent in this respect than any postulated sex differences in susceptibility. In this part of Northern Rhodesia, there is not the Islamic influence on the degree and rate of the emancipation of women. Their pro-

gressive freedom in social contacts goes on steadily, together with participation in all the civilized benefits of health, hygiene, and housing, and leads to the paradox, in one stage at least, of participation in a heavier leprosy incidence. Their growing freedom includes a freedom to acquire leprosy. Later, there should follow a fall in the total incidence, in which females would share, and final eradication would become possible. The Lovaleland findings do suggest that the idea of an inherent lesser susceptibility of the female requires some modification. Any protection against other diseases by the female endocrine functions is also disputable: in these diseases also social and environmental influences are probably much more important.

Kerr as quoted by Tolentino[15] said that the women and men are equally affected by leprosy, provided the chances are equal. Muir ([16, 17]) and several other authors record areas with an excess of females in leprosy. Davey also from his experiences in Nigeria affirmed in a personal communication that the sexes are affected about equally and that he had never found anything comparable to the 2 : 1 sex ratio. Manson Bahr[18] stated that sex seemed to have little bearing on the liability to leprosy.

Reverting to the Chitokoloki figures previously given in this paper, the preponderance of females is clear in all the groups given, but there is evidence that it co-exists with a decline in the incidence of leprosy, such as the very low childhood rate and clinical features which include lesser incidence of lepra fever, nerve abscesses, and acute leprous eye conditions. Furthermore, there is a high percentage of residual cases, which strongly suggests a previous rise in total prevalence followed now by a decline.

The decline of the leprosy endemics in Norway and England has been ascribed to effective segregation and improved hygienic conditions, one or both with differing emphasis, and both these factors have been in operation in Lovaleland, and it seems possible that the next few years will witness a rapid decline in the prevalence of leprosy. If this proves to be true, there will be a temptation to give the whole credit to the sulphones but there is much evidence that the decline had set in before sulphone therapy was introduced in Northern Rhodesia in 1950. There is no doubt that this therapy is hastening greatly the complete control and final extinction of leprosy.

Summary

The author in 1957 completed the first intensive survey in Northern Rhodesia, in the Balovale District which lies in the Zambesi basin. He found an incidence of 11.85 per thousand. Previous wider but more cursive surveys were those of Cochrane in 1932, who estimated 10 per thousand for parts of the country and Ross Innes

in 1950, who sampled the Eastern, Northern, and Southern Provinces and found an average of 12.6 per thousand. The recent Balovale survey of the author indicated that a decline in prevalence may have set in, and showed a clear preponderance of female sex incidence, which the author thinks is more rooted in social and environmental factors than anything inherent in the female, and may be a stage leading to a decline in the endemic. The stage of an early male preponderance may have been passed through already. Other authors are quoted in support of the view that the male sex preponderance is by no means universal, and there is no essential inherent sex difference in the reaction to leprosy. The author describes a decline in leprosy prevalence in his area which began before the sulphone therapy and which is likely to go on and be greatly hastened by it.

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CLINICAL OBSERVATIONS ON ERYTHEMA NODOSUM LEPROSUM (E.N.L.)

DR. I. A. SUSMAN

Medical Officer, Ghana Leprosy Service

These were made from the records of this phenomenon of recurring evanescent nodules of the skin in the case of 328 lepromatous patients in Ankaful Leprosarium (admitted between 1952 and 1958) as follows:

	Total No.	*No. with E.N.L.*	*% with E.N.L.*
Men	220	120	54
Women	55	32	58
Children (up to 16 years) ...	53	22	41
	328	174	53

The nodules were sometimes the exacerbation of existing lesions, or sometimes the eruption of fresh lesions. The nodules themselves varied from about the size of a pea to about the size of a shilling, and they were usually tender on pressure.

Ankaful Leprosarium is the headquarters of the Ghana Leprosy Service and is situated 6 miles from the coast and is 100 miles west of Accra. It admits primarily the contagious types from throughout the length and breadth of Ghana, the larger proportion of patients originating from the Northern Region.

1. There occurred 906 reactions of E.N.L. in these 174 patients, the maximum number in one patient being 31 (during a four-year period); 51 patients had only one reaction, 29 had two, 24 had three, 10 had four, 5 had nine, 6 had six and 45 had more than six reactions.

2. Generally the E.N.L. was accompanied by pain. Often the eruption was localised, e.g. to the face or to one limb and often it was associated with ulnar or peroneal neuritis. Sometimes it was accompanied by bone or joint pains.

3. Fifty-one patients (29%) invariably developed a pyrexia (99°—101°F.) with each attack of E.N.L. and the rest (123 = 71%) were invariably apyrexial with each attack.

4. There was no concurrent disease apparent in 845 of the reactions but 31 were definitely suffering from ankylostomiasis, ascariasis, or taeniasis at the time of the reaction, 26 had very positive blood films for malarial parasites and 4 had other infections (furunculosis, tonsillitis, varicella, infected ulcer with acute lym-

phadenitis). Patients of good physique and nutrition appeared to be affected equally with the weak and undernourished.

5. A cyclical occurrence of E.N.L. was observed in most patients, e.g. monthly, three monthly, or six monthly, in both the male and female patients. It was unusual for the reaction to occur more than once a month and in any case, separate attacks were never recorded more than twice in a month. The frequency of attacks was apparently slightly diminished usually with the length of treatment. Patients who developed E.N.L. in the later stages of treatment appeared to have less frequent attacks than those who were affected by reactions in the early stages of treatment.

6. The phenomenon of E.N.L. occurred especially in patients with a high bacterial index initially, those with a low bacterial index being less prone to E.N.L. Apparently those with repeated reactions took a long time to become bacteriologically negative.

7. No relationship was observed between the reaction and the anti-leprosy drug used, that is, E.N.L. occurred with equal frequency in cases treated with DDS, sulphetrone or thiacetazone. A change of drug during treatment did not appear to alter the E.N.L. rate.

8. A definite elevation of the erythrocyte sedimentation rate occurred in 405 (45%) of the 906 reactions, and did not correspond with the cases showing a pyrexia.

9. No definite correlation was found between the stage in treatment and the frequency of E.N.L. Some patients showed E.N.L. in the middle stage of treatment only, especially when the bacterial index was still high; a few patients showed no E.N.L. at the commencement of treatment but did so only after two to three years had elapsed.

10. Out of the total number of 906 reactions, 471 (52%) occurred between March and August (inclusive)—the 'wet season', and 435 (48%) between September and February (inclusive)—the 'dry season'.

11. The treatment of E.N.L. with Stibophen is only palliative and does not prevent recurrences. A.C.T.H. (Cortrophin) in doses of 25 i.u., given intra-muscularly, for adults, was administered in severe cases or those which did not respond to Stibophen, etc., and with dramatic improvement after only two or three injections. Generally, treatment with A.C.T.H. was not found necessary to be continued for longer than 3—10 days, the dosage being gradually reduced.

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APPENDIX I

OBSERVATIONS ON SMEARS

It has been stated by several authorities and can still be read in text-books that the skin of the buttocks is frequently bacteriologically positive and may remain so after all other lesions have become negative. The following observations, however, do not support this statement.

The following are the results of routine smears (monthly and diagnostic) for all patients resident in Ankaful Leprosarium, Ghana, during the past nine months, the average number of lepromatous/non-lepromatous being 370/80. The smears were taken from both ear lobes, both nostrils, one skin site and one buttock site.

Total smears = 3,143:

1. All negative	= 1,095	= 35%
2. All positive	= 886	= 28%
3. Ears (one or both) only positive	= 723	= 23%
4. Some positive, buttocks positive	= 206	= 6.5%
5. Some positive, buttocks negative... ...	= 130	= 4%
6. Ears and buttocks only positive	= 72	= 2.5%
7. All positive but buttocks negative ...	= 28	= 0.9%
8. All negative but buttocks positive ...	= 3	= 0.1%
9. Total number of cases in which buttock smears positive	= 1,167	= 37%

Thus in only 0.1% of smears taken were the buttocks positive when all other sites were negative.

In only 37% were the buttocks smears positive, the great majority of which also showed other positive sites.

The ears gave the largest number of positive results (over 54%) and were the *only* positive sites in 23% of cases.

In 28% of the total smears, positives were obtained for all six sites.

APPENDIX II

STATISTICS

The following graphs are compiled from the Ghana Leprosy Service statistics for the year ending December 31st, 1957. The total number of patients under treatment was 29,606. Patients are classified as boys or girls up to and including 16 years of age.

It can be seen from the graphs that:

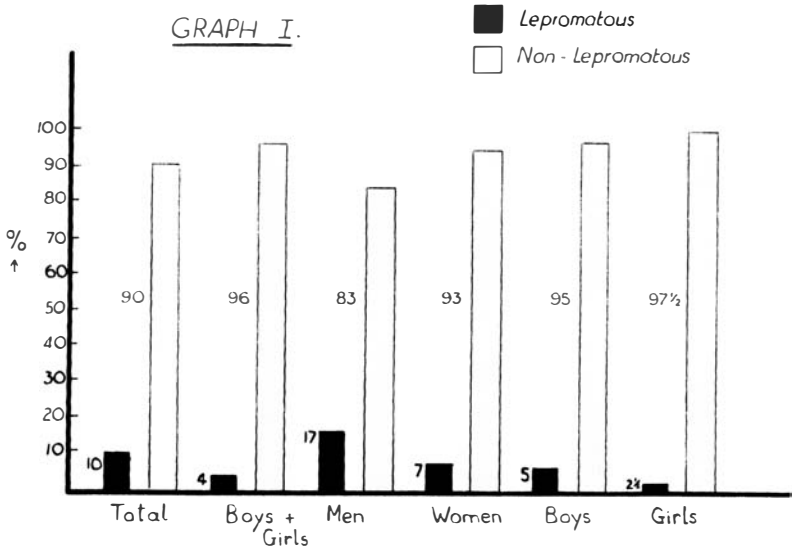
1. The ratio of lepromatous/non-lepromatous is approximately in the same region in any group, the ratio for the totals being 10/90. Actually, the ratio is somewhat lower (4/96) in the children than in the men (17/83) or women (7/93) indicating that the disease is relatively mild and probably not progressive.

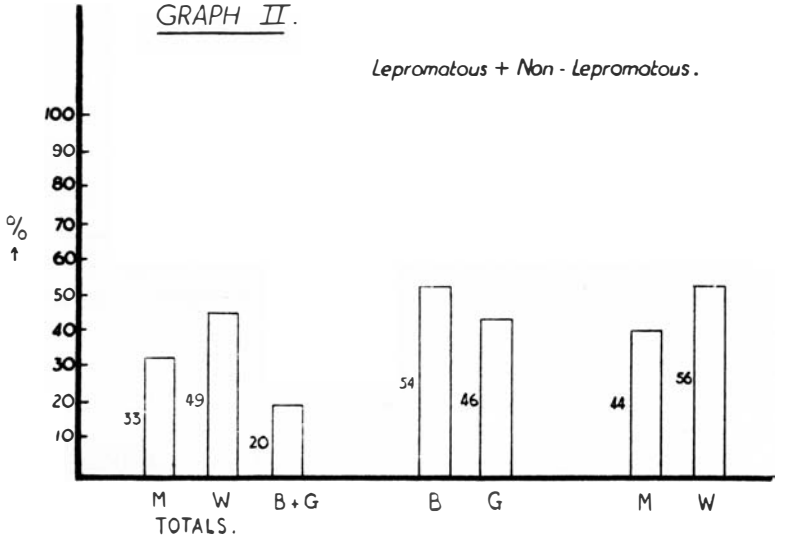
2. Although a larger proportion of women are under treatment, a slightly higher percentage of the children are boys. Usually, the disease has a higher incidence in males, especially adults.

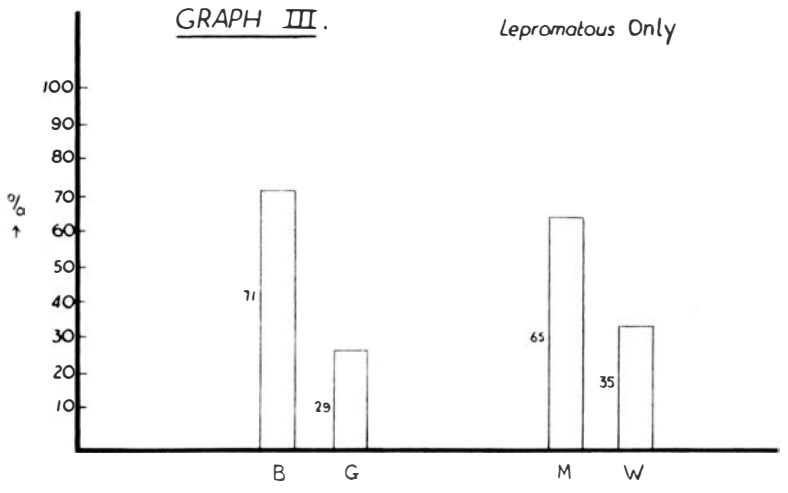
3. Of the lepromatous patients, the ratio of boys/girls is approximately that of the ratio of men/women.

4. Of the non-lepromatous patients there are more women than men in approximately the same ratio as there are more boys than girls.

5. Although there are more women under treatment than men a larger proportion of the lepromatous patients are men. However, although there are more boys under treatment than girls, a much higher percentage of the lepromatous children are boys. The females thus generally have the milder form of the disease.






GRAPH III.
Lepromatous Only
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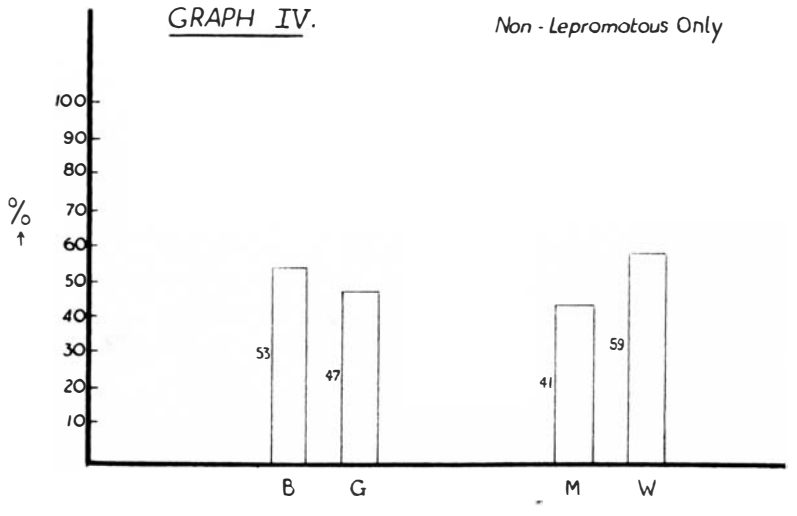
GRAPH IV.
Non - Lepromatous Only
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59
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ABSTRACTS

Transmission of M. leprae to selected hybrid black mice and Syrian hamsters. **K. R. Chatterjee.** Bull. Calcutta Sch. of Trop. Med. **6,** 2: April, 1958, pp. 83–87.

Two varieties of animals were chosen for the transmission experiment: one was a new type, the hybrid black mouse bred in the institute, and the other was the Syrian hamster bred in the laboratory. The age at inoculation was 12–20 days or three to six weeks for black mice and hamsters respectively, and the inoculum consisted of human leprosy bacilli which had been made tissue-free by differential centrifugalisation and diluted in physiological saline to contain a known number of bacilli per ml. The dose was about 1,000 million bacilli for black mouse and 3,000 million for hamster. Six to eight months after inoculation the infection developed and went on to heavy and generalised infection in the black mice, transmissible by inoculation to mice and hamsters. Intradermal injection of a lepromin made from the transmitted bacilli gave very similar results to standard lepromin. The author thinks the success of this animal transmission is due to the use of an inoculum of bacilli freed from tissue elements and to the choice of a new animal, the hybrid black mouse.

Treatment of Leprosy by Cycloserine and Treatment of Lepra Reactions by SLF. Rapport Annuel (1957), Institut Pasteur du Viet-Nam, pp. 18–19.

Chambon reports on his observations of D-Cycloserine used in six cases of lepromatous leprosy and one reactional tuberculoid. It has a great degree of activity on the lesions and also on the bacillary counts, which become negative in three months in the nasal mucosa and about eight months in the skin. The dosage used was 15 days at 0.25 g., 15 days at 0.50 g., later 0.75 g. For prevention of reaction states the anti-inflammatory drugs were given from the beginning, namely phenylbutazone, SLF (phenylbutazone with INH), or hydrocortancyl. Chambon and Destombes think that Cycloserine is the most active antileprosy drug so far.

Previa Sobre Terapeutica da Lepra (*Preliminary note on treatment of leprosy*), **A. O. Gonzalez,** Revista da Conf. Med. Panamericana, **4,** 1957, p. 454.

Dr. Gonzalez reported on his experiences with a new treatment of leprosy based on a new theory. This theory has the following lines of reasoning: Iodine and its derivatives are particularly harmful to the leprosy patient; leprosy worsens during pregnancy in a female patient but improves after the birth and during lactation; there is a marked increase in endogenous iodine during pregnancy and a decrease after the birth when the milk secretion begins; non-

saturated fatty acids have a special ability to absorb iodine; an excessive intake of fatty acids predisposes to the development of parotitis; hydnocarpus oil is a fatty acid which held a place for many years as the best treatment for leprosy; one theory of its action is that it fixed iodine because it was a fatty acid and led to a lessening of iodine content of the blood, such as is seen in the lactation period of a female leprosy patient after pregnancy; some workers report the infrequency of coincident leprosy and hypothyroid colloid parotitis (Dr. R. Serpa says they never occur together) and in a region of Palmira where parotitis is common it is reported that for the last twenty years no leprosy has been seen in a parotitis case (records of the Cali dispensary).

Accordingly in the treatment of leprosy Dr. Gonzalez has been using the sulphones along with anti-thyroid agents such as thiouracil and propylthiouracil, in moderate doses in all cases. He found that the lesions regressed rapidly, that toxic phenomena ascribable to the sulphones were minimal, that lepra reactions were benign and less frequent. He thinks the idea is worth further trial and verification.

Experimental Transmission of Murine Leprosy to the Guinea-Pig by means of induced macrophage exudate and suppression of the Natural Defence Mechanism. **L. Kato,** Int. J. of L., **25** ,3, July-Sept. 1957, pp. 193–205.

By inducing a macrophage exudate in the peritoneal cavity of the guinea-pig before intraperitoneal injection of the infective homogenized suspension, and the simultaneous suppression of natural resistance with the antihistaminic mepyramine maleate or a complement-inhibiting compound, much granulomata developed after eight weeks in the peritoneal cavities. From these granulomata, the infection was transmitted successfully to sub-generations of guinea-pigs and could be transmitted back again into the rat, signifying that *M. lepraemurium* retained its infectiousness in the resistant host. The histology of the rat and guinea-pig granuloma was essentially the same, and the tissue gives a strong positive reaction to the tetrazolium test. Hanks considers extracellular inhibitors to be a barrier to experimental transmission and the above experimental method permits the parasite to escape this action.

The Isopathic Reaction in Leprosy. **E. Waaler,** Int. J. of L., **25,** 3, July–Sept. 1957, pp. 207–212.

This author describes an experimental approach to the isopathic reaction as described by Sagher. Editorial reference by Wade to this phenomenon is given in the same issue. (Int. J. of L., **25,** 3, July–Sept. 1957, pp. 263–268.) Waaler made histological study of the reactions to tuberculin in four leprosy patients, and found that

from two of these patients, the specimens showed the typical isopathic phenomenon. The picture was like that of a leproma, with nodules or clumps of foamy cells. In the other two patients, the tissue reaction was not characteristic. The author thinks that the phenomenon is caused by an acquired reactivity of the skin in leprosy. He tried to induce the reaction in his own skin by adding a suspension of skin from one of the leprosy patients to tuberculin and injecting the mixture intradermally. The result did not show passive transfer of the isopathic reactivity; therefore it appears to depend upon the living cells. Wade in his editorial on the subject takes up many interesting lines of thought which should be considered carefully. He indicates finally that the evidence that there is a fundamental alteration in the tissue activity in lepromatous leprosy which impedes the lepromatous change should be explored as a problem for basic research in cell histology. He reports that Dr. R. Kooij has suggested that workers who take up the study of this phenomenon should co-ordinate the excitants, the time intervals after injection, and the same histological methods and criteria.

The Chemotherapy of Leprosy, **S. R. M. Bushby,** Pharmacological Reviews, **10,** No. 1, March 1958, pp. 1–41.

Dr. Bushby gives a systematic account of the treatment of leprosy by chemotherapy to the present era of the sulphones and cortisone, and discusses also combined therapy, controlled clinical trials, BCG, and the propagation of *M. leprae.* He recognizes the profound effect that chemotherapy has brought to the prognosis in leprosy and points out, as the unsatisfactory aspect of the present treatment, the length of time needed to produce a clinical cure and the final eradication of the bacilli of the disease. A lepromatous patient has a 40% chance of arrest of his disease after eight years of continuous sulphone treatment (Wolcott 1956). Dr. Bushby goes on to discuss the provocative remarks of Ross Innes (1955) which requested a search for drugs of greater speed and efficacy and the replies from Lowe and Wade. Dr. Bushby's paper contains much else of great interest and importance and its careful study is recommended.

Le Mycobacterium Marianum. Etude microbiologique, pathogénétique et immunologique. (*Study of the M. marianum.*) **G. Penso, R. Noel, M. Blanc, Soeur Marie-Suzanne.** Accademia Nazionale Dei XL, Rome 1957.

This report contains 76 pages with 66 illustrations, 36 of which are in colour. All close studies of mycobacteria are of importance to leprosy workers. In 1953, Penso suggested the name "Mycobacterium marianum" in honour of Sister Marie-Suzanne for the mycobacterium which she had isolated in 1951 from a case of

human lepromatous leprosy. The authors have made a careful study in the microbiology, pathogenesis and immunology of *M. marianum.* They concluded that it is different from other known mycobacteria and definitely belongs to them. Some authors have suggested that it should be placed in the ill-defined group of paratuberculous bacilli, but the present authors find this term too vague to be useful. The species *M. marianum* is not a saprophyte because it was isolated from human leprosy tissue. It is pathogenic, for on inoculation into susceptible animals, it caused lesions with a definite pathology and histology. Furthermore, it has been shown to have a metabolism similar to other mycobacteria which are definitely pathogenic. The connection between *M. marianum* and leprosy is shown by the fact of its isolation from deep tissues of a human leprosy case; the authors do not think that there was any chance of contamination. It is not clear whether *M. marianum* is part of the cause of leprosy or whether it is a variant and bye-product. The cultivability of this bacillus does seem to set it apart from *M. leprae*; the lesions which it causes in rats on inoculation appear to be true rat leprosy lesions. The fact that it causes local and general reactions on inoculation into human subjects indicates that it must have some meaning in the pathogenesis of leprosy and in its immunology. Many trials are in progress to test the early reports of the preventive and curative action of the antigens of *M. marianum*, when given by inoculation as a vaccine.

El Camoquin en el Brote Agudo de Lepra (*Camoquin in acute lepra reaction*). **D. A. Casals,** Revista de Sifil. Leprol. y Dermatol., Cuba, 13th Year, No. 1, Jan. to June 1957, pp. 19–21.

They previously reported their experience with two cases on this drug, and now report ten more cases. Among the many methods, they thought cortisone was the best, but the intense and resistant relapses, after cortisone was suspended, made them think again. In 1955, González Prendes, Valhuerdi and Cruz reported favourably on atebrine. Other authors have supported this and point out that it is well tolerated, is most effective in the big febrile reactions, favours the healing of the reactive lesions proper, succeeds in cases which have resisted other drugs, has the advantage of administration by mouth. The present authors used camoquin and obtained the same encouraging results. They gave two tablets of 0.20 g. daily for five to seven days. They point out its beneficial action also in lupus erythematosus and other dermatoses and suggest it has a non-specific action on tissues. The generally capricious behaviour of acute lepra reaction impedes absolute certainty about the efficacy of any agent.

REPORTS

The Leprosy Research Fund

The objects and achievements of this fund are described by Dr. R. G. Cochrane. The headquarters of Dr. Cochrane and of the Leprosy Research Fund (LRF for short) are at 11A Weymouth Street, London, W.1, England.

In 1953 the American Leprosy Missions appointed Dr. Cochrane as their technical medical adviser, wisely giving him full freedom to develop his lines of investigation and the stimulus to and aid for research in leprosy by other workers. From this the LRF and its beneficial activities have grown. One of the contentions by Dr. Cochrane was that leprosy research could enrich the basic knowledge in other diseases and branches of science, and in this he was proved correct.

The first financial grant for the LRF came from the American Leprosy Missions, and later the Wellcome Foundation granted £500 for three years because of their interest in the histology section of the programme, and by October 1953 the LRF came into being in 11A Weymouth Street, under the administration of a committee under the Chairmanship of Dr. W. A. R. Thomson (a joint editor of *The Practitioner*). The LRF does not aim to raise public subscriptions nor to finance large long term research projects. Its limited resources are used to stimulate pilot research projects and enquiries, and to assess the probable value of such approaches to basic research problems, as well as in new therapeutics. For practical early therapeutic trials of new drugs there is the norm of efficiency of the sulphones for comparison, few cases are necessary, and proved lepromatous leprosy cases are the most informative, and efficient pilot trials can save a lot of money later. The LRF is in touch with a large number of leprosaria throughout the world and finds ready co-operation in arranging such pilot therapeutic trials.

Some interesting activities of the LRF are as follows. Dr. V. R. Khanolkhar, Director of the Indian Cancer Centre in Bombay, by 1954 had re-focused attention on the histopathology of early lesions in leprosy, especially in regard to the cutaneous nerves. The LRF helped Dr. A. G. M. Weddell (Reader in Human Anatomy, University of Oxford) to visit India to study cutaneous sensibility in relation to leprosy, with results which advance our knowledge of cutaneous sensibility as well as of leprosy. As a direct result of Dr. Weddell's work, Dr. D. G. Jamison (Lecturer in Physiology, Corpus Christi, Oxford) was appointed to a research fellowship sponsored by the Royal Society, and in company with Dr. Cochrane visited Nigeria, January to March 1957, and collected material. This visit was under the auspices of the Colonial Medical Research Committee, and the subsequent studies promise to advance knowledge of the

histopathology of leprosy and in particular of the path of invasion and evolution of the disease.

The electronmicroscopic studies of *M. leprae* since 1955 by Dr. E. M. Brieger of the Strangeways Laboratories, Cambridge, were likewise fostered and financed by the LRF. He visited and obtained material from Oicha Leprosarium in the Belgian Congo. This fruitful work of Dr. Brieger and colleagues has been further supported by a two-year grant from the C.M.R.C.

Similarly in 1956 Dr. S. W. A. Kuper (Consultant in Clinical Pathology at the Brompton Hospital, London) visited Westfort Institution, South Africa, and obtained material for a detailed study of the lepromin test, and his journey was financed by the LRF. A second visit was made in 1957.

Dr. John Hanks, Bacteriologist to the American Leprosy Foundation, visited London in 1955, and the LRF had some hand in arranging this.

Because of Dr. Cochrane's long continued interest in the histopathology of leprosy, the LRF is particularly well equipped with histological slides and specimens, and clinical photographs. It has been a natural step therefore for Dr. Cochrane to suggest that a formal registry now be developed: the cost of the improvements and staff and running costs for such a registry is estimated to be £2,300 per annum. Dr. Cochrane emphasizes that the LRF is itself a pilot organization and would cheerfully disappear if some larger body took over or absorbed its functions, or independently organized itself to perform similar functions.

The 83rd Annual Report of the Mission to Lepers deals with the year 1957, and reveals a far-flung assistance to leprosy work in many countries, based on a total ordinary income of £355,680 from the free donations of the people of Great Britain and other countries. Medical statistics give some idea of this magnificent work. From 89 of the Mission's own or aided leprosaria in India, Africa and the Far East, 18,899 patients had received treatment, and of these 3,488 had progressed to the arrest of the disease (1,844 without deformity). In addition, 6,582 were much improved and it had been suitable to discharge 1,401 of these. The disease had become stationary in a further 1,409 patients. The outpatients brought under treatment numbered 38,840 and of these 3,155 had become 'arrested' and 14,604 had received some degree of improvement.

Lecture by Mr. Paul W. Brand, M.B., F.R.C.S., on Reconstructive Surgery in Leprosy. (Reported by Dr. J. Ross Innes, who was present.)

Mr. Brand is Director of Orthopaedic Work of the Mission to Lepers and is stationed in Vellore, South India. On the 18th

June, 1958, under the auspices of the Mission to Lepers and the Friends of Vellore, he lectured on reconstructive surgery in the Royal Society of Medicine, under the chairmanship of Professor H. J. Seddon, C.M.G., of the Institute of Orthopaedics.

Mr. Brand said that proper understanding of the nature of the deformity in leprosy is vital. Eleven years ago, he tried to find out why leprosy eats away tissues in hands and feet, and by studying 2,000 hands found that leprosy destroyed only digits and did that in two different ways: (*a*) by the direct activity of leprosy and (*b*) by the effect of trauma, sepsis, and burns on digits rendered anaesthetic by the leprosy. In the history of the loss of their digits, patients recalled early incidents which suggested that their loss was always due to a secondary trauma. Peculiar to leprosy among the diseases which produce granulation tissue is the great tendency to the loss and destruction of fibres. In other diseases, the part attacked by the morbid process is carefully protected, but not so in leprosy, and the loss of tissue goes on unchecked. The introduction of protection to the hands and feet in leprosy is entirely successful, even in cases where the nerves have been grossly damaged. There is no doubt that the leprosy patient uses the hand too freely and carelessly, and the blisters which appear are *not* typical of uncomplicated leprosy but of unregarded trauma. Mr. Brand checked this in a clinical experiment designed to avert trauma by splintings and dressings and general watchfulness. It was found that in 15 men after five years, only two had lost any length of finger because of associated septic infection. Special care will prevent the loss of segments of fingers. The chief causes of loss of the bones of the hand are the continuation of the use of the hand after minor injury and infection, too vigorous use of the hand at any time, or lepra reaction which tends to set up osteoporosis. The control of the force of natural movements of the hands and feet was previously thought to be due to control exerted in the muscle spindles, but it has been shown that it is almost entirely controlled by the skin reflexes. Anaesthesia of the skin of the hand abolishes or damages the pressure sense. It has been found that lack of control of even small original forces has led to pressure of 24 lb. per square inch (about 1.8 kg. per sq. cm.), and this pressure would be extremely painful in a normal hand.

Mr. Brand described the correct picture of the motor disability of the claw hand, which leads to the finger-tip clasp in leprosy patients. This also leads to concentration of force on a small area, so that the finger tips may receive 100 lb. per square inch (about 7 kg. per sq. cm.). Each day the use of a claw hand in work may set up a crushing action on the terminal phalanges and even tiny bone fractures. In one experiment, a boy was forbidden to work in farming and taught carpentry instead and given careful instruction

how to use his hands safely. He lost no part of his digits. Even when he went back to farming, he used the care of his hands that he had been taught and did not injure his hands badly, though there was some slight shortening later in his fingers. The same things apply to the feet. Special soles and sandals are devised to protect against uneven and concentrated strains on the feet in walking.

In motor paralysis in leprosy, there is a pattern and always some muscles are exempt. It seems that leprosy can affect every nerve that is near the surface of the skin but not those well protected by tissues, and there seems to be some connection with the bulk of the nerve. Thus, all thick nerves near the skin are liable to paralysis and deep nerves are not so, in spite of the thickness. In the limbs, the thickness goes with nearness to surface and hence the limbs have a great liability to paralysis in leprosy.

Mr. Brand described the fascinating features of the surgical reconstruction of leprosy deformities and successful operations for tendon transplantation and showed an instructive film of an operation of this nature, which dealt with the standard procedure for claw hand.

East African Leprosy Research Centre, Annual Report covering 1st July, 1956 to 30th June, 1957.

Dr. J. M. B. Garrod, who has been Director since 22nd January, 1957, when he replaced Dr. J. Ross Innes on his translation to Medical Secretary of BELRA, reports on the progress of this new Centre. Therapeutic trial of the diphenylthiourea (DPT or SU 1906), which was started in July 1956, has continued and 45 patients now remain on the trial. The Centre obtains patients from the adjoining leprosarium of the Kenya Medical Department. Because it is proving difficult to get large numbers of patients, Dr. Garrod has made arrangements to extend the drug trial to two other leprosaria. As well as a large share of the capital cost of the Research Centre, and the recent special expenses of biochemical work, BELRA shares in the recurrent costs and gave a special grant of £4,000 to defray the cost of connecting the Centre to mains electricity. Dr. Ralph Naylor of the Department of Chemistry of Makerere College, Uganda, has visited the Centre and is pursuing studies with tetrazolium compounds as applied to staining the human leprosy bacillus, and in applying chemical methods to observation of the growth of mycobacteria in presence of sulphones. (An interim report on the diphenylthiourea compound, by Ross Innes, Smith and Smith, was published in East African Medical Journal, July 1957, **34,** 2, pp. 395–402.)

Nigeria Leprosy Research Unit, Uzuakoli, Annual Report, 1957

This unit concentrates on problems of chemotherapy and

immunology. They had four new drugs under investigation in 1957.

(*a*) *Diphenylthiourea*, compound SU 1906 (DPT).

A report on this drug appeared in *Leprosy Review*, **29,** 1; January, 1958, pp. 25–44. At a dosage level of 25 to 40 mg./kg., there was complete freedom from toxic action and a very satisfactory therapeutic response. It was found especially useful in cases of intolerance to the sulphones and in cases with severe neuritis and persistent lepra reaction and also in cases of DDS psychosis. Trial of the drug was extended to six other centres, and the total number of patients receiving DPT rose to 167. All these centres confirmed the favourable opinion of the drug. It has also been shown that DPT combines safely and effectively with DDS and with INH. So far no satisfactory laboratory method has been devised for the estimation of DPT in body fluids. A trial has been made of twice weekly dosage, with the result that there seems to be some loss of efficiency except in some patients for whom it is satisfactory.

(*b*) *Diameno Diphenyl Sulphoxide* (DDSO).

This drug has been studied for 26 months in a dosage of 100 mgm. daily. It has a certain amount of toxicity and does not appear to be as active as DPT, but in some cases it gave good results. It has been tried also in twice weekly doses of 300 mgm. and has been found quite effective. It seems similar to DDS in both activity and toxicity, but does not seem to have notable advantages over DDS, but further study is needed.

(*c*) *Pyrazinamide.*

This was given in a small trial of 11 patients in doses of 250 to 500 mgm. daily. At this lower dosage than that used in tuberculosis, the therapeutic action was erratic. The trial was brought to an end when two cases, after 15 months, showed clear signs of drug resistance.

(*d*) *Diethyl-dithiol-isophthalate*, compound 15688.

The trial of this drug is in its early stages. It has a high antituberculous activity and the same seems to apply to leprosy but it has a very offensive odour, which is a great trouble to the patient. It is given by inunction.

Immunology.

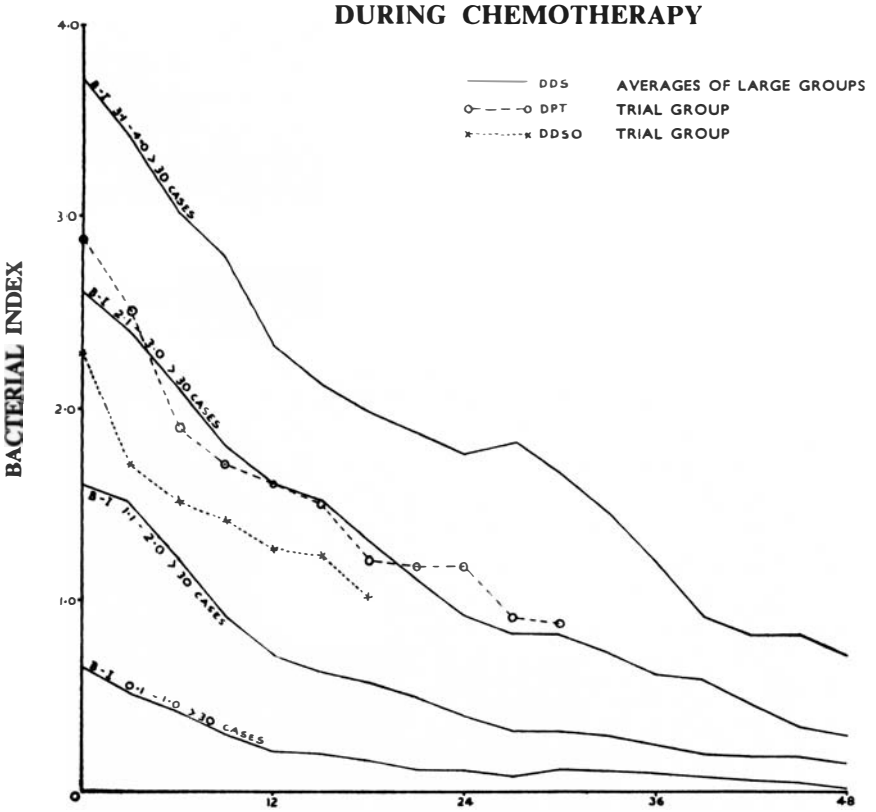
The tuberculin-lepromin relationships have been studied and reported in *Leprosy Review*, **29,** 2: April, 1958, pp. 81–101. The association between tuberculin and lepromin sensitivity found in these areas seems apparently to be due to non-specific geographical and constitutional factors. In another trial of BCG in indeterminate and early lepromatous leprosy, it was found that it completely failed to induce lepromin sensitivity. Dr. Davey thinks that these findings

make it very doubtful whether mass BCG inoculation offers any ready means of eradicating leprosy.

For the year 1957, Dr. T. F. Davey, Director of the Unit, was assisted by Mr. S. E. Drewett, and records the visits of Dr. R. G. Cochrane, Dr. J. Ross Innes, Dr. D. S. Ridley, Dr. D. G. Jamison, Dr. V. Ekambaram and Dr. Khushu.

UZUAKOLI, 1957

GROUP DECLINE IN BACTERIAL INDEX DURING CHEMOTHERAPY



REVIEWS

Leprología, **2,** No. 1 of Jan. to June 1957, pp. 1–84, Organ of the Argentine Society of Leprology, Buenos Aires.

G. Basombrío discusses *Leprosy Teaching and Prevention*, pointing out that the all-important need of early recognition of leprosy drives us back to the need for a sufficiently large body of leprologists and efficient and pervasive arrangements for the teaching of leprosy in medical schools. At least the medical faculty should give leprosy its just place as one of the national problems. The diminution of syphilis in importance gives a chance of paying more attention to leprosy, which still remains a problem. Health propaganda should not be forgotten. The formation of a body of trained leprologists still lags behind and is urgent. In spite of the special courses and the study bursaries that have been available in Argentina, leprologists are few and this problem is shared with the whole world. Perhaps the specialty is held in too low estimation and certainly the pay is not good, but the scientific possibilities are opening up and are fascinating. The Patronato de Leprosos in Argentina has understood this, for it has recently created the annual Baldomero Sommer prize for the best work in leprosy.

The Fernández Reaction using Total Protein Lepromin is reported on by N. O. Castro and P. B. Arcuri. They found that in subjects who were not leprosy patients and not contacts the Fernández was positive in 3.6%; in the lepromatous, it was positive in 0.5%, and in the tuberculoid 77.2%. If the healthy non-contacts had been sensitized previously by one or more intradermal injections of Mitsuda-Hayashi whole lepromin, the positives were 75.2%, and if they had been given BCG six weeks before, the positives were 81.2% for intradermal BCG and 46.8% for oral. In subjects with active tuberculosis who were positive to Mantoux 1/1000, the Fernández positivity was 43.0%. The results showed that total protein lepromin is an antigen which is sensitive enough to show grades of reaction and of co-sensitivity. The activity of protein antigens does tend to fall off with lapse of time, but this antigen did not lose its activity in one year. The total protein lepromin also does not produce sensitivity of the tuberculin type and is a valuable antigen for the study of co-sensitivity with BCG and especially in the study of the sensitivity in leprosy contacts, in whom it can be used as often as necessary without creating sensitivity states.

Inoculation of M. leprae in Rats fed on Pro-oxidant Diet; the Bacteriological Results up to ten months from the first Inoculation, by M. Bergel.

This author has been conducting a series of experiments to transmit the human leprosy bacillus to rats and previously found

that the transmitted bacilli had greatly multiplied and continued their multiplication up to seven months from inoculation. He now reports on the results of a re-inoculation of a new group of rats. In all cases, the rats were fed on the special diet. At ten months after the re-inoculation, he found an enormous quantity of bacilli in the testes of the rats. These bacilli seemed to be typical *M. leprae* in their shape and staining and tendency to form groups and globi.

Value of Segregation in the Prevention of Leprosy by J. A. M. Fernández, E. A. Carboni and T. A. Fernández Podestá.

These authors pointed out the failure of the modern anti-leprosy campaign which has been noted in some countries after twenty-five years of trial, and try to discover what are the responsible factors. They arrive at the conclusion that indiscriminate and rigorous isolation without control of the time factor is one of the causal elements in failure. They favour selective and temporary isolation of cases which are carrying bacilli, the intensive treatment of all known cases, and the faithful control and protection of all contacts.

Leprosy in the Province of Córdoba (1906 *to* 1956) by L. A. Pitt and C. A. Consigli.

They found that the leprosy endemic in this province had increased greatly during the years mentioned, from 0.1 to 0.6 per thousand. In one particular area, it rose from 0.6 to 2.2 per thousand.

Control of Tuberculoid Lepra Reactions by Means of Prednisone by E. D. L. Jonquières.

He thinks that the tuberculoid reaction brings no benefit to the course of the disease and should be suppressed, especially as atrophy and scars and nerve destruction often follow. In a few cases he tried prednisone, and found a quick and satisfactory involution of the phenomena of reaction. It was possible to continue the administration of the sulphones during the period of reaction, and there was no interference with their beneficial effects. In cases where the reactions are in some way connected with the sulphones, it was found that after the use of prednisone, the patient had a better tolerance to the sulphones.

The Therapeutic Status of the Thiosemicarbazones, by S. Schujman.

He found that the thiosemicarbazones are active and efficient during the first three years of treatment but afterwards, in most lepromatous cases, the effect fails in some and others have exacerbations of their disease. Drug resistance seems to become established. Therefore, he places this drug in a place after the sulphones and chaulmoogra, and prefers to use it as an auxiliary medication.

Revista Brasileira de Leprologia, **25,** 4, Oct.–Dec. 1957, 417 pages.

This issue reports a symposium on the basic principles and

practices in the use of BCG in the prevention of leprosy held at Rio de Janeiro in September 1957 under the auspices of the Brazilian Association of Leprology.

Professor Rabello took up the consideration of the plan of study of the relationship between leprosy and tuberculosis and dealt with it systematically; in spite of a close connection in the immunology of the two diseases, there are many doubtful points which require further study. Dr. Rotberg discussed the fundamental principles in this connection between leprosy and tuberculosis. He pointed out the importance of the acidfast mycobacteria of both diseases and that the serological reactions are bound to be interrelated because of the fundamentally similar chemistry of these organisms. Therapeutic results of the two diseases to the same drugs differ considerably and it is interesting that the sulphones which are a standard treatment for leprosy have been abandoned for tuberculosis. It is possible that the results of using BCG for both diseases will be similarly divergent and that BCG may have only minor value as a prophylactic. Professor Bechelli gave an exhaustive study of the factors, with quotations of the findings of many countries, and concluded by saying that he thinks that the parallelism in the tuberculin and lepromin curves depend upon the relation of cause and effect and not on an association. There is probably a transitory sensitization caused by *M. leprae* and *M. lepraemurium.* The cross sensitization between *M. leprae* and *M. tuberculosis* is of slight importance, and the influence of the one disease on the clinical course of the other is not strongly established. Similarly, in epidemiology, a definite conclusion is not possible on the influence of one disease on the other. Professor Hadler described the results of histological studies in the lepromin test and the action of BCG. In man, the histology of the site of the lepromin injection at twenty to thirty days shows diverse pictures. In cases of a clinical negative, the reaction is discrete and made up of isolated or numerous lepra cells containing bacilli in the cytoplasm. There are also non-specific cell reactions which do not contain bacilli. It seems that in the negative lepromin, the macrophages do not destroy the bacillus and they are transformed into lepra cells. The histology of the positive reaction shows epithelioid cells with few or absent bacilli. The reaction to lepromin is of a different nature from that to BCG. In study of the action of BCG on the lepromin reaction, histology has not been much used. All the evidence suggests there is a conversion by the BCG. Professor Azulay considered the same subject and concluded that the conversion of the lepromin reaction by the means of the BCG is true, because of the qualitative cell changes. Dr. Nelson Souza Campos and Dr. Quagliato reported on actual results of the use of BCG and concluded that there is much evidence for the prophylactic action of BCG against leprosy.

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The letters after the entry have the following significance: Original Articles (O); Editorials (E).

A