

# LEPROSY REVIEW

The Quarterly Publication of  
**THE BRITISH LEPROSY RELIEF ASSOCIATION**

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**VOL. XXXI. No. 3**

**JULY 1960**

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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 any responsibility for views expressed by writers.

Contributors of original articles will receive 25 loose reprints free, but more formal bound reprints must be ordered at time of submitting the article, and the cost reimbursed later.

## EDITORIAL

1. *A Trial of BCG Vaccine as a Protection against Leprosy*

Drs. J. A. McFadzean and R. Bhagwan Singh have made a very interesting trial on an island off Malaya in which the population at 1957 was 7,369. Their paper appears in this issue on page 145. There were interesting findings in the preliminary leprosy survey, in which 3,720 persons in the age group 0–25 years were examined, in whom the incidence of leprosy was found to be 19 per thousand. Of persons without any clinical signs of leprosy 3,649 were given the tuberculin test and 3,222 were found eligible for vaccination with BCG, and random groups of 1,648 were vaccinated and 1,574 left as controls. These groups are to be observed over the next ten years, and a level of protection by the vaccine should be demonstrated to the value of 50% or more. In the tuberculin testing the conversion rate was found lower than expected and emphasises that much care must be taken in handling the vaccine, especially in the tropics, and that counts for viability should be made after the BCG has reached the consumer. This BCG trial is very promising and we expect that a useful answer will eventually be supplied on the efficiency of BCG as a prophylactic against leprosy.

2. *Plantar Ulcer in Leprosy*

Mr. E. W. Price, F.R.C.S.E., has been providing a series of articles on this subject and the final one appears in this issue, page 157 (the others appeared in *Leprosy Review*, **30**, 2, p. 98; **3**, p. 180; **4**, p. 242; and **31**, 2, p. 97). Mr. Price has been thinking out the causation and practical points of care and treatment. In this last paper he gets down to details about the management of plantar ulceration and of infection during the course of it and of skin loss and of the healed ulceration. Successful treatment depends a lot upon the plaster cast and suitable footwear and useful details are given about these.

3. *Deutsches Aussätzigen-Hilfswerk or German Leprosy Relief Association*

We welcome the foundation of this association and its considerable activities which have grown up in such a short time. A note will be found about it in the Reports, page 219.

4. *Lepromin Sensitivity*

Dr. J. A. Kinnear Brown has been working for some time on the multipuncture depot lepromin test and we draw attention to his paper in this issue, page 172. In addition to the more basic investigation of Drs. McFadzean and Bhagwan Singh we welcome the

practical steps taken by Dr. Kinnear Brown to show that the multi-puncture method is an adequate method of applying both BCG and the lepromin antigen.

5. *Bacteriology of Rat Leprosy and of Human Leprosy*

Our distinguished colleague, Dr. H. C. de Souza-Araujo of Brazil, has given an account of his work in this field which will be found in this issue on page 178.

6. *Fading of M. leprae in Sections of Patients Treated with Etisul*

Mr. R. Rhodes-Jones has brought up this interesting matter (his paper is on page 200). Dr. D. S. RIDLEY has kindly commented on the matter as follows: "Mr. Rhodes-Jones has made an interesting observation and I believe the same phenomenon has been observed by Dr. T. F. Davey, though I have no reference to any report on the subject. My own experience of sections from Etisul treated patients is limited to a few cases. None of these sections has shown any fading, either in the incubator or during subsequent storage for six months. This might be due to some unnoticed detail of technique in which the two laboratories differ. Another possible explanation, however, is that all our Etisul patients had received previous chemotherapy; bacilli were already granular and they were not apparently affected by Etisul".

DR. T. F. DAVEY, C.B.E. comments as follows:

"The fading of bacilli in stained biopsy specimens has been a constant problem in recent years at Uzuakoli, but appears to have lacked any distinct pattern. I am afraid we attributed it to some obscure local factor of climate or working conditions without undertaking any such analysis as Mr. Rhodes-Jones describes. His findings are of great interest and deserve further study. It is true that during recent years a majority of our biopsy specimens were derived from patients receiving Etisul, but our problem was certainly not confined to them, and was evident before work on Etisul began. Although the possibility cannot be denied that some specific factor may have operated in our Etisul specimens, any effect it may have produced was masked by the wider problem of fading encountered in specimens regardless of chemotherapy. We have not found the problem of fading to be of such practical importance where routine smears are concerned. Although consecutive biopsies provide a very useful check on progress, and are a necessary accompaniment to clinical trials, this experience is one of the reasons why great importance in assessing progress has been placed on the findings of multiple smears, frequently repeated."

Dr. Ridley himself has an interesting article in this issue (page 189) on the effect of chemotherapy in superficial tissues and in the reticulo-endothelial system. The number of bacilli in the reticulo-endothelial system seems to decline rapidly after 12 months' treatment and to disappear long before those in the skin or other superficial tissues and the reticulo-endothelial system seems the main site of destruction of bacilli.

#### *7. Leprosy in Antigua*

Dr. K. H. Uttley has given in his paper (page 193 of this issue) a valuable account of the problem there. It is interesting that he finds, contrary to many voices raised recently against the idea, that leprosy is much more prevalent in a hot, humid climate than in a cold, dry one. Antiguan leprosy at present seems to be at the rate of 1.4 per thousand.

## THE INITIATION OF A TRIAL OF BCG VACCINE FOR LEPROSY

by JAMES A. MCFADZEAN

*National Institute for Medical Research, London; and The Research Unit, Sungei Buloh Settlement, Sungei Buloh, Malaya*

and R. BHAGWAN SINGH

*The Institute for Medical Research, Kuala Lumpur, Malaya*

This paper describes the initial laying down of a trial of BCG vaccine as a prophylactic for leprosy. Since the introduction of BCG for tuberculosis, leprologists have discussed its possible value for leprosy. Much indirect work has been undertaken on this question, but the direct approach has largely been ignored. It is clear that the answer can only be supplied in the following manner:

1. By having a static, relatively isolated population with a high incidence of leprosy.
2. The population should be examined clinically for leprosy and then tuberculin tested.
3. The negative tuberculin reactors should be randomised into two groups and one given BCG while the other is left as a control.
4. There should be a constant intake of new born children one half of whom should receive BCG and the other half again left as a control.
5. The population should then be examined at intervals and the incidence of leprosy recorded in each group.
6. The duration of the trial would depend on the size of the population and the incidence of leprosy but a period of 5-10 years would be necessary.

The initiation of such a trial is described in this paper.

### Location

The population chosen for the trial was that of an island called Pulau Ketam which lies in the Klang Straits off the west coast of the Federation of Malaya (see map). The island is a tidal mangrove swamp measuring some 4 miles by 2 miles (3.2 by 6.4 km.). The population of 7,369 (1957 census) is entirely Chinese consisting principally of Teochew, Hokkien and Hylam. The only occupation is fishing. As the island is entirely tidal mangrove all the houses are on stilts with the majority concentrated into 3 towns. The houses are crowded together and each house is overcrowded. Sanitary arrangements are simply holes in the floor with the hope that the tide will be high enough in the course of a few days to undertake the flushing. No long standing records of the community could be obtained but it is believed that it has existed for at least 100 years. The population

is static. On the whole, the community is well off as the fishing is good and fish fetch high prices in Malaya. The diet of the population is excellent with a high intake of protein.

There were a number of existing contacts with the island through patients with leprosy who had come from the island to Sungei Buloh Settlement for treatment. The large number of patients from the island suggested that it might be suitable as a place for a BCG trial. A meeting was arranged with the Committee which was responsible for the 'internal affairs' of the island. It was explained that after clinical examination a vaccine would be given to a certain number of the population which would help to protect against tuberculosis and that it might be of value in preventing leprosy. It was stressed that persons found suffering from leprosy would not be compulsorily isolated (as laid down by the existing antiquated law in Malaya). They would be offered the choice of out-patient treatment on the island or of going to the Settlement for in-patient treatment.

Close contact with the population began with the posting of an assistant male nurse and his family to the island. Both the nurse and his wife had been cured of leprosy and had originally come from the island. A small dispensary was established where the nurse could treat minor ailments and gain the confidence of the people. It must be remembered that western medicine is still something new to many Chinese and that their traditional remedies are still believed by many to be the more effective. As it is the practice in Malaya to keep people who have had leprosy on sulphone maintenance treatment for life, the male nurse also carries out the follow-up treatment of patients who have been discharged to the island from the Settlement.

### **Methods of Survey**

All houses on the island had previously been numbered from 1 upwards for purposes of taxation. These numbers are clearly shown on a plate above the door of each house. There was also available a map of the island (Scale 1 chain/1 inch, i.e., approx. 20 metres/2.5 cm.) showing each house by number. This map had been produced by the Survey Department of Malaya 10 years previously. The male nurse first of all checked all the house numbers, erased from the map houses which had fallen down and added houses which had been built in the preceding 10 years.

All children from 0-12 years had birth certificates and those over 12 years had identity cards with a photograph. These were of great assistance during the survey.

It was decided to start in the town of Pulau Ketam where the density of population was greatest and to restrict the trial to the age group of 0-25 years. Propaganda posters were placed at strategic points in the town and the male nurse visited houses systematically in a given area and recorded the names, ages and sex of all those in

each house who were in the age group to be investigated. Notice was given to groups of 250 persons—the maximum number of persons who could be dealt with in one day—to present themselves at a central place at a given time. Examinations were conducted in such varied places as a cinema and Chinese temple.

The team which undertook the project was as follows:

- (a) Two medical officers.
- (b) A nursing sister.
- (c) A secretary.
- (d) The assistant male nurse.
- (e) A technician.
- (f) An orderly.

As no suitable accommodation was available on the island for the team, a launch was obtained on which they could live. Owing to other work on hand, the work of the survey could not be undertaken full-time but in blocks of four days allocated as follows:

- Day 1. Examine and tuberculin test 250 people.
- Day 2. Examine and tuberculin test a further 250 people.
- Day 3. Read the tuberculin from Day 1 and administer BCG to the relevant group.
- Day 4. Read the tuberculin from Day 2 and administer BCG to the relevant group.

This meant that the great majority of tuberculin reactions were read at 48 hours. The allocation of duties on Days 1 and 2 was as follows:

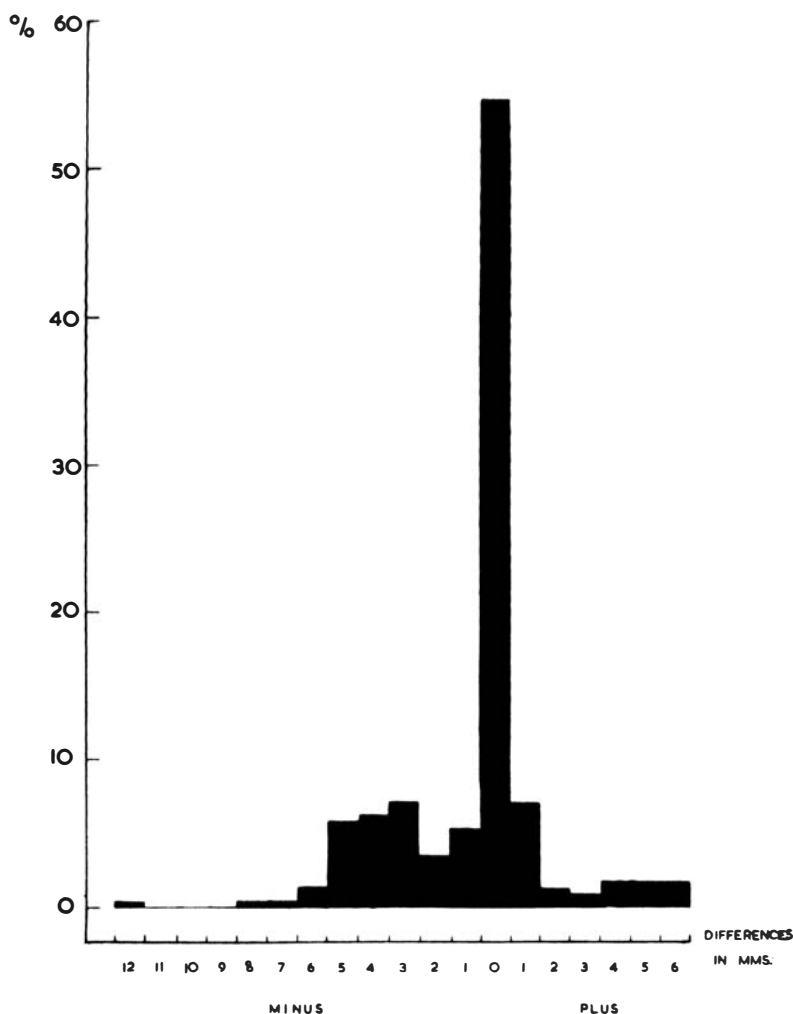
- (a) The orderly ushered the population in, one family at a time.
- (b) The assistant male nurse checked the details of the family against his records and acted as the interpreter for the secretary.
- (c) The secretary recorded names (Chinese usually have more than one set of names), sex, date of birth, address and father's name. She insisted on seeing every birth certificate or identity card.
- (d) One medical officer with the nursing sister examined as much of the skin surface of each person as was permitted. Some difficulty was encountered among the older females. He also examined for nerve enlargement, muscle wasting and contractures of fingers. Records were made of any lesions found. If the person had leprosy, or was suspected of having it, the patient was examined in detail later by himself. Leprosy is much feared by the Chinese and carries a stigma which can never be overcome by an individual and therefore all possible cases of leprosy had to be dealt with confidentially.
- (e) The second medical officer tuberculin tested each patient on the flexor surface of the forearm.
- (f) The technician supervised the syringes, etc.



On days 3 and 4 each individual was again carefully checked with his birth certificate or identity card. One medical officer then read the tuberculin reactions and the other vaccinated those who had to be given BCG.

### The Tuberculin Test

(a) *Tuberculin employed:* The tuberculin employed throughout was that prepared at the State Serum Institute in Copenhagen. This was sent to Malaya in concentrated form and diluted at the Institute for Medical Research in Kuala Lumpur. The bulk of tuberculin employed was RT 22 in doses of 5 TUs in 0.1 ml. Subsequently



*Histogram No. 1* shows the percentage frequency distribution of the differences in reaction between 5 T.U.'s of RT 22 and 1 T.U. of RT 23. (Reaction to 5 T.U. RT 22 minus reaction to 1 T.U. RT 23.)

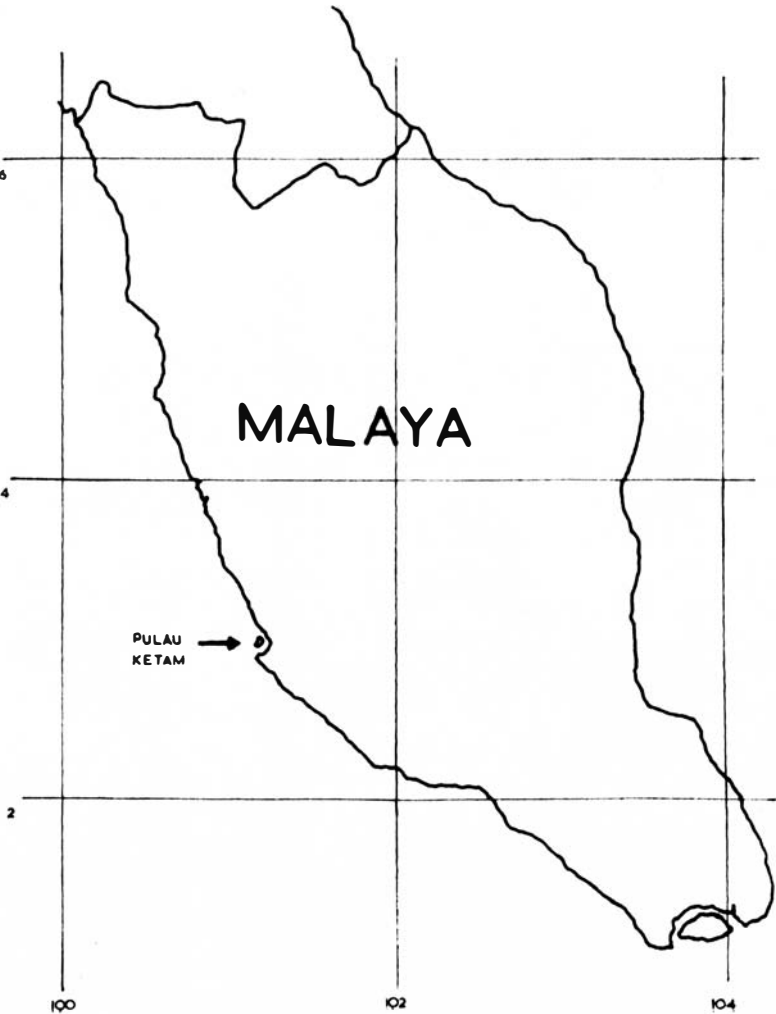


TABLE 2  
*The Tuberculin Reactions of the Population of 0-25 Years*

<i>Age Group in Years</i>	<i>Number in Group</i>	<i>Tuberculin Reactions in mms.</i>									
		0-4	5	6	7	8	9	5-9	10-14	15-19	20 and over
0-5	1442	1378 (95.5%)	23	8	3	3	3	40 (2.8%)	13 (0.9%)	3 (0.2%)	8 (0.6%)
6-10	1064	755 (71%)	93	56	31	25	16	221 (20.7%)	59 (5.6%)	15 (1.4%)	14 (1.3%)
11-15	642	297 (46.3%)	80	57	35	19	21	212 (33%)	88 (13.7%)	15 (2.3%)	30 (4.7%)
16-20	332	84 (25.3%)	37	40	25	18	20	140 (42.2%)	71 (21.4%)	14 (4.2%)	23 (6.9%)
21-25	169	32 (18.9%)	17	12	14	10	10	63 (37.3%)	44 (26.0%)	17 (10.1%)	13 (7.7%)

however, the supply of this was discontinued and RT 23 was employed in equivalent strength which was 1 TU in 0.1 ml. (Circular from Statens Serum Institut, Denmark, June, 1958). To ensure that these two tuberculins were identical in the doses employed, a group of 226 persons on the island were tested simultaneously with the two tuberculins on opposite arms. Histogram No. 1 gives the percentage frequency distribution of the differences between the two tuberculins. 1 unit of RT 23 gave a higher reading than 5 units of RT 22. (Mean difference 0.681; standard error of the mean difference 0.163;  $t = 4.18$ ;  $P < 0.001$ ). This difference is of interest as the true equivalent of 5 units of RT 22 is 0.7 unit of RT 23. However, from the practical point of view the two tuberculins in the doses employed are very similar.

(b) The injections were given on the flexor surface of the forearm with a 1 ml. all glass tuberculin syringe and a No. 26 g.  $\times$  7.5 mm. platinum needle.

(c) The reaction was read at 48 hours in the majority of cases but a number were read at 72 hours. The reading was done with calipers which were read against a mm. scale on a ruler. The maximum diameter of induration was read.

### **Eligibility for BCG Vaccination**

The standard of eligibility for vaccination was that laid down by the World Health Organisation (WHO/TBC/Int./38.1957), which is that those persons with a reaction of 9 mms. or less to 5 TU or RT 22 tuberculin should be given BCG.

### **Randomisation procedure for giving BCG**

The following procedure was followed:

1. Those eligible for BCG vaccination born in an odd year up to, and including 1957, were given BCG while those born in an even year were not vaccinated.
2. Those eligible for BCG vaccination born in 1958 and subsequently in an odd month were given BCG while those born in an even month were not vaccinated.

### **BCG Vaccine**

The vaccine employed was the freeze-dried vaccine manufactured by Messrs. Glaxo Ltd., and the majority were vaccinated with batch numbers 148 and 146. It was administered by the same type of syringes and needles used for tuberculin but the two groups of syringes and needles were kept separate. The vaccine was given intradermally about the insertion of the deltoid muscle. When the vaccine was received from the distributors it was kept in a refrigerator; when required for use it was transported in a large thermos jar with ice.

When a group of patients was assembled for vaccination an ampoule was removed from the thermos jar, reconstituted, and used immediately.

### Record Keeping

Adequate detailed and accurate records were absolutely essential to the trial. The secretary employed was a librarian with considerable knowledge of detailed record keeping and cross indexing. Records were initially entered into ledgers and subsequently the information was transferred to punch cards. Adequate space for follow up records was left in the ledgers and on the punch cards.

### Results

#### 1. *The Leprosy Survey*

In the 0-25 years group a total of 3,720 persons were examined clinically for leprosy. A total of 71 cases of leprosy was recorded as follows:

- (a) Number of new cases found in the population 16
- (b) Number of patients on the island discharged from Sungei Buloh Settlement 25
- (c) Number of patients from the island at present in the Settlement 30

This gives an incidence of leprosy of 19 per thousand.

The age distribution of the persons with leprosy is given in Table 1.

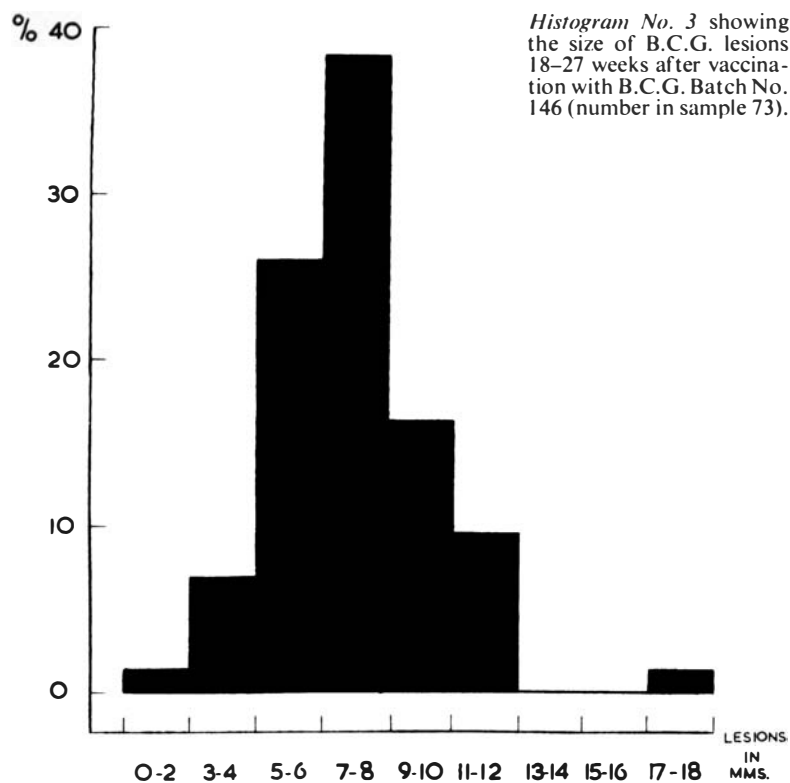
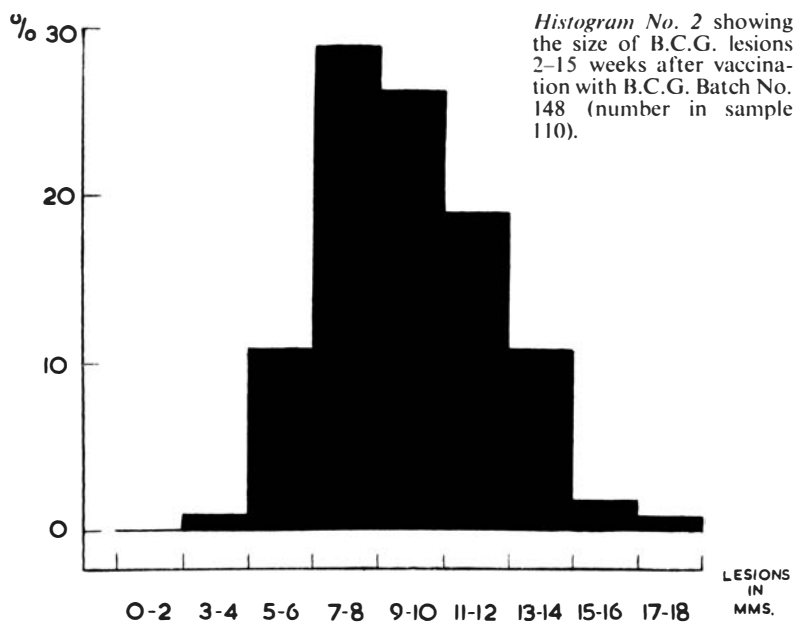
TABLE 1  
The age distribution of leprosy in the 0-25 years age group

<i>Age in years</i>	<i>Number in group</i>	<i>Leprosy patients</i>	
		<i>Number</i>	<i>Percentage</i>
0-5	1442	0	0
6-10	1072	8	0.7
11-15	665	23	3.5
16-20	358	26	7.3
21-25	183	14	7.7

Of the 71 cases of leprosy, 49 (69%) were lepromatous or atypical and 22 (31%) were tuberculoid. 57 (80%) of the patients were male and 14 (20%) were female. The incidence in males was 57/1793, i.e., 32 per thousand and in females 14/1927, i.e., 7 per thousand.

#### 2. *Tuberculin Reactions*

The number of persons without clinical signs of leprosy who were given tuberculin was 3,649. Details of the tuberculin reactions are given in Table 2. Four hundred and twenty-seven persons were



positive (induration of 10 mms. and over). The remaining 3,222 who were eligible for vaccination were randomized as described previously and 1,648 received BCG leaving 1,574 as controls.

### 3. Response to BCG Vaccination

No untoward reactions to BCG vaccination were observed or reported. It was noticed that a number of persons applied some 'Chinese medicine' to the vaccination lesions in spite of our requests to leave them uncovered.

Random samples were taken of school children 2–15 weeks after vaccination with Batch No. 148 and 18–27 weeks after vaccination with Batch No. 146. The sizes of the lesions produced by the BCG were measured and these are shown in histograms 2 and 3. The mean diameter of the vaccine lesions produced by Batch No. 148 was 9.4 mm. and by Batch No. 146 7.2 mm. In Britain the figure obtained with freeze dried BCG was 8.4 mm. at 5–7 weeks and 7.9 at 10–17 weeks. (Preliminary Report to the Medical Research Council, 1958). These children were retested at the same time with tuberculin and the tuberculin conversions are given in Table 3. The conversion rates

TABLE 3  
The conversion rates for BCG Vaccine Batch Nos. 148 and 146

	<i>BCG Batch No. 148</i>	<i>BCG Batch No. 146</i>	<i>British Freeze Dried trials (1958)</i>
Number in sample	110	74	1772
Number absent on retest	0	5	
Nos. converted to 10 mm. or more	27 (25%)	28 (41%)	
Mean diameter of these reactions	10.9 mm.	13.7 mm.	
Original reaction less than 5 mm.	78 (71%)	51 (69%)	1772
No. absent on retest	0	2	0
No. converted to 5 mm. or more	62 (79%)	31 (63%)	*1602 (90%)
Mean diameter of these reactions	7.2 mm. * to 3 TU	10.1 mm.	10.7 mm.
<i>Viable counts × 10<sup>6</sup>/ml.</i>	<i>Batch No. 148</i>	<i>Batch No. 146</i>	
Ex-works	3.8	9.0	
Ex-Malaya	0.03	1.1/2.7	

to 10 mm. and over were 25 % and 41 % respectively for Batch Nos. 148 and 146. Comparable figures were not available from other trials as the standard of eligibility for vaccination employed was that only recently introduced by the World Health Organisation. The conversion rates to 5 mm. or over were 79% and 63% compared to 90% in the British Freeze Dried Trials in 1958. An obvious cause of this lower conversion rate could have been a drop in the viable counts in the vaccine employed. Therefore samples of the batches employed were sent in refrigerated containers by air to London where the viable counts were performed. The results of these are given in Table 3 along with ex-works counts for the same batches. There had been a considerable fall in the viable counts particularly in Batch No. 148. It is considered likely that this was responsible for the lowered conversion rates obtained. It seems most unlikely that the fall could have occurred after the vaccine was received at Sungei Buloh Settlement as the material was kept refrigerated throughout. It appears however, that the damage may well have been done in the transport of the vaccine between the agents in Singapore and the consumer when there was a failure to maintain the vaccine at the recommended temperature.

### Discussion

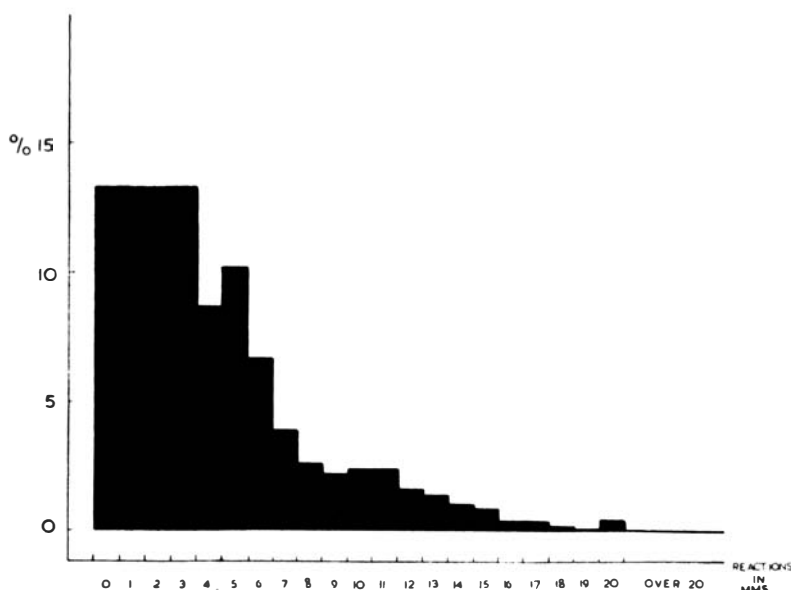
The initiation of the trial had its minor difficulties but on the whole the island proved to be an ideal place for the project. The ease of identification of houses and persons was an advantage which would be difficult to find elsewhere.

The incidence of leprosy found in the 0-25 years age group, namely 19 per thousand, was lower than expected. The reason for this is that many patients in Sungei Buloh Settlement who had stated that they had come from Pulau Ketam had in fact come from Indonesia and had been smuggled through the island to Malaya for treatment. The high reputation of Sungei Buloh Settlement was responsible for this desire for treatment in Malaya.

While an attempt was made to see everyone up to the age of 25 years, it is known that a number of persons were not seen. This applied particularly to the older groups. In the case of males, they often spent long periods at sea, and the females were shy of being examined. From census figures available from other parts of Malaya it seems that approximately 80% of the population from 0-25 years were seen. It is now known that a number of cases of leprosy did not come forward. Certainly a number of ex-patients from the Settlement did not present themselves.

The pattern of age incidence of leprosy on the island is different from that found in Africa. As this was the first leprosy survey undertaken in Malaya no other figures are available from there for comparison. In Gambia (McFadzean and McCourt, 1955) 20% of





*Histogram No. 4 showing the tuberculin reactions in the age group 6-15 years.*

the cases of leprosy are found up to the age of 10 years while in the present survey only 11% occurred before the age of 10.

The incidence of the type of leprosy also differs from that found in Africa. In Malaya 69% of the cases are lepromatous or atypical while in Gambia, for example, 70% of the cases were tuberculoid. On the island the incidence in males was significantly higher than that found in females, while in Gambia there was no difference in sex incidence.

To compare the incidence of tuberculin sensitivity on the island with that found elsewhere it is necessary to take a restricted age group such as shown in histogram No. 4. 38% of the children from 6-15 years reacted to 5 TUs of RT 22 tuberculin with 5 mm. or more. This is a similar reaction rate to that recorded in other parts of the tropics (WHO Document EB 24/5, May, 1959—*Review of BCG Vaccination Programmes*—Preliminary reports by the Director General).

The size of the lesions produced by the two batches of BCG and the subsequent reactions to tuberculin unfortunately cannot be compared directly owing to the different times after vaccination of making the observations. The tuberculin conversion rates with both batches of vaccine were lower than those obtained in Britain (see Table 2). The explanation for this lies almost certainly in the drop in the viable counts in the vaccines. It is clear that, particularly in the tropics, the method of handling and despatching the vaccine must

receive greater supervision. As a further check viable counts should be made on samples of the batches of vaccine sent back to this country from the consumer. The major problem of tuberculosis now lies in underdeveloped tropical countries and it is to be expected that BCG vaccination will be widely undertaken in tropical areas. Unless adequate precautions are taken in supervising and checking the vaccine, control schemes may well be jeopardized.

### **The Future of the Trial**

The data have been kindly analysed by Dr. Ian Sutherland and it is estimated that, allowing for losses, the number of cases in the unvaccinated group which can be expected over 10 years is 30. This means that no benefit could be claimed from BCG vaccination unless the apparent degree of protection was 50% or more. As a level of less than 50% protection is of little value or interest this part of the trial is certainly worth continuing.

The expected addition to the number of cases by extending the intake to include successive generations of new-borns is very small and this part of the trial is not worth continuing and has been abandoned.

It is clear that the introduction of a nation-wide BCG vaccination project in Malaya would, for ethical reasons, almost certainly result in the abandonment of the trial.

### **Summary**

The initiation of a controlled trial of BCG vaccine as a prophylactic for leprosy is described. The trial is being undertaken on an island off the West Coast of Malaya. 3,720 persons in the age group 0–25 years were examined. The incidence of leprosy found was 19 per thousand with a significantly higher incidence among males. 3,649 persons with no clinical signs of leprosy were tuberculin tested. Of these, 3,222 were eligible for vaccination with BCG and by randomization 1,648 were vaccinated and 1,574 left as controls. The expected incidence of leprosy in the unvaccinated group over the next 10 years would be sufficient to demonstrate a level of protection of the vaccine of 50% or more. The expected incidence of leprosy in the new born intake is too low to give significant results and this part of the trial has been abandoned. It is intended that the present population of 0–25 years be examined for leprosy at intervals for the next 10 years.

The conversion rate after vaccination was lower than expected and this was due almost certainly to a fall in the viable count of the vaccine employed. It is clear that much care must be taken in handling BCG vaccine especially in the tropics and it is suggested that in future trials the viable counts of the vaccine should be checked after it has reached the consumer.

**Acknowledgments**

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STUDIES ON PLANTAR ULCERATION IN  
LEPROSY

## VI. The Management of Plantar Ulcers

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

*formerly Orthopaedic Surgeon, Leprosy Service, E. Nigeria*

The management of plantar ulcers in leprosy reflects the uncertainty as to the cause of the condition, and has been largely discouraging. Trophic ulceration of the foot is not peculiar to leprosy but occurs in other neuropathies, including tabes dorsalis, syringomyelia and diabetes mellitus. It is therefore the expression of a lesion common to these widely diverse diseases. The present studies support the contention that the responsible factor is a failure of the mechanisms which protect normal plantar tissues from the damage which would otherwise result from the pressures and frictions of walking.

The methods of treatment which have been advocated cover a wide field, ranging from local injections of anti-leprosy drugs (Cochrane, 1940, Dharmendra *et al.* 1955, Ekambaram, 1960) to methods aimed at control of mechanical factors, e.g., novocaine blockade (Vischevsky, 1938) or local excision of tissue (Newman *et al.* 1955). The only consistent observation is that the use of a plaster cast permits healing if it is continued long enough. The earliest reference to this appears to be that of Khan (1939) and represents the application of principles enunciated by Trueta in the treatment of war wounds during the Spanish civil war. The success of the method has been confirmed by several observers (Milroy Paul, 1947, Fisher, 1955, Bose, 1956) and by the present writer. Healing proceeds under a plaster cast without local treatment, without relief of pressure, without antibiotic therapy; and it can only be concluded that the essential factor is mechanical. The reluctance of many to employ this method stems undoubtedly from a natural fear of applying plaster to an anaesthetic foot, and to the frequency with which the ulceration recurs after removal of the plaster.

The important questions are why does a plaster cast permit healing and why does the ulcer recur after removal of the cast? The answer appears to be that the active factor promoting healing is control of the movements of extension, under pressure, of the various flexures of the sole; and control of the rotations under pressure, round the point of contact at the heel and push-off at the tips of the toes during each step of walking. The ulcer recurs because these movements are renewed when walking is resumed.

The solution of the problem of plantar ulceration can be summed up as follows: the control of plantar damage during walking, the

avoidance of ulceration, and the control of infection and of loss of skin if ulceration does occur.

It is stressed that ulceration need not occur, and is a serious complication of the plantar lesion. The management of the condition is therefore discussed under the headings:

1. The pre-ulcerative stage.
2. The stage of frank ulceration.
3. The stage of healed ulceration (threatened recurrence).

### **1. The Management of the Pre-Ulcerative Stage**

If ulceration is avoided, the disabilities of the neuropathic foot are largely obviated. To avoid ulceration, there is no substitute for regular inspection of the feet by a trained observer. It should be a maxim of leprosy treatment that regular hand and foot inspection is a necessity for rehabilitation. This is especially the case when the patient himself cannot be relied upon to observe and report early signs and symptoms of foot damage. If treatment is to be carried out adequately, a method of recording rapid and accurate observations is essential. The following is found to serve well:

(a) Record the extent of anaesthesia to light touch (Fig. 1). The degree of sensation to light touch is tested by light stroking with a feather and recorded on charts of the plantar, medial, and lateral aspects of the foot. The feather is drawn centrally from the tips of the toes along the sole and towards the knee. It is unnecessary to denote the upper limit of anaesthesia reaching above the ankle. The observer will be surprised to find how sensitive is the normal sole of barefooted people to this minimal stimulus.

(b) Record or indicate on a chart the areas of actual and possible plantar damage, or use a system of abbreviations (Fig. 2).

The presence of an ulcer should not detract from the importance of palpating the other classical points of plantar damage.

(c) Assess the extent of loss of skin. The diameter of the ulcer in cm. serves to indicate the minimal extent of loss of skin. Any gain in skin that could be obtained by traction on the edge of the skin is certainly offset by the loss due to poor viability of the skin and its fixation to the underlying tissues by infection.

(d) Estimate the degree of involvement of deep tissues. Infection must first be controlled, and this may call for prolonged treatment if bone is involved. An X-ray is useful but underestimates the extent of bone infection. A useful clinical guide is the amount of discharge from the ulcer or sinus. The cessation of discharge is a favourable sign, but it is stressed that chronic bone infection may be ineradicable. Extensive scarring of the plantar tissues following infection may render the foot incapable of rehabilitation for walking, even when the infection is eradicated.

Using the above methods of recording the clinical condition, the *initial control of neuropathic feet* can begin. The following is a suitable procedure:

- (a) Examine every patient for anaesthesia of the sole to light touch.
- (b) Cases without anaesthesia are excluded from further immediate observation.
- (c) Cases with anaesthesia are then examined in detail and the results recorded.

The patient sits before the examiner and rests his Achilles tendon on a support so that the whole sole is visible. The toes are observed for degree of spreading, and the plantar surface for breaches of skin or areas of callosity. The danger areas are then systematically palpated while the patient is kept under scrutiny for signs of discomfort. Localised swelling is also sought at these areas.

In the early days of control, it may be better to let pass some cases that appear suspicious, so as not to increase the number of patients to be treated, as this number will be surprisingly large; but it is safer to regard any cases with local swelling, local tenderness to palpation, or local splaying of the toes as potential cases of ulceration.

The patients will then be divided into groups, those without anaesthesia, those with anaesthetic soles but without localising signs of plantar damage, those with anaesthetic soles but with localising signs, and finally, those with plantar ulceration. Treatment for each group is then instituted as described below.

The initial control of a leprosarium of 500 patients will take a month before treatment can be begun. It is as important to exclude those who can be safely excluded as to include those who ought to be under observation.

After the initial control and initiation of treatment, the second phase begins—that of *routine control* of the feet (and hands) of patients with leprosy. The frequency of inspection depends on the anaesthesia, on the general condition of the patient and on his intelligence.

Those without plantar anaesthesia are examined at three-monthly intervals to record the progress of the nerve damage. This is important even in cases with definite ulceration. It is not infrequent to find that sensation to light touch returns to a sole that presents an ulcer. In these cases, the chronicity of the ulcer is due to underlying bone infection, inadequate skin cover, or to other complicating factors such as circulatory deficiency.

Those with anaesthetic soles are examined at least every two weeks; unco-operative patients need weekly inspection, as do those of low intelligence. Frequent inspections are also needed at periods of special stress on the feet, such as the planting season, or the dry season.

When the leprosarium is under continuous adequate control, the occurrence of any plantar ulceration will be considered as a penetration of the lines of defence that should put the medical attendant on his mettle.

The treatment of threatened plantar ulceration is on the following lines. The patient is put to bed with the foot of the bed raised, though he is allowed to move with the help of a crutch to perform his toilet. The plantar oedema and tenderness will disappear in a week or ten days and the patient then resumes normal activities with rigid sole footwear. Alternatively, the patient remains in bed for three days until the initial oedema has subsided, and a plaster cast is then applied to enable him to be ambulant. The advantage of the latter method is that he can return home until his footwear is ready, work which may be delayed in a busy shoe shop.

## **2. The Management of Plantar Ulceration**

It must be remembered that the principles of plastic and orthopaedic surgery apply to these ulcers as to others. Much of the disappointment in the treatment of trophic ulcers stems from failure of treatment that would be inadequate in the ulcerated foot of an otherwise healthy adult. Long-standing infection is difficult to eradicate in ideal cases. The healing of a large ulcer by scarring will not support the strain of walking in the best feet; extensive deep scarring will not support the pressures and tensions of activity in any case without some support.

The adequate care of plantar ulceration includes the management of infection, and measures against loss of skin.

### *Management of infection*

In general, infection will be overcome if the tissues are protected from repeated trauma and if the circulation is adequate. Antibiotics can speed the healing. The best encouragement of healing is the application of a walking plaster after infection and oedema are controlled. It is not necessary to apply a weight-bearing cast, but one reaching to the tibial condyles will be found more comfortable than a shorter one, and less likely to cause pressure sores. A suitable cast is described in Appendix I.

After control of the oedema and infection by a few days in bed (assisted if desired by the administration of an antibiotic), the simple saline dressing which has been used in bed is replaced by a vaseline gauze cover, and the plaster cast is applied before the patient leaves the bed. When it has dried, the patient begins to walk, assisted at first by a stick or crutch. If necessary, casts can be applied to both feet simultaneously and the patient soon learns to walk as on stilts.

He is seen daily for the first week and any site of pain is exposed by opening a window in the cast; if no skin damage is found, the plaster is repaired. Attention is also paid to the odour at the ends of

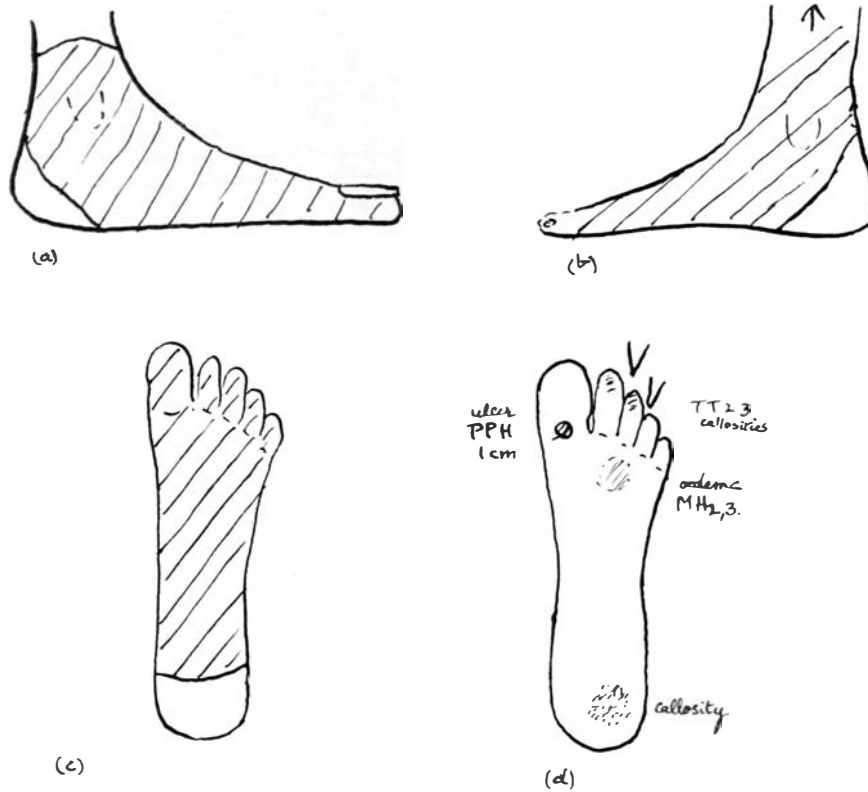


FIG. 1. Chart for recording foot lesions

(a), (b) and (c) indicate areas of anaesthesia to light touch. The upper level of anaesthesia above the ankle is unimportant in plantar lesions.

(d) represents the extent of plantar damage. The abbreviations are described in Figure 2. The V sign is placed between two toes which show splaying.

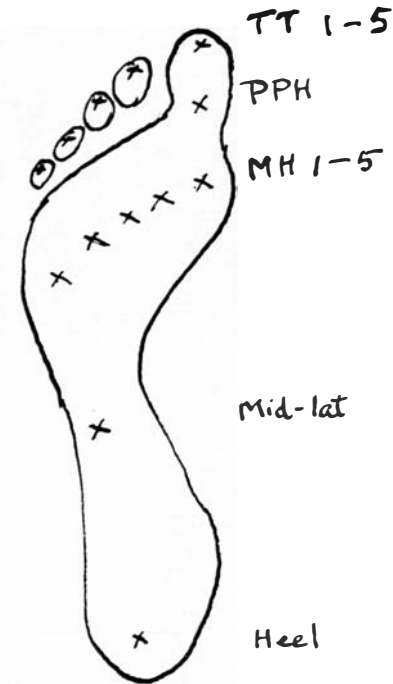
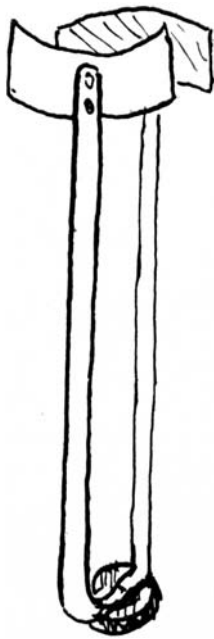


FIG. 2. Sites of plantar damage

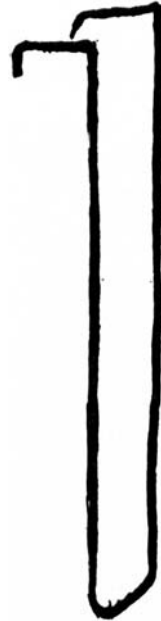
It is useful to indicate concisely sites of observed damage. The scheme is as follows:

- TT = toe tips
- PPH = proximal phalangeal head (of 1st toe)
- MH = metatarsal head
- mid-lat = mid-lateral (tubercle of 5th metatarsal)

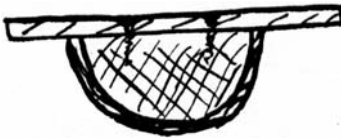




(a)



(b)



(c)



(d)

FIG. 3. *Supporting frames for walking plaster casts*

- (a) the common U-iron is made of steel band, with welded top and rubber heel.  
 (b) a simple substitute is  $\frac{1}{4}$  in. (0.64 cm.) iron rod, used by builders.  
 (c) alternatively, a wooden sole bearing a rocker can be added to a simple cast.  
 (d) another substitute is 3 in. (7.62 cm.) welded mesh, used by builders. This can reach the ground, or be used as a support and incorporate the wooden sole.

In all cases the projecting part beneath the sole must be high enough to enable the toes to clear the ground when walking.

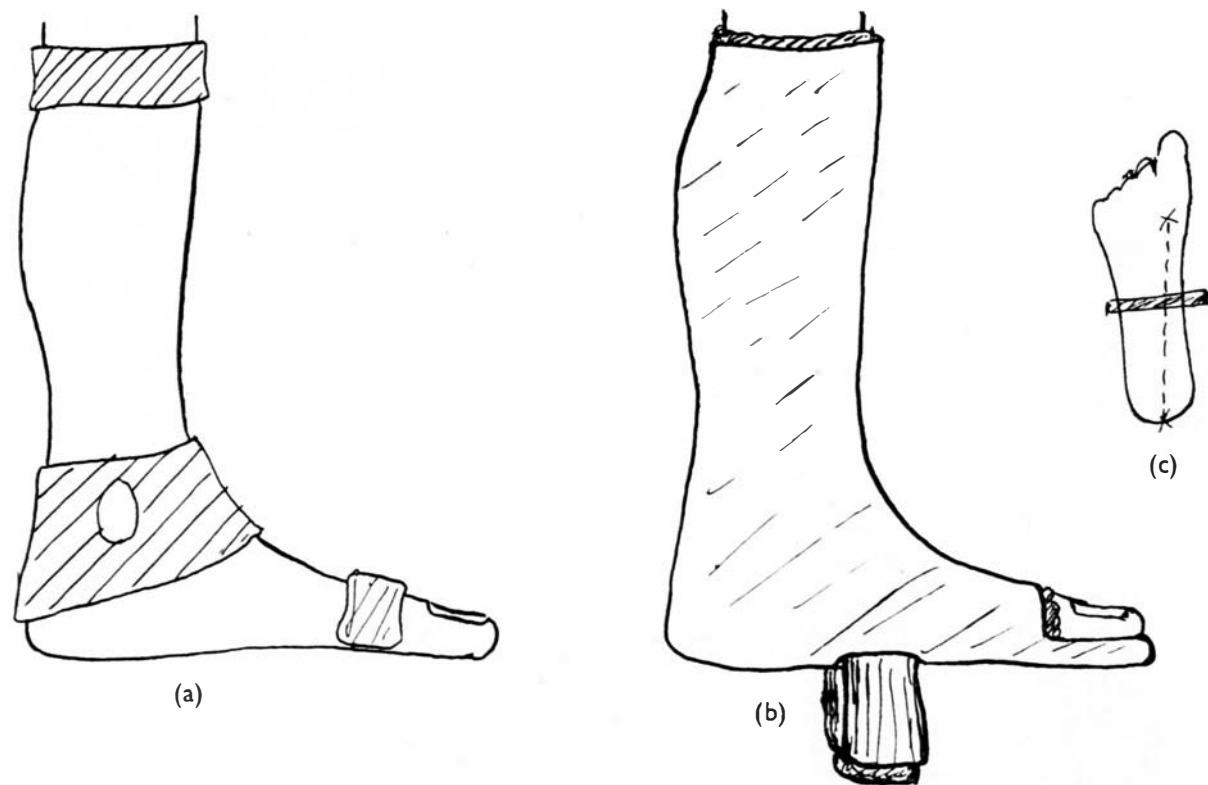


FIG. 4. *The walking plaster cast*

(a) Felt padding. This is used at the upper and lower limits of the cast, except across the sole. It is important to protect the tendons in front of the ankle, as well as the malleoli and heel.

(b) The adequate cast must support the toes and protect the tips, be sufficiently high off the ground to avoid damage to the 'heel' or 'toe' of the cast when walking, and be supported at the optimal point.

(c) Optimal point of support. This is just anterior to the mid-point of a line joining the metatarsal pad to the back of the heel.

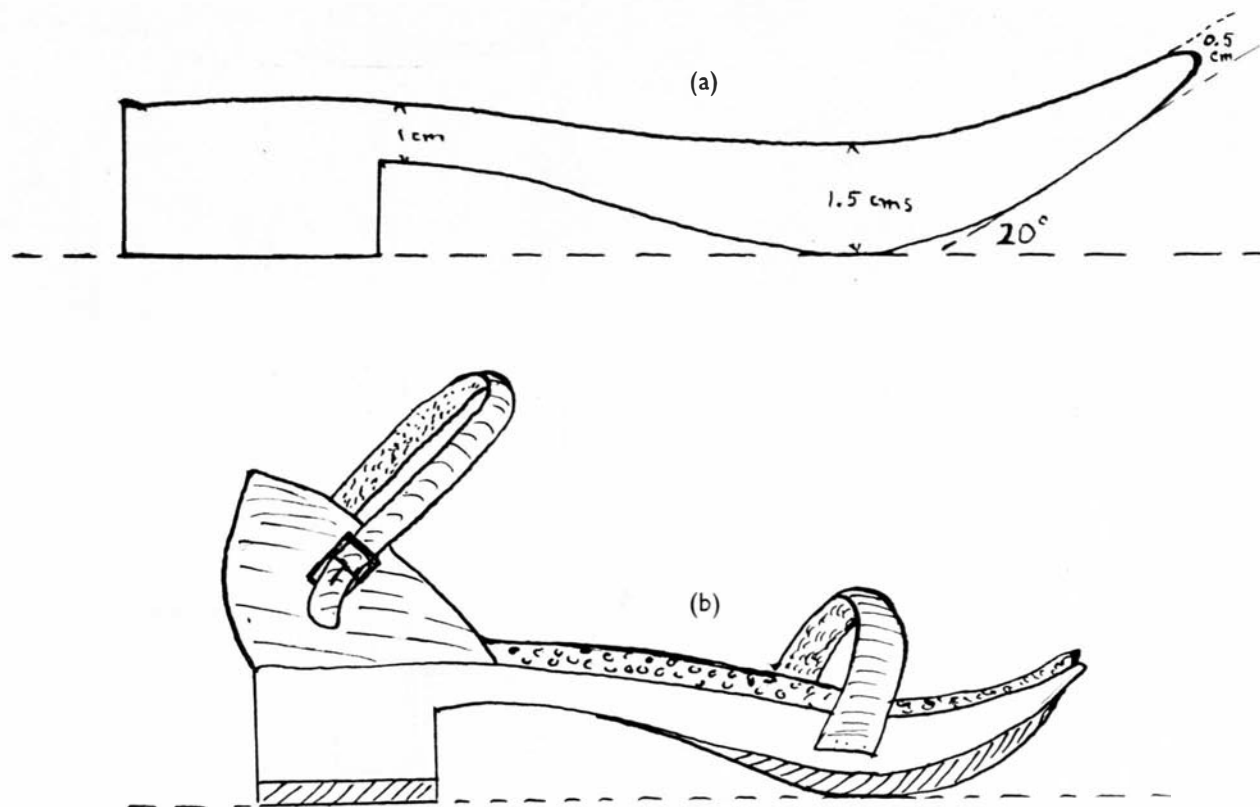


FIG. 5. *The Standard Rigid Sole Sandal*

(a) The wooden sole. This must be long enough to protect the toes, and rise sharply enough from the metatarsal pad to make possible the rolling movement needed for walking.

(b) The complete sandal. The leather heel piece incorporates a heel stiffener; the straps also are of leather and all are lined with felt. The insole is sponge rubber bonded to canvas as used for carpet underlays. The heel and sole are protected by rubber; special sizes and shapes are obtainable from clog manufacturers.

the cast, and one soon recognises the healthy smell of a healing ulcer from one due to skin damage.

In a short time it becomes possible to apply a cast with confidence securing the absence of traumatic points of pressure.

The cast is then examined weekly after the first week, and is removed after six weeks. In many cases, the ulcer is already healed. If not the cast is reapplied repeatedly until healing occurs. This may take a year in difficult cases. With experience the initial healing can be hastened by the judicious use of Thiersch skin-grafts, but this must not be considered as permanently adequate cover. When healing has occurred, the question of the soundness of skin cover arises.

### *Management of Skin Loss*

This is a problem of plastic surgery, and few except specialised centres will have the necessary skill or facilities. It must be emphasised however that a healed ulcer will break down under stress unless skin cover is adequate. Skin cover is adequate if the area of skin loss is replaced by skin in complete or partial thickness; it is not adequate (except in minimal cases) if cover consists of scar tissue with an epithelial or Thiersch-graft surface. The breaking down of a healed ulcer may therefore represent the call for a plastic procedure beyond the possibilities of a local leprosarium. The ulcer is then 'incurable' under local circumstances. But if adequate footwear is provided scars otherwise precarious may support the strains of walking surprisingly well. Description of adequate footwear now follows.

### **3. The Management of Healed Ulceration**

The healing of a plantar ulcer must be considered as only a stage in the treatment. If further measures are not taken, there is likely to be a recurrence. These measures include provision of special footwear, for which the essentials are a rigid sole and a soft insole. The rigid sole forestalls deep damage between soft tissues and the bony skeleton of the plantar region. The soft insole forestalls damage caused by friction between the skin surface and the immediate points of contact. The writer has found that the above criteria are best met in Africa by the use of wooden soles, carrying a sponge rubber insole. All available alternatives have been tried, plastics, rubber tyres, felt, etc., but found unsatisfactory for various reasons.

A foot without deformity can be fitted with a standard sandal (Appendix 2) but any marked deformity from scarring necessitates specially prepared footwear (Appendix 3). Regular foot inspection is as important for those with footwear as for those without, inspection which includes the footwear as well as the foot.

In brief, rigid sole footwear is indicated for all cases which fall into the following categories:

- (a) Feet with threatened plantar ulceration.
- (b) Feet with healed plantar ulceration.

In the early days of control, most cases will be those with recently healed ulcer; but as control proceeds the proportion changes, until finally footwear is only found on patients with threatened ulcer, no cases of actual ulceration being permitted to occur.

The failure of adequate rigid sole footwear to control the occurrence, or recurrence, of plantar ulceration is an indication of the existence of an untreated complication.

For convenience of reference, the common complications are summarised here, though treatment is described elsewhere: an unco-operative patient; inadequate skin cover for the ulcer; persistent bone infection; badly fitting sandals; inadequate circulation, whether hypostatic and connected with lack of exercise, or due to lymphatic or venous blockade; other debilitating conditions, such as diabetes.

### *The Results of Treatment*

A series of cases has been under careful study at Oji River, and the following observations have already been made.

Attendance at the 'ulcer shed' fell from 75 daily to under 15 (not all foot ulcers). The 'ulcer shed' as a part of leprosarium organisation should be no longer necessary.

The early uncomplicated plantar ulcer will heal in about 3 weeks with complete rest in bed, but takes a week longer if treated in a walking plaster from the start.

A simple ulcer of longer duration will take six weeks to heal in a walking cast, and this had been the usual time before removal of the first cast. The longest time necessary to achieve healing was 15 months. There was no obvious correlation between the length of time during which an ulcer had remained unhealed and the time taken to heal under plaster.

Ulcers which had persisted for three years healed sometimes in two months, whereas some recent ulcers took a longer time.

This means that the duration of the ulceration is less important than the actual complications which are present.

It is too early yet to say when, if at all, it will be safe to relax the use of rigid sole footwear. If anaesthesia persists, it can be surmised that special footwear will be necessary permanently, and in this case it will demand the help of a professional shoemaker to conceal (in traditional footwear) the particular therapeutic features.

It can however be confidently expected that the odour, prolonged hospitalisation, and associated unpleasantnesses of the many

cases of chronic plantar ulceration can be averted, and that we can aim at the complete suppression of this complication in leprosy.

*Appendix 1. The Walking Plaster Cast (Figs. 3, 4)*

To apply a satisfactory plaster cast for walking, attention must be given to protection of pressure points and of the toes, and to the position of the supporting frame.

Before applying the plaster, the patient should be recumbent with the foot of the bed raised for at least 24 hours in order to combat any oedema present. If this is not done the cast rapidly becomes loose in the first few days.

The skin is best protected with a sleeve of stockinette, but if this is omitted for reasons of economy the hair of the leg should be shaved to avoid the discomfort of hairs trapped in the plaster. It is often wise to sprinkle a parasitocidal powder such as DDT on to the skin before applying the cast.

Pressure points (Fig. 4a) are then protected with a half-thickness of grey orthopaedic felt ( $\frac{1}{4}$  in. or 0.64 cm.); this felt readily pulls apart into two layers and is much cheaper than the white variety.

The supporting frame may be of steel, iron or wood (Fig. 3). In either case, the point of support should be just anterior to the midpoint of the line joining the metatarsal pad to the back of the heel (Ruding, 1956). The projecting part must be high enough to prevent the 'toe' of the plaster from scraping the ground at the end of the step.

The toes are protected by ensuring that the plaster sole projects beyond the tips, and is strong enough to give adequate protection. After drying, which must take place in bed before the patient begins to walk, the patient is allowed up and to walk with the help of a crutch or stick (if necessary). A coat of varnish for the cast is a useful protection against water and rain.

After a few days of use the cast will become looser than it was on application. Even if it is obviously weight-bearing, this is not of significance so long as it effectively controls the extension movements of the sole. However, loose casts are more likely to cause friction sores than casts which fit snugly.

*Appendix 2. The Standard Rigid Sole Sandal (Fig. 5).*

In providing rigid sole footwear it is convenient to prepare pairs of standard sizes of sandals. This is done after a preliminary survey of the commonly prevailing size of feet in the region. The sole of the sandal is then prepared in wood, and uppers in leather, and the insole in sponge rubber. The best materials depend on local conditions, but in Africa the following were found most suitable after trial of rubber tyres, thick leather, and plastics such as polythene:

*Wood* is the easiest and cheapest material to work for soles. It is

easy to obtain and can be worked by local craftsmen using their traditional tools. It is best to rely on their judgment as to the best wood to use; a kapok tree provides enough wood for a large leprosarium for over a year. The wood is cut into lengths of a metre or so; the core of heart wood is removed and the segments of trunk are then stacked to dry. Ideally, the wood should dry for a year or more, but work can begin on the fresh wood. The shape of the sole is indicated in Fig. 5a. The sizes given indicate convenient proportions. It is important to note that:

- (i) the patient's foot should slope slightly downwards, from heel to metatarsal heads;
- (ii) the sole then rises sharply to the toe of the sandal;
- (iii) the point of contact of the forefoot underlies the metatarsal heads of the foot, and the sole then rises at an angle of  $20^\circ$  to the ground.

These standards are those that meet the mechanical conditions of the walking forefoot, and are observed in all rigid sole footwear such as clogs, army boots, farm wear.

The *uppers* are made from local leather, and must be soft enough not to chafe the skin. The heel is stiffened by a heel stiffener that fits between two layers of leather as in a pocket. The best and cheapest are the ordinary commercial heel stiffeners supplied to sandal makers. The heel piece must project a definite distance up the back of the heel; if it is too short, it tends to leave the heel at the end of the step, while if it is too long it will cause a friction sore at its upper end. The heel of a normal shoe can be observed for this purpose. The straps are of soft leather, but only the ankle strap needs a buckle. All leather is lined with a half thickness of  $\frac{1}{4}$  in. (0.64 cm.) grey orthopaedic felt, using an adhesive.

The *insole* is best made from one of the types of rubber underlay manufactured in Europe and America for carpets. It consists of sponge rubber bonded to a canvas fabric which is readily cut to measure and can be fixed to a wooden sole by adhesive or by tacks. An example is Duralay.

The complete sandal is fitted to the patient, and may need slight modification. The patient is observed daily for the first few days, especially when the anaesthesia extends up the ankle. In some cases it is essential to provide short socks, when the skin is particularly susceptible to injury.

When the patient is discharged and lives or works in a town he will want the characteristics of his footwear to be concealed and this can be done easily by a skilled shoemaker but it is a professional job that will be outside the scope of the average leprosarium.

#### *Appendix 3. Rigid Sole Footwear for Deformed Feet*

Deformed feet cannot be satisfactorily fitted with standard sandals, and in most cases it is necessary to make special footwear.

It will be noted that in cases where infection has already disorganised the forefoot the desiderata of rigid sole footwear do not apply and the only purpose of the sandal is to protect the foot from injury. Grossly deformed feet may need amputation.

The procedure for a sandal is as follows:

A plaster cast is made of the foot. A wood carver then prepares a negative of the sole on the upper surface of a block of wood from which the sandal will finally be made.

The negative need not be an exact fit but should follow the general contour of the foot. When this is done the sandal is completed as for a standard model; but the position of the point of contact with the ground and of the straps of the uppers will vary from case to case and demands skill and perseverance.

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## LEPROMIN SENSITIVITY

J. A. KINNEAR BROWN, B.Sc., M.D. (MANC.), M.R.C.S., D.T.M.  
*Specialist Leprologist, Uganda*  
and M. M. STONE, S.R.N., S.C.M.  
*Kumi Ongino Leprosarium, Uganda*

### 1. Introduction

Lepromin conversion following BCG vaccination is now a well accepted fact although opinions differ about the extent to which the initial lepromin injection is responsible for the change. Wade (1956) has suggested that the test dose contributes by conditioning the individual to react; it would indeed be strange if the injection of leprosy bacilli had no effect whilst lepromin sensitivity had often to be ascribed to unrecognised contact with unrecognised organisms, that were probably less virulent.

Ignacio, Palafox and José (1955) produced lepromin positivity in children after repeated lepromin injections, work which has since been confirmed by Bechelli (1959). In an important controlled experiment, in which children were vaccinated with BCG, Doull, Guinto and Mabalay (1957) showed that 11.5% of the lepromin positives that followed the vaccination were due to 'natural causes' (i.e., causes unknown), 7.2% to the initial dose of lepromin and 33.4% to the actual vaccination. These studies have helped to evaluate some of the important causes of group sensitivity. The proportions, however, that became lepromin positive as a result of the lepromin test, or 'natural causes', should not obscure the still larger proportion that owed their conversion to BCG vaccination, nor the value of the mechanism 'lepromin test plus BCG vaccination plus lepromin test' which produced more conversions than any of the components alone.

### 2. The Multipuncture Depot Lepromin Test

In every investigation a test dose of 0.1 ml. of 1 in 20 lepromin, a tissue suspension of leprosy bacilli, has been injected intradermally. In the work now recorded we used the multipuncture depot lepromin test we previously described (Kinnear Brown and Stone). This correlates well with the classical Mitsuda over which it has advantages. It economises antigen, produces no discomfort, and need be applied only once to ascertain the effect of BCG vaccination. It is therefore especially useful for detecting poor reactors among contacts of patients or among the general population, and it can be used in any strength from 1 in 20 to 1 in 100 where it is desired to know who ought to be protected. Where the multipuncture injection was employed as an indicator, only those children who were subsequently BCG vaccinated showed lepromin conversion, suggesting that the small test dose had itself no appreciable effect on lepromin sensitivity.

3. The Influence of Tuberculin, Lepromin, and BCG Vaccination on Lepromin Sensitivity

Children attending 11 primary day schools were tested with lepromin, tuberculin, or both. Their ages ranged from 5 to 16, and the age distribution in corresponding classes was similar. The allocation of children to the experimental series was either by school or by class to obtain comparable groups.

Some children received both test injections at the same time; others at intervals. The lepromin used was a 1 in 20 depot preparation, except where stated that it was 1 in 100. It was given by the multipuncture route. The tuberculin P.P.D. was obtained from The State Serum Institute, Copenhagen. It was administered as a Mantoux test (using 5 TU), or by the Heaf multipuncture method. The children chosen for vaccination were those reacting with less than 10 mm. infiltration to the Mantoux test, or with less than Grade II to the Heaf, the assumption being that small and intermediate responses were not generally due to infection with the tubercle bacillus (WHO, 1959). The expression tuberculin negative in this report implies only that the response was less than the standard defined above. The BCG used was the Glaxo freeze dried preparation.

The first part of this work and its results can be summarised as follows:

<i>Group A</i>	Percentage of lepromin positives in 472 children none of whom had had any test except the single lepromin test now given:	56 %
<i>Group B</i>	Percentage of lepromin positives in 255 children none of whom had had any previous test and who now were given the Heaf tuberculin and depot tests together:	59 %
<i>Group C</i>	Percentage of lepromin positives in 124 children none of whom had had any previous test except the Heaf tuberculin test 5 weeks earlier:	55 %
<i>Group D</i>	Percentage of lepromin positives in 179 children who had been Mantoux tested 6 months earlier with BCG vaccination of the tuberculin negatives:	86 %
<i>Group E</i>	Percentage of lepromin positives in 148 children who had been Heaf tuberculin tested 5 weeks earlier with BCG vaccination of the tuberculin negatives:	87 %

The tuberculin tests made at the time of the lepromin tests, or earlier, had no significant effect on the lepromin results. The 851 children in Groups A, B and C had a lepromin positive rate of 57 %.

In the schools where the tuberculin negatives had been BCG vaccinated, the lepromin positive rates were the same whether the lepromin tests were made one month or six months after vaccination.

They were higher by 29% than in comparable groups of children, in which the tuberculin negatives had not been vaccinated. It did not appear to matter whether the Mantoux or Heaf standard was used.

(The difference between Groups A and B is 3%; less than the Standard Error of 3.8: that between Groups B and C is 4%, less than the Standard Error of 5.4. Neither of these differences is significant. The tuberculin could have had no effect. The difference between Groups B and D is 27% nearly 7 times the Standard Error: that between Groups A, B and C taken together and D and E combined is 29%, nearly 10 times the Standard Error. These differences are therefore significant. The BCG vaccination was responsible for the change.)

In 316 children belonging to Groups D and E the tuberculin test was repeated. Of these 234 had been tuberculin negative. After BCG vaccination 231 became tuberculin positive. The results are given below:

*Comparison of Lepromin and Tuberculin Results*

<i>Tuberculin test used</i>	<i>Group F Lepromin result in natural tuberculin positives</i>		<i>Group G Lepromin result in converted tuberculin positives</i>		<i>Lepromin result in persistent negatives</i>	<i>Total</i>
	+	—	+	—		
Mantoux	40	13	105	9	0	169
Heaf	23	6	107	10	0	147
Total	63	19	212	19	0	316
	82		231		3	

*Group F* The percentage of lepromin positives among the naturally occurring tuberculin positives (63/82) was: 77%

*Group G* The percentage of lepromin positives among the BCG converted tuberculin positives (212/231) was: 92%

(If the Mantoux and Heaf groups are separated there is little difference, e.g., percentage of lepromin positives in the natural tuberculin positives: Mantoux 75%, Heaf 79%; percentage of lepromin positives in the BCG'd tuberculin positives: Mantoux 92%, Heaf 91%.)

*Group H* In 615 other children in comparable age groups the percentage of lepromin positives among the natural tuberculin positives (289/400) was: 72%

*Group J* If groups F and H are taken together the percentage of lepromin positives among the natural tuberculin positives (352/482) was: 73%

In none of this work was there any interference by a previous lepromin test. The lepromin positive rate was significantly higher among the tuberculin negatives who converted after BCG than among those who were already tuberculin positive.

(The difference between Groups F and G is 15%, 3 times the Standard Error of 5; that between Groups J and G is 19%, 7 times the Standard Error of 2.7. These differences are significant. The BCG vaccination was responsible for the change.)

#### **4. Strength of the Lepromin Response**

Of 644 children, none of whom were vaccinated:

40% were lepromin negative,

36% were lepromin positive Grade I

24% were lepromin positive Grade II or stronger.

Of 281 other comparable children, whose tuberculin negatives were BCG vaccinated:

10% remained lepromin negative,

32% became lepromin positive Grade I,

58% became lepromin positive Grade II or stronger.

The BCG vaccination was not only followed by a significant increase in the number of reactors, there was also a significant increase in the strengths of the reactions. This confirms the observations of Convit (1956).

#### **5. Comparison of 1:20 and 1:100 depot lepromin**

Six hundred and fifteen children were Heaf tuberculin tested. They were also lepromin tested with 1 in 20 depot lepromin; 274 others were Heaf tuberculin tested but a lepromin test was made with 1 in 100 depot lepromin. 65% of the 615 and 66% of the 274 were tuberculin positive.

The 1 in 20 lepromin discovered 59% positive reactors, the 1 in 100 lepromin only 45%. The stronger antigen is thus more efficient in provoking a reaction in those who have any capacity to respond. The diluted antigen on the other hand makes a clear cut distinction between those who would react satisfactorily to normal antigen and those whose response would be negative or inadequate. Where the supply of antigen is limited, a multipuncture depot lepromin test, using a concentration weaker than 1 in 20, will safely indicate those who need further protection.

#### **6. Lepromin results according to age**

The following table gives the percentage of lepromin positives and negatives in each two year age group. (It is difficult to assess the ages of children with greater exactness.)

<i>Ages</i>	<i>Percentage Positive</i>	<i>Percentage Negative</i>
5 and 6	29	71
7 and 8	46	54
9 and 10	56	44
11 and 12	62	38
13 and 14	71	29
15 and 16	78	22

The positive reactor rate increases steadily with age; it has not yet been established among any group older than age 16. The reactor rate after BCG was 86%–87%. It might have been higher had the lepromin tests been read again after the 21st day. (In one group it was 92%.) It follows that any measure that will increase the lepromin positive rate from 29% at ages 5 and 6 to 86% (which had not been reached in this series at age 16) is worth considering. It could certainly do no harm.

### Conclusions

1. The test injection of tuberculin did not affect the response to lepromin whether given previously or at the same time.
2. In comparable groups, the lepromin reactor rate after BCG vaccination of the tuberculin negatives was 29% higher than in the controls who had only the one lepromin test. The same results were obtained one month after BCG vaccination as after six. The difference between the control and vaccinated groups is significant and is due to the vaccination.
3. The lepromin reactor rate among those who became tuberculin positive after BCG vaccination was significantly higher than among the naturally occurring tuberculin positives. Sensitivity probably includes more than one or two elements. The BCG vaccination was responsible for the change.
4. BCG not only increases the lepromin reactor rate; it increases significantly the number of strong reactors.
5. A less concentrated antigen can be used where it is desired only to distinguish weak or negative reactors from those whose response is adequate.
6. The lepromin reactor rate varies from 29% at ages 5 and 6 to 78% at ages 15 and 16. BCG vaccination produces within one month a rate which would not otherwise be reached for many years.
7. Doubt has been thrown on the part played by BCG in producing lepromin conversion because lepromin injected intradermally in much larger doses than were used in this work can itself sensitise. This work was so planned however that the test injection could not contribute to the sensitivity that developed.

8. In the anxiety to establish the respective parts played by the injection of lepromin and BCG vaccination the importance of the sequence 'lepromin test plus vaccination plus lepromin test' may have been overlooked. The synergic or adjuvant actions of the lepromin and BCG may produce more lepromin conversions than either could alone. The subject should be explored more fully with the object of producing a combined technique that will deal with those who are persistently lepromin negative. The value of BCG is not lessened because lepromin itself helps to sensitise.
9. This work confirms the advantages of the multipuncture depot lepromin test. In one group the used injection apparatus produced a series of positive results on the arms of each volunteer without the application of fresh antigen to the skin.

### Acknowledgments

We are indebted to Dr. H. W. Wade, Editor of *The International Journal of Leprosy* for suggestions that helped us to plan this work. We are grateful to Dr. G. Murray Short, Medical Officer (Tuberculosis), Uganda, for his advice, and to Dr. J. M. Lea, Medical Superintendent of the Kumi Ongino Leprosarium for his co-operation.

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I. Bacteriology of Rat Leprosy: Electron Micrographs of Rat Lepromas and Cultures with Three Plates  
*From the Instituto Oswaldo Cruz, Rio de Janeiro*

by H. C. de SOUZA-ARAUJO, M.D., DR.P.H.  
*Professor of Leprology (1936-1960)*  
*University of Rio de Janeiro*

In 1936 I started working with three strains of lepromas of rats, from Berlin, London and Paris, obtained respectively through Professor Ficker, Professor Laidlaw and Professor Marchoux<sup>1</sup>. With them I tried many times to isolate and cultivate the bacillus of Stefansky, but failed.

At the time I studied the two strains of acidfast bacilli obtained in the U.S.A. from rat leprosy, being culture N.367 'Rat 2' and culture N.368 'Rat McCoy', of the American Type Culture Collection (ATCC) isolated about 1910 and 1911<sup>2</sup>.

In 1931 and 1932 Dr. Schuzo Asami obtained, in Japan, two strains of acidfast cultures from rat leprosy, which he named *Mycobacterium leprae muris cremeum* and *Mycob. leprae muris vitellinum*<sup>3</sup>, pathogenic for laboratory animals.

On 12th September, 1947, Doctor Roland Chaussinand kindly furnished to me, in Paris, his strain of rat-leproma of the Institut Pasteur. With this good strain I made 'S' lepromin and antigen for immunological researches and inoculated white rats, laboratory-bred, obtaining from their lesions in 1948 two chromogenic strains (yellow, type smooth 'S' of pure acidfast bacilli) and in 1949 obtained also from experimental lesions of black mice, American race C-57, two other strains which were non-chromogenic (eugonic type 'R'). All four of these cultures were infective for rats and mice, always giving positive retrocultures. I exhibited these four cultures to the Vth International Congress for Microbiology, on 19th August, 1950, in Petropolis, completing my report with the following notes:

" . . . these two non-chromogenic cultures are more pathogenic than the chromogenic ones. Recently Dr. Laerte Andrade proved, by repeated tests, that the strains I and II (chromogenic) treated by auramine are fluorescent, and negative to the Dubos cytochemical test for virulence, while the strains III and IV (non-chromogenic) are positive for both<sup>4</sup>".

I sent to Dr. R. Chaussinand samples of all four original strains of rat leprosy, advising him that probably his rats were infected with an association of two *Mycobacteria*, perhaps the chromogenic being a symbiotic. I sent also these four cultures for study to Professor Pierre Hauduroy, Director of the International Centre of Type Cultures, Lausanne, Switzerland; Professor Giuseppe Penso, Director, Instituto Superiore di Sanità, Rome, Italy; Professor

Charles M. Carpenter, Medical School, University of California, Los Angeles, Calif., U.S.A.; Dr. Frederick Eberson, Chief Pathologist, Veterans Administration, Memphis, Tennessee, and Dr. F. Johansen, Medical-in-Charge, National Leprosarium, of Carville, Louisiana, U.S.A.

Testing the bacteriostatic action of Hydrazide Schering, I mixed one part of a solution of this product with another of rat leproma, and inoculated batches of white rats and black mice, proving that the classical rat leprosy lesions were produced normally. From such experimental lesions I obtained, by Loewenstein and Petroff methods a mixed white and yellow culture, which I was able to separate by successive transplants in Loewenstein medium. These findings I communicated to the VIth International Congress for Microbiology, held in Rome, Italy, in September, 1953, finishing my paper with the following notes:

“*Yellow strain*: Dubos cytochemical test for virulence, negative (although pathogenic for murines). Fluoroscopy: positive, 1-plus. Stained by Ziehl-Neelsen: median size bacilli strongly a.a. fast; by ‘Fontes’: typical bacilli, most homogeneous with pale cytoplasm and dark-blue granules. *White strain*: Test of Dubos, positive 2-plus. Fluoroscopy positive 2-plus, very bright fluorescence of bacilli and granules, showing the aspects of fresh suspension of rat leproma. Stained by Z-N: mainly coccobacillary forms, strongly a.a. fast; by Fontes: all classical forms of Mycobacteria. These cultures seem to be the same previously isolated, many times, from the same source . .”

### Conclusions

1. Hydrazide did not change the morphology and staining properties of the Stefansky's bacilli and did not cure leprous rats nor delay the progress of the disease.

2. Hydrazide seems to have facilitated the isolation and culturing of the inoculated acidfast bacilli originating from rat leprosy<sup>5</sup>.

Some of the electronmicrographs of Plates 1, 2 and 3 are similar to those published by Bishop, Suhrland and Carpenter<sup>6</sup> and others.

### Acknowledgment

Many thanks are due to Professor Mario G. Malfatti, Chief, Laboratory of Electronic Microscopy, Navy Hospital of Buenos Aires, and Drs. Hans Muth and Penna Franca, of the Electronic Microscopy Laboratory, Instituto Oswaldo Cruz, Rio de Janeiro, who made the electronmicrographs of rat leproma and my cultures.

## II. Bacteriology of Human Leprosy

Since 1928 I have been working in the bacteriology of leprosy. From 1930 till 1940 I made intensive studies with the fourteen classical



strains of 'Bacillus leprae' from the Lister Institute of London and six others of the ATCC, from the National Institute of Health of Washington. During this decade I tried many times to isolate and cultivate the bacillus of leprosy, from various kinds of human material, and failed. Only in October and November of 1941 I secured two absolutely identical strains of a chromogenic (golden-yellow) culture of a permanent acid-alcohol-fast bacillus, from close skin lesions of a seven-years-old boy (José F.) coming from the North of Brazil (State of Piauhý), son of leprous parents and having an elder sister also a lepromatous case and another with pulmonary tuberculosis, who died within one year of residence in Rio.

Such culture I baptised as strain 'José I', which was used to infect guinea pigs, rats and mice, from whose lesions I recovered the culture.

The original strain was used in April, 1943 to prepare a kind of leprolin (Leprolina 'Souza-Araujo', Strain José, 1941), similar to that prepared in Burma, in 1904, by Major Dr. E. R. Rost, using his original acid-fast culture of leprosy bacillus. My leprolin is being employed in the treatment of leprosy and of some neurological diseases, and also in immunological studies.

From 1941 to 1958 I secured about fifteen new strains of acid-fast bacilli from human and rat leprosy lesions, most of them already published.

In this article I will report only the electron microscopy of a few bacteria of said cultures. The complete material will be used in another future article, entitled: 'A review of 30 years work in bacteriology of leprosy'.

The electronmicrographs of this paper, in many occasions from fields selected by myself, were kindly made by Professor Dr. M. G. Malfatti, University of Buenos Aires, and Drs. Hans Muth and Penna Franca, of the Instituto Oswaldo Cruz, Rio de Janeiro, to whom I am most grateful.

*Nota Bene: All electronmicrographs of Professor Malfatti were taken at 3,700x and enlarged as convenient. The morphology of bacilli is different according to solid or liquid state of the culture media.*

Rio de Janeiro, 28th April, 1960, Instituto Oswaldo Cruz.

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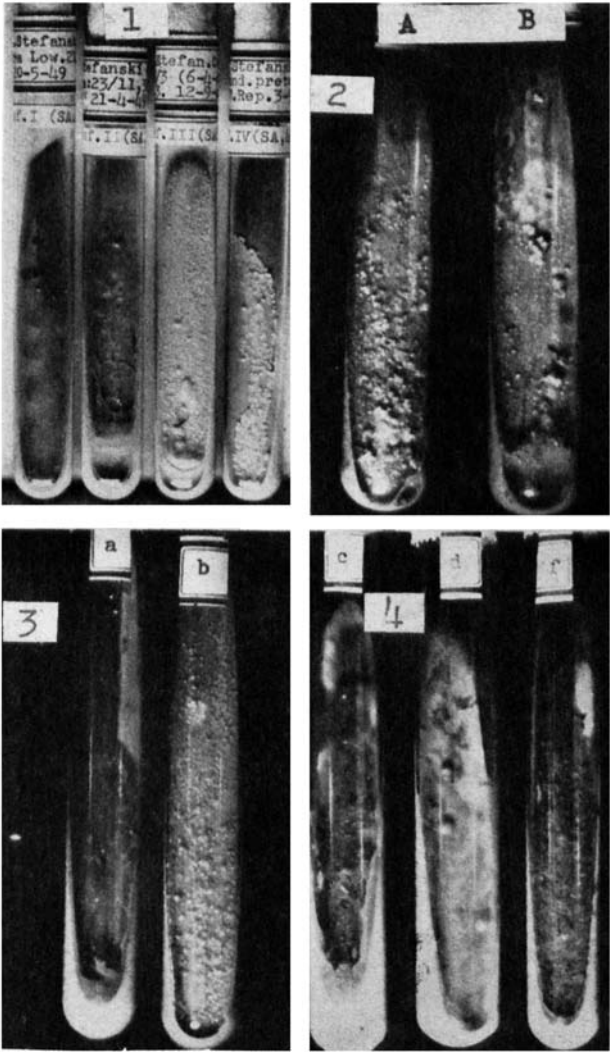


PLATE I

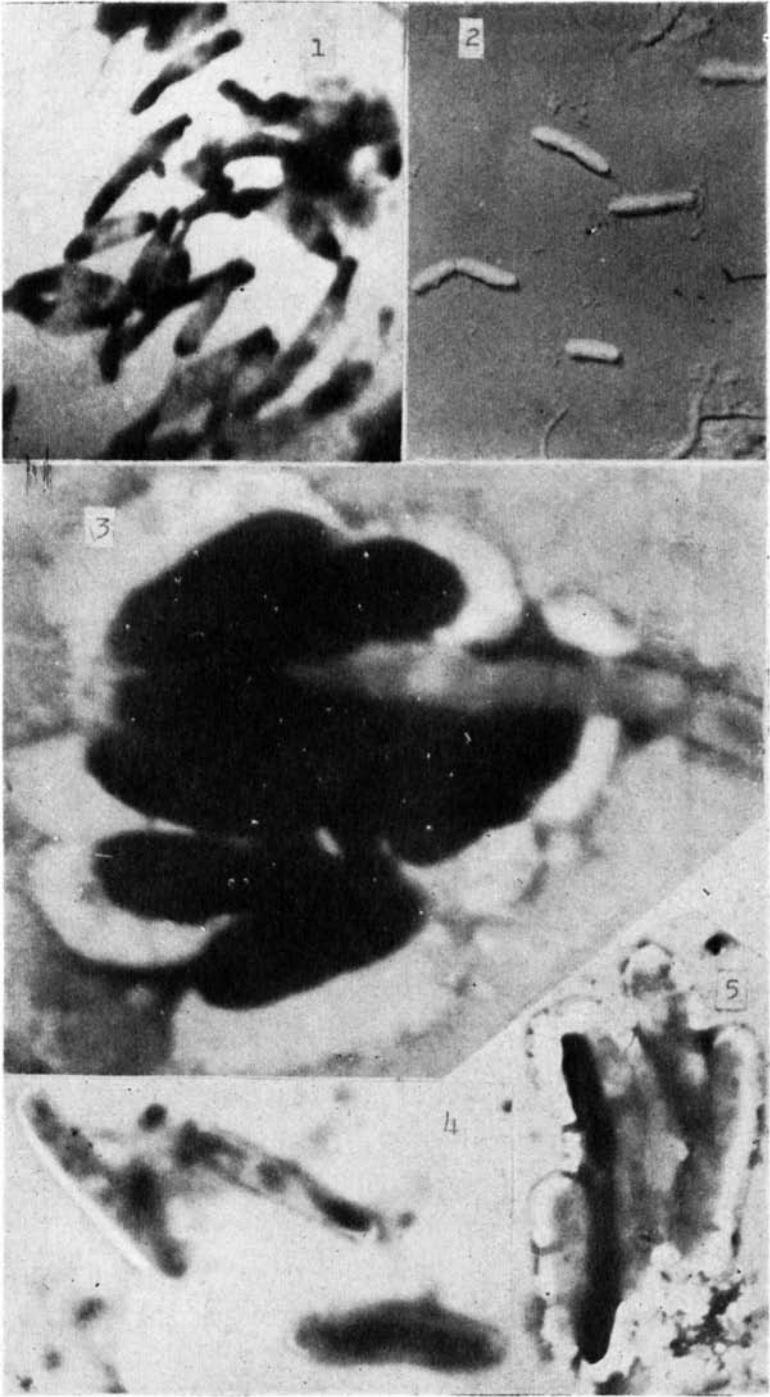


PLATE 2

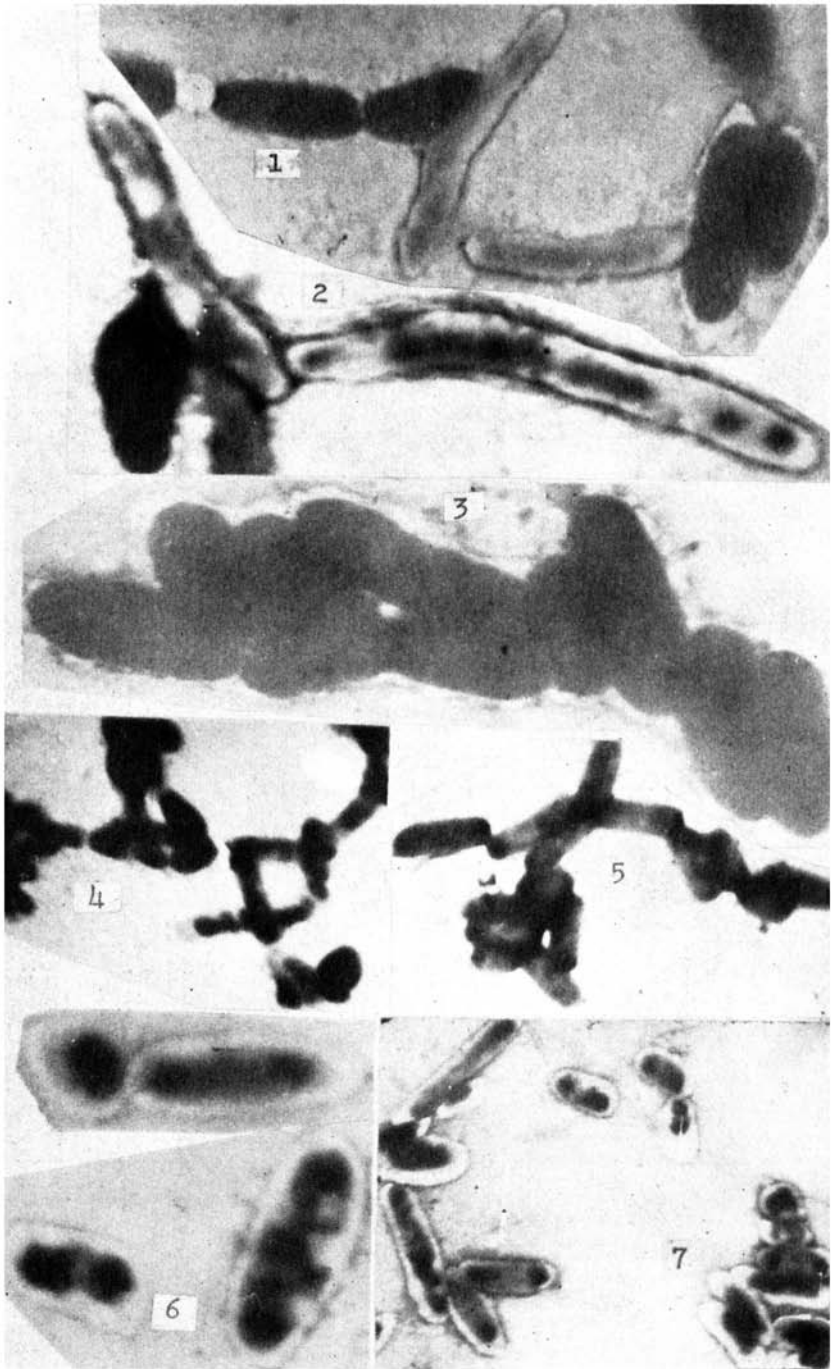


PLATE 3



PLATE 4

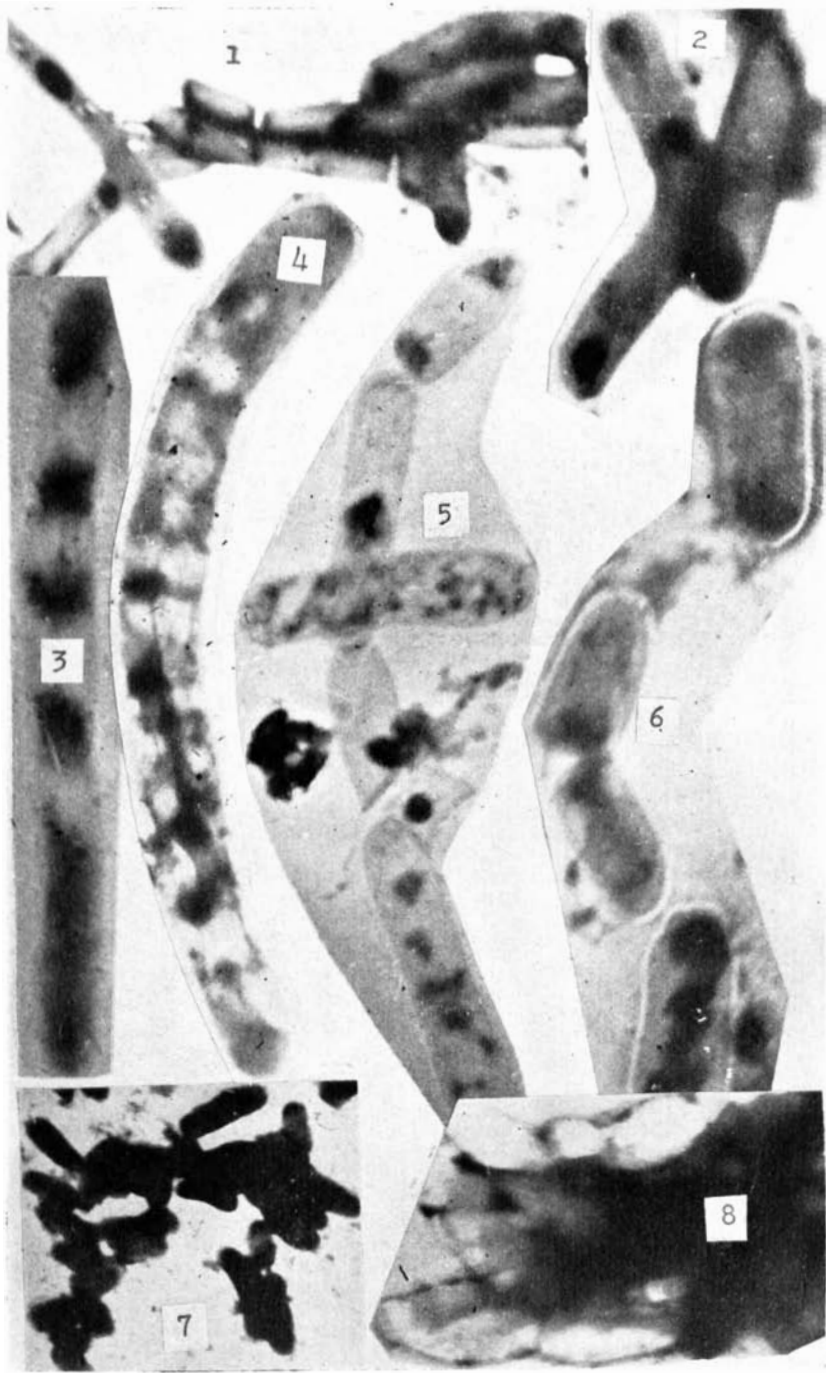


PLATE 5

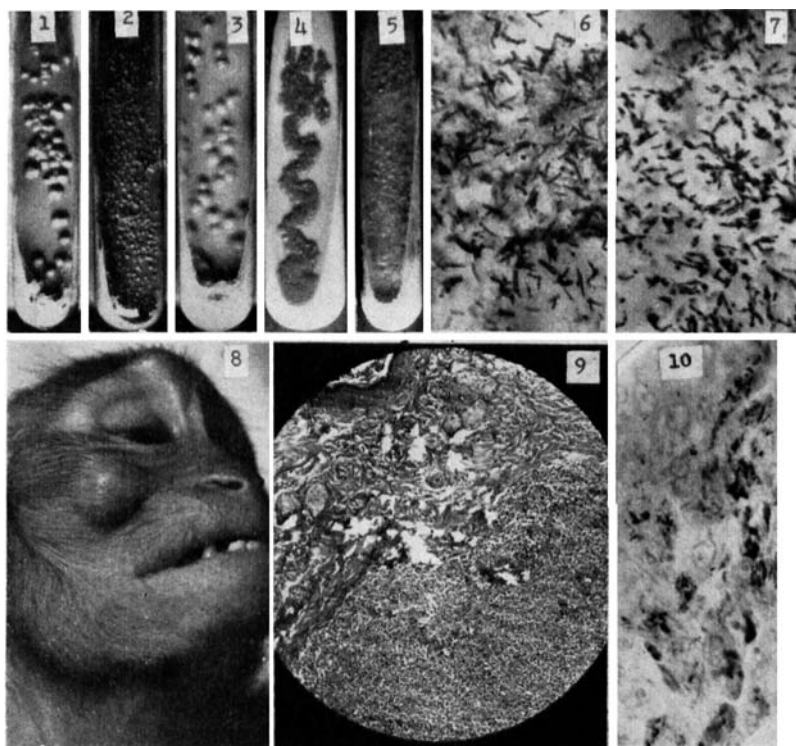


PLATE 6

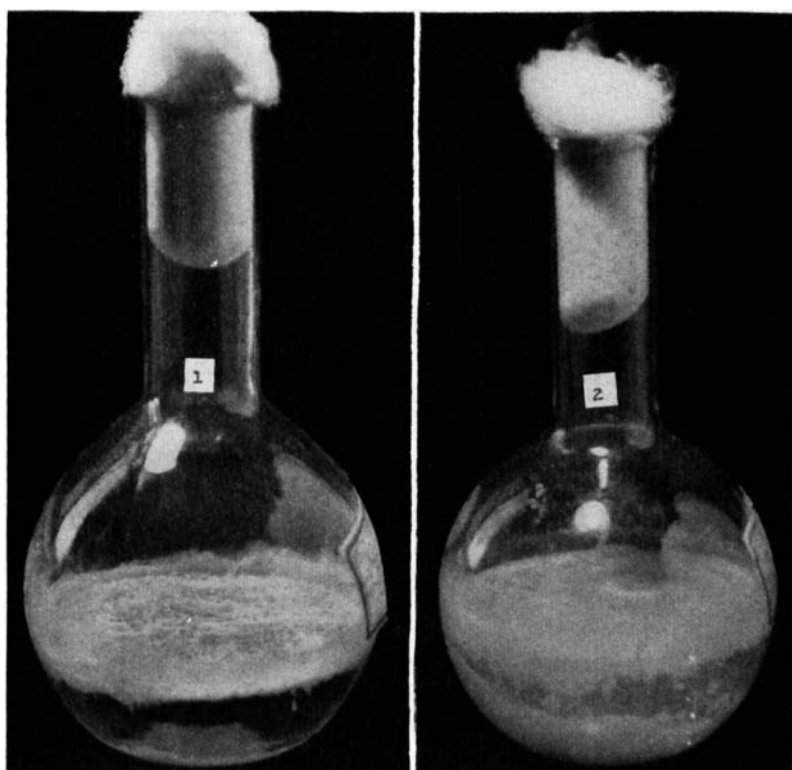


PLATE 7

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## PLATE 1

FIG. 1. Stef. I and Stef. II yellow cultures, 'S' type, isolated from white rat inoculated with Institut Pasteur strain in 1948; Stef. III and Stef. IV non-chromogenic, isolated in 1949 from black mice, type 'R'.

FIG. 2. A and B cultures in Loewenstein of strains III and IV, type 'R', cremeum, isolated from experimental lesion in black mice.

FIG. 3. (a) Yellow 'S' culture isolated from white rat inoculated with a mixture of suspension of rat leproma and solution of Hydrazide, after six months of incubation. (b) White culture isolated from white rat lesion produced by the above mixture of Hydrazide and rat leproma.

FIG. 4. (c) the original yellow culture from rat, 1948, in Loewenstein. (d) Yellow 'S' culture obtained from lesion of pectoral skin of a rhesus monkey infected with rat leproma. (f) The same above culture recovered from the pellicle produced in Dubos medium: yellowish, granulated, mutating to eugonic 'R' type.

(Photos: Jose Mello)

## PLATE 2. Electron Micrographs

FIG. 1. Fresh suspension of rat leproma, Inst. Pasteur strain, showing normal bacilli with bipolar condensations, or central, of the metachromatic granules. Increased from 3,700x. (Malfatti).

FIG. 2. Rat leproma suspension shaded by chromium vapour. (H. Muth).

FIG. 3. Emulsion of rat leproma: bacilli in mass circumscribed by neat gloea. 19,000x. (Penna Franca).

FIG. 4. Three Stefansky bacilli with their condensed metachromatic granules and gloea. 14,000x. (Penna Franca).

FIG. 5. Group of Stefansky bacilli from lesion of black mouse infected with leproma of a rhesus infected with rat leproma; with fringed large gloea. 18,000x. (Penna Franca).

## PLATE 3

FIG. 1. Fresh suspension of rat leproma, 5 months incubation, showing the association of two mycobacteria. Two short ones with gloea. 18,000x. (Penna Franca).

FIG. 2. Another photo of the same suspension above confirming the association of two mycobacteria: one large bacillus with 3 nodules in its ends and 2 bars of condensations and membrane. 22,000x. (Penna Franca).

FIG. 3. Another photo of the same suspension showing a large mass of short bacilli, with neat gloea. 19,000x. (Penna Franca).

FIG. 4. Photo of Stef. II culture, chromogenic, similar to one of the 3 above made by Penna Franca. 3,700x. (Malfatti).

FIG. 5. Suspension in sterilised distilled water of culture strain Stef. III: large bacilli, some massive, some granulated. (Malfatti).

FIG. 6. Culture Stef. III deposit of glycerine broth culture, suspended in distilled water: short trapus bacilli with gloea. 18,000x. (Penna Franca).

FIG. 7. Suspension of culture of tumour of black mouse infected with material from skin lesion of a rhesus infected with rat leproma. Short and large bacilli with condensed nodules or bars, similar to those of Fig. 6.

*N.B.—Fig. 5 is similar to Fig. 1 of Plate 2.*

## PLATE 4. Bacteriology of Human Leprosy

FIG. 1. Suspension of strain 'Chaves I', isolated from leprous skin. Bacilli shaded by aluminium. (Malfatti)

FIG. 2. Same strain 'CI' recovered from experimental lesion produced in the same patient. (Malfatti)

FIG. 3. Same strain 'CI' recovered from Mitsuda test of patient's wife (Maria D.), also a case of leprosy. (Malfatti)

FIG. 4. Same strain 'CI' recovered from experimental lesion produced in the patient 'Jesus', a case of suspected leprosy: large granulated and short homogeneous bacilli. (Malfatti)



- FIG. 5. The same strain above, from 'Jesus': shaded. (Malfatti)  
 FIG. 6. The original strain 'CI': large bacillus with clear spaces simulating vacuoles and many condensed bars. (Malfatti)  
 FIG. 7. The same strain 'CI' cultured in glycerine-broth, a large beautiful bacillus with many condensed granules, sample recovered from 'Adelina', a female leprosy patient. 20,000x. (Penna Franca)  
 FIG. 8. The same strain 'CI' culture in Loewenstein, sample recovered from 'Loureiro', a male leprosy patient. Large bacillus with 4 condensed bars and clear cytoplasm. 30,000x. (Penna Franca)  
 FIG. 9. The same strain 'CI' in pure culture after passage in a series of three rhesus monkeys. 22,000x. (Penna Franca)

## PLATE 5

- FIG. 1. Strain 'Emilia' obtained from leprosy skin, bacilli with nodules. (Malfatti)  
 FIG. 2. The same strain 'E' recovered from skin lesion of Rhesus 'Sofia', after 95 days incubation. 19,000x. (Penna Franca)  
 FIG. 3. The same Rhesus sample with large bacillus with six metachromatic condensations. 22,000x. (Penna Franca)  
 FIG. 4. The strain 'Emilia' recovered from abscess of Mitsuda test in patient 16 of Pernambuco. 28,000x. (Penna Franca)  
 FIG. 5. Strain 'Hecke', non-chromogenic, in glycerine-agar: Bacilli with defined granules and one with many small scattered granules. 21,000x. (Penna Franca)  
 FIG. 6. Another aspect of the same 'Hecke' strain in 5% glycerine-broth: bacilli with condensed bars and thin gloea. 26,000x. (Penna Franca)  
 FIG. 7. Strain chromogenic from nasal mucus of the leprosy patient 'Maria Nascimento', in Loewenstein medium: homogeneous bacilli. (Malfatti)  
 FIG. 8. Strain chromogenic from nasal mucus of the leprosy patient 'Dalva', in Loewenstein: Mass of bacilli showing a neat gloea, similar to material of human leproma: one large and another short bacillus with condensed bars and clear cytoplasm. 22,000x. (Penna Franca)

## PLATE 6

- FIG. 1. Photo of strain 'CI', chromogenic, in Loewenstein medium, obtained in September 1949 from skin lesion (7th biopsy) of José Chaves.  
 FIG. 2. Photo of strain 'Maria D.', chromogenic (sub-strain of CI) recovered from biopsy of abscess on scar of Mitsuda test of left arm, in January 1950. Maria D. is the wife of Chaves, above. She was inoculated with her husband's strain 'CI'.  
 FIG. 3. Photo of strain 'H', non-chromogenic, in Loewenstein medium, obtained from biopsy of skin lesion of patient Hecke, in September 1949.  
 FIG. 4. Photo of strain 'E' chromogenic, in Loewenstein medium, obtained from leproma of left knee of patient Emilia, in March 1950.  
 FIG. 5. Photo of strain 'E' in Loewenstein (sub-strain recovered from abscess in scar of Mitsuda test in patient n.21 of Pernambuco, inoculated with the original strain 'E').  
 FIG. 6. Photomicrograph of smear of left ear leproma of patient Chaves, biopsy of 24th June, 1949, stained by Z-N. 1,000x.  
 FIG. 7. Photomicrograph of smear of the original strain 'CI' obtained from skin lesion of the above Chaves (Fig. 6) stained by 'Fontes' method, 1,000x. The morphology of bacilli of Fig. 6 and Fig. 7 is absolutely equal.  
 FIG. 8. Photo of Rhesus I inoculated with culture in glycerine-broth of strain 'CI' (Fig. 1), after 14 days incubation.  
 FIG. 9. Photomicrograph of section of the facial nodule of *Macaca mulatta* above, showing characteristic experimental leproma. 150x.  
 FIG. 10. Photomicrograph of section of facial nodule of a *Cebus fatuellus* monkey infected with strain 'CI'. Leproma structure with many acid-fast bacilli. 1,000x. Stained by Z-N.

## PLATE 7

- FIG. 1. Culture of strain 'CI' in 100 ml of broth with 5% glycerine, 20 days incubation at 37° C.: veil and deposit yellow. Culture ready for preparation of Leprolin for immunological studies and treatment of leprosy.  
 FIG. 2. Culture of strain 'H', non-chromogenic, recovered from rat, in 100 ml of broth with 5% glycerine, after 12 days incubation at 37° C. The 100 ml of this culture gave 1 litre of good Leprolin.

## THE COMPARATIVE ACTION OF CHEMOTHERAPY ON *M. leprae* IN SUPERFICIAL TISSUES AND IN THE RETICULO-ENDOTHELIAL SYSTEM

D. S. RIDLEY, B.Sc., M.D.  
*Hospital for Tropical Diseases, London*

That the reticulo-endothelial system (RES) is heavily involved in leprosy has been widely recognized for many years, but there have been few studies of the effects of treatment on leprosy bacilli in the RES. Ferrand (1954) and Benhamou *et al.* (1956) found leprosy bacilli and lesions in liver and marrow unchanged after 8–10 months treatment, and Furniss (1953) found bacilli in a lymph gland when the skin had for long been nearly clear. Powell and Swan (1955) sometimes found bacilli in other tissues after they had disappeared from skin. The question has been raised whether the reticulo-endothelial system acts as a reservoir of bacilli and possibly as a source of re-infection after treatment. This paper reports the incidence of bacilli in different parts of the body at different stages of treatment of lepromatous leprosy.

### Material and Method

Post-mortem material of four cases of untreated lepromatous leprosy and of eight cases at different stages of treatment has been examined for acid-fast bacilli; in some instances two or more specimens of one type of tissue were examined. All the patients, except one, were at the Jordan Hospital, Redhill, England or at Sungei Buloh Settlement, Malaya. Treatment in all cases had been by sulphones.

Cases 11 and 12 differ from the others in that treatment had been severely interrupted by reactions, and full doses of the drugs were never maintained; Case 11 had received no treatment for eighteen months prior to death; these two cases, therefore, are considered separately. The method of histological preparation was that described by Lowy (1956). The number of bacilli was assessed as the average per field according to a bacterial index with a range of 1 to 6, in which each unit represents a ten-fold difference in actual numbers. The granularity of bacilli was assessed by an index previously described (Ridley, 1960); in the range of 0 to 10, 0 represents all solid bacilli and 10 all granular.

### Results

The results are summarized in the Table. Before treatment and during the first six months, numbers of bacilli in the RES were comparable with those in skin. By twelve months there was a signifi-

cant decline in the RES compared with the skin and after three or more years of treatment no bacilli were found in any of the organs of the RES, although they were still abundant in some cases in skin. Case 7 suggests that bacilli may persist longer in lymph glands than in liver or spleen but there is not enough information to establish this point.

Bacilli in superficial nerves (the ulnar nerve in Cases 3 and 10, and the auricular nerves in Case 7) were comparable with those in skin, before and after treatment. In other organs, bacilli were very scanty, apart from the testis.

Bacilli in the RES were more granular than those in skin or nerve. Before treatment the index ranged from 4 to 9 in the RES sections, compared with a mean of 2.5 for skin bacilli in another series of comparable cases; (the only case, No. 3, in this series for which the index for skin was available before treatment was not typical because the patient was undergoing a reaction). After treatment bacilli in the RES were more granular in every instance than those in skin or nerve.

In the two cases (11 and 12) in which treatment was interrupted and inadequate, the bacteriological state of the RES was closer to that of the untreated than the treated cases. In Case 11 there was clear evidence of regeneration of bacilli in one at least of the skin sections; there was no sign of recrudescence of the bacilli in the RES.

### Discussion

These few cases demonstrate that under chemotherapy bacilli generally disappear from the RES before the skin or other superficial tissues (nerve or testis). The RES is not a reservoir of bacilli which threatens re-infection after the skin has been cleared.

Brand (1959) has pointed out that leprosy is a disease of superficial tissues, possibly because *M. leprae* is favoured by a lower temperature than that of the internal environment. To this the only exception is the RES. It is known that the primary function of the RES is the collecting and disposing of foreign particles and noxious agents. The macrophages or related cells in which leprosy bacilli are to be found, whether in skin, liver, spleen or elsewhere, are members of the same physiological system. It is reasonable to assume, therefore, that bacilli in the liver and spleen are there only because they have been filtered off from the blood stream. The results of this investigation indicate that they do not thrive. In lepromatous leprosy, in which the tissue reaction to *M. leprae* is quite passive, it is likely that the RES is the principal site of destruction of the bacterial bodies. When infection is arrested and the inflow of bacilli to the liver and spleen is reduced, numbers rapidly decline.

### Summary

A series of necropsies showed that in lepromatous leprosy numbers

TABLE  
The number and condition of bacilli (Bacterial/Granularity indices) of bacilli in  
different tissues at different periods of treatment.

Case No.	Race	Treatment (months)	Skin	Lymph glands	Liver		Spleen	Marrow	Nerve (superficial)	Other Organs
					Portal Tracts	Parenchyma				
1	I	0		4.6/7 2.1/6 4.5/7	4.7/5	3.8/4	4.0/8			
2	C	0		2.5/8 3.3/6	5.3/9	3.8/9	3.8/9 4.0/9			
3	C	0	4.0/7 4.2/8	2.1/9	3.4/9	3.4/9	3.4/9		4.1/8	Lung <1
4	N	0	4.5/-	2.2/9	3.5/9	1.3/9	2.0/9	2.0/-		
5	EA	1½	4.4/5		4.0/9	2.6/9				
6	E	6	2.4/3		3.0/7	1.0/9	2.0/9			
7	E	12	4.8/8	3.8/9	2.0/10	0.3/10	1.2/10		4.4/8 4.6/8	Adrenal <1
8	C	36	0		0	0	0			
9	E	55	2.5/7	0	0	0	0	0		
10	C	60	1.1/10		0	0	0		0.4/10	
					0	0				
11	E	(66)	2.4/5 3.8/2		1.0/6	1.0/6	1.8/6	0		
12	E	(156)	3.7/8	3.0/6	3.7/5	2.5/4	3.4/5			Testis: (superficial) 4.4/2 (deep) 2.2/2 Adrenal <1

C = Chinese    E = European    EA = Eurasian    I = Indian    N = Negro

of bacilli in the reticulo-endothelial system declined rapidly after twelve months' treatment, and disappeared long before those in the skin or other superficial tissues. Bacilli in the RES were more granular than those in skin or nerve.

These findings support the view that leprosy bacilli find their way to lymph glands, liver and spleen only as a result of filtration of lymph and blood streams; and that in lepromatous leprosy the RES is the main site of destruction of bacilli.

### Acknowledgments

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## THE MORTALITY FROM LEPROSY IN THE NEGRO POPULATION OF ANTIGUA, WEST INDIES, FROM 1857 TO 1956

by K. H. UTTLEY, M.A., M.D., D.T.M. & H.  
*Senior Medical Officer, Antigua*

### Introduction

Antigua is a small island of 108 square miles (282 sq. kilom) in the Caribbean Sea. It is one of the Leeward Islands lying between Puerto Rico to the West, and Guadaloupe, the Windward Islands and Barbados to the South-east. The population is an agricultural one, being engaged in the growing and processing of sugar, the cultivation of cotton, and in fishing. The only town, with 12,000 inhabitants, is concerned with the supplying of the needs of the rural inhabitants, and apart from a sugar mill, there is no industrial activity on the island. Indeed, from an epidemiological point of view the population is a rural and not an urban one. The people are pure negro except for perhaps 10% who are of mixed stock. The white population has never numbered more than 5% of the whole and was usually very much less. The coloured people live in about forty small villages scattered fairly uniformly over the island which except for some hills to the south-west is mainly rolling plain less than 250 feet (76·2 m.) above sea level.

As the author has indicated elsewhere (Uttley, 1960), the island is singularly well situated for a historical survey of the mortality from certain infectious and other diseases, because censuses have been taken on seven occasions since 1861, and fairly complete births and deaths registrations cover nearly all that period. Certificates of the cause of death have been compulsory since 1856, a physician or or coroner having to sign them. No body may be buried without the presentation of both a burial order and a certificate of cause of death. A sufficient number of physicians trained in the British Isles or Canada have always been resident in Antigua, and internal communications are good.

One hundred years ago the population was 36,000; it fell slowly to 28,800 in 1921 since when it has risen rapidly, being 54,200 in 1956. A certain amount of emigration, mostly of young adult males, has taken place at times of unemployment, but a low male/female sex ratio at birth combined with a higher death rate in males than in females has resulted in an adult male/female ratio of 754/1,000, which has varied little over the century.

### The Survey

This survey is one dealing with all the deaths registered as having been due to leprosy in negroes in Antigua between the years 1857

and 1956 inclusive. The death registers were investigated to collect the details about the age, sex and year of each leprosy death.

During the century under review there were 158 deaths from leprosy in males and 147 in females, making a total of 305.

The first table gives (a) the deaths from the disease (b) leprosy deaths as a percentage of all deaths, and (c) the crude death rate from leprosy.

TABLE I  
Leprosy in Antigua, 1857-1956.

(a) Deaths per decade;

(b) Leprosy deaths as a percentage of all deaths;

(c) The crude death rate from leprosy.

<i>Decade</i>	<i>Deaths in the decade</i>	<i>Leprosy deaths as a percentage of all deaths in the decade</i>	<i>Average annual crude death rate from leprosy per 1,000 living</i>
1857-1866	26	0.20	0.07
1867-1876	17	0.13	0.05
1877-1886	32	0.26	0.09
1887-1896	46	0.40	0.13
1897-1906	51	0.49	0.15
1907-1916	38	0.45	0.12
1917-1926	41	0.51	0.14
1927-1936	14	0.23	0.04
1937-1946	28	0.42	0.07
1947-1956	12	0.21	0.03
	305	0.32	

During the four decades from 1887 the ratio of leprosy to all other deaths remained remarkably constant at about one death per two hundred, but after 1927 the ratio fell both absolutely and relatively. Commensurate with this, the crude death rate also was very steady during the same four decades.

As regards males, the decades with the greatest percentage of leprosy deaths were 15-24 and 25-34 with about one quarter of all the deaths in each age group, followed by the groups 35-44 and 45-54 with approximately one-eighth of all leprosy deaths in each decade. In the case of females the maxima are in the groups 35-44 and 55-64.

The persons curve rises to a maximum of 22% in the age group 25-34, to fall by the next decade to two-thirds of that value, where it remains almost constant for thirty years.

The next table shows the number of leprosy deaths at ages and the percentage of them occurring in each age group:

TABLE 2  
Leprosy in Antigua, 1857-1956  
Deaths at ages, and percentage of  
deaths at each age.

<i>Numbers</i>				<i>Percentage of all leprosy deaths at ages</i>		
<i>Age group</i>	<i>Males</i>	<i>Females</i>	<i>Persons</i>	<i>Males</i>	<i>Females</i>	<i>Persons</i>
0 -	-	-	-	-	-	-
5 -	1	2	3	0.6	1.4	1.0
10 -	4	4	8	2.5	2.7	2.6
15 -	14	8	22	8.9	5.4	7.2
20 -	24	12	36	15.2	8.2	11.8
25 -	48	21	69	30.4	14.3	22.6
35 -	20	28	48	12.7	19.0	15.7
45 -	22	21	43	13.9	14.3	14.1
55 -	13	28	41	8.2	19.0	13.4
65 -	8	13	21	5.1	8.8	6.9
75 plus	4	10	14	2.5	6.8	4.6
Total	158	147	305			

TABLE 3  
Leprosy in Antigua, 1857-1956  
Average annual death rate per 100,000  
at ages over the century. (\*)

<i>Age group</i>	<i>Males</i>	<i>Females</i>	<i>Persons</i>
0 -	—	—	—
5 -	0.54	1.04	0.79
10 -	2.03	2.23	2.13
15 -	8.77	4.39	6.44
20 -	16.24	7.24	11.48
25 -	21.38	7.27	13.44
35 -	11.12	12.04	11.64
45 -	17.11	12.10	14.23
55 -	17.78	24.56	21.91
65 -	22.04	20.16	20.83
75 plus	22.10	34.36	29.66
All ages	10.68	8.09	9.28

(\*) Based on the means of the numbers in each age group at the seven censuses taken during the century.



In each sex the decade 15-24 has a moderately high mortality per 100,000, but following a fall in the next decade, the rate rises steadily for the rest of life.

The death rate per 100,000 for all ages suggests that males have been killed by the disease about one-fifth more than females.

TABLE 4  
Leprosy mortality in the negro elsewhere  
in the Caribbean; Crude death rates  
per 100,000 of population (\*)

<b>Leeward Islands</b>			
<i>Antigua</i>	<i>St. Kitts</i>	<i>Montserrat</i>	<i>British Virgin Islands</i>
1857-1866, 0.07		No data available in the annual reports of these islands	
1867-1876, 0.05			
1877-1886, 0.09			
1887-1896, 0.13			
1897-1906, 0.15			
1907-1916, 0.12			
1917-1926, 0.14			
1927-1936, 0.04	1928-1936, 0.14		
1937-1946, 0.07	1937-1946, 0.03		
1947-1956, 0.03	1947-1956, 0.05		
<b>Windward Islands</b>			
<i>St. Vincent</i>	<i>Grenada</i>	<i>St. Lucia</i>	<i>Dominica</i>
1931-1936, 0.02	1923-1933, 0.007		1933-1936, 0.06
1937-1946, 0.02			1937-1946, 0.05
1947-1953, 0.005	1949-1953, 0.07	1948-1956, 0.004	1947-1954, 0.005
<i>Barbados</i>	<i>Trinidad</i>	<i>British Guiana</i> (Negroes only)	
1919-1926, 0.05			
1927-1936, 0.04	1931-1936, 0.07	1930-1938, 0.07	
1937-1946, 0.02			
1947-1954, 0.005	1939-1953, 0.03	1952-1954, 0.03	
<i>Jamaica</i>	<i>Bahamas</i>	<i>Bermuda</i> (Negroes only)	
1928-1936, 0.02	1927-1936, 0.02	1935-1946, 0.01	
	1937-1938, 0.005	1947-1956, 0.008	
1950-1954, 0.003	(no accurate data for later years)		
<i>American Virgin Islands</i>		<i>Puerto Rico</i>	
1939-1946, 0.15		1939-1946, 0.003	
<i>Curaçao</i>			
1939-1946, 0.18			

(\*) My authorities are given in the list of references under the names of the various islands.

Much care must be exercised in interpreting these figures, because in many cases they are by no means comparable. For instance, in the case of Trinidad one-third of the population are East Indians; in Jamaica one-third of all deaths are not medically certified, and furthermore the author is not aware of the degree of care which is exercised in the various territories concerning the medical certification of the cause of death, nor to what extent doctors do in fact sign death certificates.

## Discussion

As regards the effect of climate on the prevalence of leprosy in a country, Rogers (1923) showed that, other things being equal,

leprosy is much more prevalent in a hot humid climate than in a colder, dry one. For instance, it is absent, or the incidence is very low, in Peru, the Sahara or South-West Africa, where the rainfall is less than 10 inches a year, but common in the Congo or West Africa which are very hot, damp and humid areas. In the wet northern climates the incidence is intermediate.

In Antigua the prevalence of leprosy is intermediate between the extreme prevalence of Central Africa, and the low incidence of the wet colder climates, as would be expected from a knowledge of the data, which are:

Rainfall	44 inches annually. (111·76 cm.)
Mean temperature	79° F. (approx. 26°C) with a variation of less than 10° (6° C) on either side of the mean.
Mean humidity	79·2°, with a variation between 76·9° in April and 81·5° in October.

Other factors which favour a high incidence of the disease are present in Antigua: poverty, overcrowding in small houses, a low standard of culture and of personal and environmental hygiene. Over most of the period much of the population has lived on the borderline of malnutrition.

In leprosy, more than in many diseases, the mortality figures are not a good guide about the prevalence of the disease over a short period, because the physician so frequently inscribes the cause of death as being due to some intercurrent condition, and the fact of leprosy being present or contributing materially to the death is omitted. In this way mortality statistics understate the situation. However, this factor has played a part throughout the history of the disease and there is no reason to suppose that it is a factor that has fluctuated much from one period to another. Consequently, until the advent of the newer anti-leprosy drugs, the mortality figures are probably a reasonable guide to the secular trends over a long period of time such as a century. This is especially true of Antigua, for reasons already given.

The Antigua mortality figures suggest that the mortality is falling, and is now perhaps one-fifth of what it was half a century ago, and a comparison with current statistics from neighbouring territories indicates that there is no great difference between the mortalities of the disease in the various islands.

### **The incidence of leprosy in Antigua**

In Antigua leprosy has been a notifiable disease for many years. Legislation controlling leprosy patients extends back to 1896, but records of notifications, because of fires and the destruction of old records by insects, do not go further back than 1936 and are very incomplete, so as to be valueless for the purpose of this paper. Muir (1944) when visiting this island stated that there were 90 known

cases, a rate of 2.4 per 1,000; this was at a time when the crude death rate from the disease was 0.07 per 1,000. He considered it likely that there were others not detected, and I would agree with him. In more recent years the figure is lower and the present known rate is 1.4 per 1,000.

### **Summary and conclusions**

Antigua is well placed for a good assessment to be made of the mortality of leprosy over the hundred years 1857–1956 in the negro population of the island.

It was a fairly common disease but its mortality was not as high as might have been expected because many dying of the disease were certified as having died of some intercurrent condition.

The Island has had a coloured population varying over the century from 28,000 to 54,200, and among these there have been 305 deaths, of which 158 were in males and 147 in females.

The crude death rate has fluctuated between a maximum of 0.15 per 1,000 for the decade 1897–1906 and a minimum of 0.03 in the decade 1947–1956, but for the forty years from 1887 the rate was remarkably steady.

The percentage of leprosy deaths, in all deaths, was also very steady for the same forty years, being around 1 in 200 deaths.

Since that date the mortality from the disease has been steadily falling and is now about one-fifth of what it was half a century ago.

As regards the age groups of leprosy deaths throughout the century, in males the maximum was in the age group 25–34, with a value of 21.4 per 100,000, but it rose to about the same figure in old age. In females there was a moderately high rate of 12 per 100,000 for the twenty-year age group 35 to 54; it then rose steadily to old age.

The death rate per 100,000 at all ages throughout the century was 10.68 in males and 8.09 in females. There was no death under the age of five years in this series.

In comparing the present mortality in Antigua with that of neighbouring territories in the Caribbean, allowing for various factors mentioned in the paper, the death rate and the secular changes appear to be much the same throughout the area, as would have been expected when considering the fact that all the populations are poor rural communities living under unhygienic conditions, and that the climate of the area is fairly uniform.

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authorities of the National Library of Medicine, Washington, for being kind enough to supply him with data for calculating the mortality statistics of some of the neighbouring islands.

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## PRELIMINARY REPORT ON THE RAPID FADING OF *M. leprae* IN SECTIONS FROM PATIENTS TREATED WITH DIETHYL DITHIOL/SOPHTHALATE

R. RHODES-JONES

*East African Leprosy Research Centre, Alupe, Kenya;  
(postal address: Box 1044, Busia, Tororo, Uganda)*

All patients on drug trials at this Centre are submitted to skin biopsies at regular intervals, in order to assess the progress of the patient by Ridley's Index (RIDLEY, D. S., Therapeutic Trials in Leprosy Using Serial Biopsies. *Leprosy Review*, **29**, 1; Jan. 1958, pp. 45-52). Our biopsies are processed in the manner described by Ridley.

Immediately after mounting a batch of skin biopsies from patients treated with diethyl dithiolisophthalate (which is the drug 'Etisul' of Imperial Chemical Industries Ltd.), on examination masses of deeply stained acidfast bacilli were seen distributed about the section. The slides were then placed in a 37° C. incubator to dry off the mountant. When next examined in order to assess the Ridley Indices at 24 hours later, the bacilli had faded, and completely so in most cases.

The process was then repeated with a set of biopsies from patients treated with other drugs as control, being processed at the same time and by the same method. While fading again occurred in all Etisul sections, the others remained acidfast.

Biopsies from patients treated with Etisul were then stained, and examined at once and at hourly intervals, to determine the fading time. All sections showed fading between 6 and 24 hours. In one patient who had been treated with one third of a tube of Etisul for only 4 days prior to taking of the biopsy there was fading. Smears on slides, taken from the same Etisul-treated patients, do not fade.

Attempts to prevent this fading in biopsy sections by changing the fixative and reagents used have all been unsuccessful up to date. Fading recurs when the sections are restained.

As it is usual for the person who examines sections to wait 24 hours after staining until the mountant is dry, it seems that a false result may easily be recorded in the process of examining slides from patients under Etisul treatment. Further investigations into this phenomenon are being carried out.

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## ABSTRACTS

*Inoculación de Mycobacterium Leprae a Ratas en Carencia de Vitamina E: Estudio Experimental: Nota Previa. (Inoculation of M. leprae into rats deficient in Vitamin E: experimental study: preliminary note).* F. F. WILKINSON, R. A. CHERI, and E. FOLLMANN. *Leprológia*, **4**, 1: Jan.-Apr., 1959, pp. 35-44: 5 microphotographs, 14 figs.

The conclusions put forward by Meny Bergel from his work on the inoculation and reproduction of *M. leprae* in rats deprived of Vitamin E caused these authors to repeat the experiments. Bergel sought to favour the mechanisms of tissue oxidation in the rat by his special diets. These authors also used such a diet deficient in Vitamin E. They soon found the great drawback of a high mortality in the rats, due to the polyvalent vitamin deficiency, but think the method is promising and should be pursued with a modified diet, and more rats in the experiment (these authors had few).

*Hipersensibilidad de Vacunación y de Infección por el Mycobacterium Leprae. (Hypersensitization from Vaccination and Infection by M. leprae).* N. OLMOS CASTRO, P. B. ARCURI, R. L. USANDIVARAS, and colleagues. *Leprológia*, **4**, 1: Jan.-Apr., 1959, pp. 3-11.

The authors made a comparative study of the reactions caused by lepromin injections in healthy human subjects and in dogs, with reactions in the same conditions in subjects of tuberculoid leprosy. By this it was hoped to compare inoculation hypersensitization with hypersensitivity belonging to the disease. They found that the mechanism of the development of the hypersensitization seemed to be the same in all cases, and that the early reaction at 48 hours was conspicuous, and accelerated development of the small tubercle or nodule at the end of the first week. They think that this early Fernández reaction in these cases certainly means a state of hypersensitivity to *M. leprae* and should have the value of the Mantoux reaction in tuberculosis. They interpret the Mitsuda or late reaction as the terminal stage of the increase of tuberculin-type hypersensitization which began a few weeks before. Thus the early Fernández and the late Mitsuda reactions are different stages of the one process and it is not right to give them different meanings. They insist that in the immunology of leprosy the phenomena of hypersensitization should be studied independently from those of resistance or immunity and that there are many arguments which favour their being distinct states which obey different pathogenic mechanisms.

*Persistencia de la Hipersensibilidad a Leprolina Proteica Total (L.P.T.) Inducida por BCG en el Hombre. (Persistence of Hypersensitization to Total Proteic Leprolin Induced by BCG in Man.)* N. OLMOS CASTRO, P. B. ARCURI, L. B. TORNANZOS and colleagues. *Leprología*, **4**, 1: Jan.-Apr., 1959, pp. 12-17.

They made a statistical study of the hypersensitization to total proteic leprolin and Koch's crude tuberculin 1/1000 at 6 weeks and at 7 months after BCG inoculation of healthy persons. They found that BCG is able to change a negative Fernández to positive at 6 weeks after inoculation in a high proportion of cases; but at 7 months there is a loss of hypersensitivity to total proteic leprolin, while that to 1/1000 crude tuberculin remains. It seems that this co-sensitization phenomenon (a specific group-hypersensitization) is maintained during the development of the immune process resulting from inoculation, but is lost in a short time; however the monovalent specific sensitivity to the causal germ remains.

*Sensibilización de Cachorros por Mycobacterium Leprae (Sensitization of Pups by M. leprae.)* N. OLMOS CASTRO, P. B. ARCURI, R. L. USANDIVARAS, and colleagues. *Leprología*, **4**, 1: Jan.-Apr., 1959, pp. 18-20.

Ten dogs (pups) were sensitized to *M. leprae* by previous injection of an aqueous suspension of heated lepromatous tissue (whole lepromin) and unheated suspension. They were then injected intravenously with Mitsuda-Hayashi whole lepromin and showed no symptom of anaphylactic shock. The lack of this shock causes the authors to think that the hypersensitization produced in the Wade phenomenon is of tuberculinic type, a bacterial hypersensitization, and they affirm the specific nature of the Wade phenomenon.

*Hipersensibilidad y Reacción Peritoneal en el Cobayo Inyectado con el M. leprae (Hypersensitization and Peritoneal Reaction in the Guinea Pig Injected with M. leprae.)* N. OLMOS CASTRO, M. CONEJOS, P. B. ARCURI, and colleagues. *Leprología*, **4**, 1: Jan.-Apr., 1959, pp. 24-30.

They studied histologically and bacteriologically the peritoneal reaction provoked in healthy guinea pigs by the injection of a suspension of lepromatous tissue rich in *M. leprae*. This suspension was heated or unheated. They found many signs of an active and effective mechanism of resistance, and point out the peculiarity of guinea pigs in that they do not react to lepromin by intradermal injection, even when repeated, but have an effective defence mechanism, as shown by these peritoneal reactions.

*Naturaleza de la Reacción Nodular Tardía en el Fenómeno de Wade*  
(*Nature of the Late Nodular Reaction in the Wade Phenomenon.*)

N. OLMOS CASTRO, P. B. ARCURI, R. L. USANDIVARAS, and colleagues. *Leprológia*, 4, 1: Jan.-Apr., 1959, pp. 31-34.

Seven dogs were sensitized to *M. leprae* and its proteic derivative by a previous injection of an aqueous suspension of lepromatous tissue rich in *M. leprae* which was heated or unheated, and were then given injections of total proteic lepromin, an aqueous suspension of normal human skin, and total proteic lepromin plus an aqueous suspension of normal skin. The latter two groups gave hypersensitization reactions at 48 hours, decreasing in intensity on the following days: at 14 and 21 days there was no inflammatory reaction nor late nodular reaction. The suspension of normal skin provoked neither early nor late reactions. The authors think that the late nodular reaction observed in the second part of Wade's phenomenon is specific and only attributable to *M. leprae*.

*Recent Advances in Leprosy Research.* R. J. W. REES, *West Afr. Med. J.*, 8, 6: Dec., 1959, pp. 325-329.

The causative organism of human leprosy, described by Hansen in 1874, was one of the first bacteria to be identified, but progress has been slow and awaits its successful cultivation and/or transmission of the disease to an experimental animal. Any success in the treatment of leprosy in recent years has been obtained with drugs known to be active against tuberculosis, the causative organism of which is related to *M. leprae*. While direct attempts to culture and transmit *M. leprae* must go on, much of value may be learned from studies on other closely related and particularly non-cultivated strains of mycobacteria. In recent years there have been a number of studies based on rat leprosy. This was first described by Stefansky and Dean in 1903, and is a natural disease of wild rats throughout the world. Like human leprosy, it is a chronic infection in which the mycobacteria exist as intracellular parasites of cells of mononuclear type, nor, until recently, was there any convincing evidence that they will grow *in vitro*. The disease can be transmitted experimentally to rats and mice. Rees, and Hilton and Elek in 1957 reported quantitative techniques, adapted from those in tuberculosis work, and were able to determine the generation time *in vivo* of *M. lepraemurium*. They found that the bacteria divided every 10 to 12 days in the mouse and every 7 to 8 days in the rat. These generation times are the longest recorded for any micro-organism (c.f. every 20 to 24 hours for *M. tuberculosis*) and calculations based on transferring them to *M. leprae* would give an incubation period for human leprosy of 2 years or more, which fits in with clinical observations.

The use of tissue culture systems for attempts to grow human and rat leprosy mycobacteria follows from (a) the intracellular



position of the bacillus *in vivo*; (b) the failure of the murine leprosy bacillus to derive energy from a wide range of extracellular substrates (Gray, 1952); and (c) inhibition by serum of the endogenous metabolism of *M. lepraemurium*. In these respects the leprosy bacilli tend to resemble viruses. Rees and Wong (1958) first tried monocytes. Though they did not obtain multiplication, some of the bacilli from these cell cultures were viable at 40 days. They next obtained limited multiplication in cultures of spleen tissue, and similar results were reported by Wallace, Elek and Hanks (1958). Methods were also developed for precise enumeration of bacilli in cultures, and hence the definite detection of multiplication.

Primary cultures of explanted tissue from previously infected animals offer the greatest chance of success, but such cultures cannot be maintained in a healthy state for long-term studies. Garbutt, Rees, and Barr (1958) have succeeded with initiating multiplication in a strain of mouse fibroblasts.

The electronmicroscope is also proving of value in distinguishing live and dead bacilli of *M. lepraemurium*, (McFadzean and Valentine; and Rees, Valentine, and Wong, 1958). The degenerate forms predominate in animals receiving effective chemotherapy. This technique provides a new approach.

(McFadzean and Valentine have recently reported on this technique as applied to *M. leprae*. See *Leprosy Review* **31**, 1: Jan., 1960, pp. 6-11. They found normal and degenerate forms. The percentage of the latter increased after 6 months of sulphone therapy. The fragmented and granular bacilli found after treatment when stained by Z.N. and examined with the light microscope correspond with the degenerate bacilli with disordered protoplasm as seen by the electronmicroscope. EDITOR.)

*Electronmicroscopic Studies of Tubercle Bacilli. Studies on Fixation in Ultrathin Sectioning.* K. FUKUSHI. Reports of the Research Institute for Tuberculosis and Leprosy: **9**, 1: Dec. 1959, pp. 1-17. Tohoku University, Sendai, Japan.

With 18 figures on plates and full descriptions of material and methods and results Fukushima has reported on his studies in fixation for ultrathin sectioning by osmium tetroxide. Thin sections of *M. tuberculosis* var. *hominis* and *M. avium* and BCG were fixed under varying conditions of time and temperature. It was found that *M. tuberculosis* was fixed by 5 days at room temperature with the best results. For BCG, fixation at room or higher temperatures for 4 to 9 days gave the best results. For *M. avium*, fixation at room temperature for 2 days was best. Structures revealed were those resembling mitochondria, cell walls, cytoplasmic membranes, electron-dense granules, nuclei, vacuoles, and cytoplasmic granules, as the basal ultrastructures of mycobacteria.

*Mutual Influence between Tuberculous and Leprous Infections in the Organs of Rats and Mice. Histopathological Study.* T. HORIUCHI. Reports of the Research Institute for Tuberculosis and Leprosy, Tohoku Univ., Sendai, Japan, **9**, 1; Dec., 1959, pp. 34-53: 16 figures on plates.

Observing the double infection of murine leprosy bacilli and tubercle bacilli in rats and mice over several months, the author noted that in the early stage it is very difficult to differentiate the lesions. The only sure way is the finding of typical lepra cells with many bacilli. The evolution of murine leprosy is prevented by tuberculous infection. The occasional appearance of lepra cells is noted very early in tuberculous foci when both tubercle and murine leprosy bacilli are inoculated simultaneously into animals. It has been shown that early development of lepra cells follows rapid destruction of tubercle bacilli in the viscera. This finding suggests that cells infiltrated by tuberculous infection are temporarily liable to be invaded by leprosy bacilli in the early stage in which tuberculostatic activity has not developed. The process of tuberculosis is prevented by the infection by murine leprosy bacilli. When animals with mild leprosy are infected with tubercle bacilli of low virulence, tuberculous nodules in the viscera are delayed two weeks in formation, compared with the control animals. When the challenge is by tubercle bacilli of high virulence there is not much difference in the severity or extension of murine leprosy and of tuberculosis. But when rats with serious leprosy are inoculated intravenously with tubercle bacilli of low virulence, nodule formation is considerably prevented. Both tuberculous and leprotic lesions develop under mutual influence in lung, liver, spleen of rats and mice. The tuberculous lesions are suppressed and replaced by leprosy lesions, because the former develop rapidly but do not progress and the latter slowly but always progressively and decisively. Murine leprosy finally produces generalized lesions in rats and mice. Polymorph leucocytes, foreign body giant cells, and eosinophils often appear in parts invaded simultaneously by leprotic and tuberculous infections.

*Histopathological Study on the Inoculation of Human Leprous Tissue into Guinea Pigs.* T. KAWAWAKI. La Lepro, **28**, 6: Nov., 1959, pp. 285-301. 10 plates.

The author investigated histologically the tissue reactions arising from the insertion of human lepromatous tissue into guinea pigs. He found the first reaction is a nonspecific inflammation in the subcutaneous tissue of the guinea pig into which the human lepromatous nodule had been inoculated. Later a specific granulation tissue appears, composed of an infiltration of round cells with leprosy bacilli, and some epithelioid cells, proliferation of reticulum

cells and leprosy bacilli appear in the adjacent lymph glands. The initial exudative tissue reaction around the inserted lepromatous nodule is greater in young than in adult animals. Necrosis is greater in adult animals, often with abscess formation. The reactive exudate is more myxomatous in young animals than in adults. Giant cell formation begins on the 6th day after inoculation. Firstly come cells of foreign body type, then Langhans type, lastly giant cells with very large nuclei.

*Studies on the Infection Mechanisms of Murine Leprosy.* M. SUZUKI.

La Lepro, **28**, 6: Nov., 1959, pp. 301-309 and pp. 311-317, 319-340.

Colloidal suspension of carbon black was used to block the cells of the reticulo-endothelial system in 104 mice and observed for 5 months. A marked inhibition of development of murine leprosy was noted in the group injected with carbon black before the inoculation of murine leprosy bacilli, and the group with before and after inoculations. Another group in which the blocking was done by the 15th day after inoculation also showed a marked inhibition. Blocking done after the 20th day of inoculation showed only slight inhibition. A marked acceleration was noted in the group of mice injected with a mixture of carbon black and murine leprosy bacilli.

In another experiment percutaneous blocking of the reticulo-endothelial system with carbon black was done in 35 rats. This caused a marked degeneration of the murine leprosy bacilli in the subcutaneous leproma and the inhibition of the development of fresh leproma and the dissemination of bacilli into whole organs. A group of rats injected with the mixture of bacilli and carbon black was not different from the control group in regard to the development of subcutaneous leproma but the dissemination of bacilli into whole organs was remarkably accentuated.

In another experiment murine leprosy was inoculated intraperitoneally and an intravenous injection given of carbon black. The dissemination of bacilli was not different from the control group. Next, intraperitoneal injections of carbon black were frequently repeated in animals who had been given subcutaneous inoculations of murine leprosy. Marked development of leproma was noted early, but the dissemination of bacilli into whole organs was inhibited as compared with the control group.

In the last experiment a reversed allergic reaction was induced in 126 rats by using the anti-monocyte serum obtained from rabbits who had been sensitized by the intraperitoneal monocyte of rats. It was found that in intraperitoneally inoculated murine leprosy there was marked inhibition of the multiplication of murine leprosy bacilli in the intraperitoneal monocyte. Leproma development was also markedly inhibited, as shown in autopsies at 40 days. After 5

months autopsy showed inhibition of dissemination of bacilli. In one group, which had been injected with liquid paraffin prior to the injection of anti-monocyte serum, multiplication of murine leprosy bacilli was inhibited as compared with the untreated group.

*Detection of Acid-Fast Organisms in Tissue Sections by Fluorescence Microscopy.* S. W. A. KUPER and J. ROBERT MAY, *J. of Path. and Bact.*, **79**, 1; 1960, pp. 59-68, 6 figs. on plates, 5 in colour.

The authors describe their method, with practical details, of staining mycobacteria by auramine-rhodamine and examination by optical apparatus delivering light of about 4320 to 5660 A.U. from a mercury-vapour lamp to the microscope using a dark-ground condenser and filters. The objects fluoresce reddish-gold in colour with great distinctness. Details are fully given in the paper with illustrations of the apparatus as set up and of the bacteria as they appear, and the work is well worth consulting in the original by all laboratory workers in leprosy. In the preparation of tissue sections an interesting addendum is that the authors have found that tissue sections are best treated with a mixture of 2 parts xylol and 1 part ground-nut oil. The authors think that this procedure is very good for the detection of tubercle bacilli and is indispensable for leprosy bacilli.

*Studies on in vitro Reaction between Guinea Pig Peritoneal Cells and Leprolin or Tuberculin Antigens.* K. OKAMURA. *La Lepro*, **28**, 6: Nov., 1959, pp. 331-360.

His previous work showed that guinea pig peritoneal cells which had been sensitized either with tubercle bacilli or BCG have a common factor reacting against leprolin and tuberculin. There was no passive transfer of this reactivity from rabbit to guinea pig. It has been found that both sensitized and non-sensitized peritoneal cells of the guinea pig combine leprolin antigen *in vitro*. This is only with the peritoneal cells of the guinea pig and cells heated previously at 48° C. for 15 minutes failed to show this combination. When leprolin antigen combines it seems to be freed easily by heating at 48° C. for 15 minutes. When peritoneal cells of a guinea pig sensitized by BCG combine leprolin, the common reaction factor of the sensitized cells was inactivated and the cells failed to transfer the passive reactivity against leprolin and tuberculin.

*Classification of Experimental Mouse Leprosy.* Y. KAWAGUCHI. *La Lepro*, **28**, 6: Nov., 1959, pp. 378-390. 2 plates.

Stefansky in 1903 in the first report of murine leprosy described two forms, glandular and muco-cutaneous. Now most workers think that these are merely early and late stages of the same disease. The present author has found remarkable differences between the various inbred strains of mice, and thinks that mouse leprosy should

be classified into benign and malignant. In the benign type the skin lesions appear early, and are small, hard, and sharply defined. Those of the malignant type appear later, and are soft and much larger, with a diffuse thickened appearance. These two clinical types are an expression of varying degrees of resistance. The malignant type progresses steadily, usually with fatal termination in about 30 weeks. In the benign type there may be gradual regression and sometimes spontaneous healing in the late stage.

It is of interest that giving BCG can sometimes convert the malignant to the benign type.

*Mechanism of Blister Formation in Leprosy Patients.* S. N. CHATTERJEE. *Internat. J. of Lep.*, **27**, 4: Oct.-Dec., 1959, pp. 305-320, 7 figs.

Blisters are more commonly found on anaesthetic hands than on any other part of the body. Heat which is not enough to cause burns of normal parts can still produce blisters in anaesthetic parts. The author describes illustrative cases. He used a thermocouple and light-trace galvanometer to investigate this matter in 22 patients, recording the temperatures of the anaesthetic and corresponding non-anaesthetic parts before the application of heat at 52° C. for 5 minutes, and also immediately afterwards. There was usually a lower temperature in the anaesthetic parts before the application of heat. He thinks this is due to a contraction of blood vessels and a less active blood circulation, compared to the normal parts. When heat was applied the anaesthetic parts always rose to a higher temperature than the normal parts, because heat was less well dissipated, based on insufficient dilatation of blood vessels. Blisters arise in anaesthetic parts because of these 2 factors of lower initial temperature before being heated and more accumulation of heat after heating. A temperature not enough to produce blisters in a normal part may be just enough to do so in an anaesthetic part. This study confirms the author's previous observation that the neural signs in leprosy are closely associated with capillary contraction and consequent diminution of blood supply in the skin of anaesthetic parts, and that the temperature of anaesthetic is lower than in normal parts. A new and fruitful line of study is opened up.

*A Study of Myositis Interstitialis Leprosa.* S. ISHIHARA. *Internat. J. of Lep.*, **27**, 4: Oct.-Dec., 1959, pp. 341-346. 6 figs. on plates.

Dr. Ishihara of Suruga Leprosarium, Japan, reports on a study of interstitial leprotic myositis. It is a rare but genuine part of lepromatous leprosy. He took specimens of muscle tissue from the calf of the leg in 4 cases, and found atrophic changes and lepromatous infiltrates and acidfast bacilli. In a case which had improved greatly under treatment there were swellings in the calves of both legs which were found to consist of an inflammatory exudate containing giant

cells and eosinophilic leucocytes; and few bacilli apart from globi. In the other 3 cases there was muscle atrophy and inflammatory infiltrates of histiocytes or macrophages and lymphocytes, with more or less abundant bacilli in various areas.

*Reticulo-Endothelial Response in Murine Leprosy.* L. KATO and B. GOZSY, *Internat. J. of Lep.*, **27**, 4: Oct.-Dec., 1959, pp. 347-354.

In murine leprosy in rats the authors studied the capillary-endothelial and reticulo-endothelial responses, compared with those in uninfected controls (80 rats in each group). The inoculation of 0.5 ml. of a freshly prepared suspension obtained from a leproma of a rat 3 months old was given subcutaneously to 80 rats. The controls received saline inoculation. At 20, 70, and 120 days, the capillary and reticulo-endothelial responses were investigated on normal and serotonin-depleted rats: (the serotonin-depletion was achieved by an intraperitoneal injection of 0.3 mgm./100 gm. of Reserpine 18 hours before the experiment). Capillary reactions were provoked with dextran and with histamine, then made visible with India ink. As the disease progressed there was a definite fluctuation in capillary response. There is a stimulated systemic capillary response in the early stages of the infection, but this lapses in the late stage. There is a similar stimulation of endothelial response in the early lesions of inoculation, and none in the late necrotic stage of the granuloma. The phagocytic function of the reticulo-endothelial system is unchanged, as evidenced by the India ink test made 20 and 70 days after inoculation.

*Results of Inoculation of White Rats with Human Leprosy Bacilli by the Intraneural Route: Preliminary Report.* N. MUKERJEE and S. KUNDU, *Internat. J. of Lep.*, **27**, 4: Oct.-Dec., 1959, pp. 355-359.

On the basis of the affinity for nerve tissues on the part of *M. leprae* the authors attempted to transmit it to white rats by exposing the sciatic nerve and injecting it with a suspension of leprotic tissue rich in bacilli, mixed with an equal amount of sterile egg albumen. One out of 5 rats so inoculated showed at 3½ months evidence of massive infection with an acidfast organism. Passages of this acidfast organism have been attempted in other rats and in guinea pigs. Lesions developed in one of the first-passage rats, and a second passage has been attempted in rats and mice. The guinea pig inoculations were negative, and cultures were negative. The bacillus therefore was probably not the tubercle bacillus nor any other mycobacterium readily cultivable; it may be the Stefansky bacillus as a rat of the first-passage group was infected by it. This brings out the importance of excluding the Stefansky bacillus as a chance infection in experiments where human leprosy material is inoculated into rodents.

*The Bacteriologic Diagnosis of Early Leprosy by the Trypsin Digestion Method.* J. LEW and M. CHUNG. *Internat. J. of Lep.*, **27**, 4: Oct.-Dec., 1959, pp. 360-363.

As a practical method of obtaining bacilli free of tissue debris the authors chose and tried out the trypsin digestion method in 175 cases. The tissue specimen, freshly obtained or formalinized, about 0.5 g. in weight, was autoclaved for 15 minutes at 15 pounds pressure. It was then ground in a mortar in 7 to 8 ml. of Sorensen's buffered solution (pH 7.8) containing 0.5% trypsin (Difco 1/250). The preparation was then inoculated with frequent shaking for 3 hours at 39° C., and then centrifuged for 30 minutes at 3000 to 4000 r.p.m., and the supernatant fluid decanted. In the case of formalinized tissue the stage of autoclaving was preceded by washing in running water for 6 hours. This method was found very useful in the important early diagnosis of leprosy. It revealed acidfast bacilli in 26% of suspected cases which otherwise would have eluded certain diagnosis, and it was successful in almost 100% of clinically diagnosed leprosy lesions as yet untreated. The technique and instruments needed are simple and the method avails for specimens preserved by formalin and sent from a distance.

*Acetate and Fumarate Permeases of Mycobacterium smegmatis.* G. A. ELLARD and PATRICIA H. CLARKE. *J. of Gen. Microbiol.*, **21**, 2: Oct., 1959, pp. 338-343.

The impermeability of mycobacteria to many compounds which are normal cell metabolites has long been thought to be related to the high lipid content of the cell wall. The authors wished to test the hypothesis that it might be due to the absence of specific permeases. They grew *M. smegmatis* on Lemco agar in the presence and absence of acetate and fumarate. Organisms grown with fumarate oxidized fumarate rapidly, and Lemco-grown and acetate-grown organisms oxidized fumarate after a lag period at an increasing rate; this was inhibited by chloramphenicol. Disrupted bacterial preparations oxidized fumarate rapidly, irrespective of the growth medium. Acetate-grown organisms oxidized acetate at more than twice the rate of fumarate-grown and Lemco-grown. There was slight adaptation to acetate oxidation by acetate-grown and greater adaptation by Lemco-grown and fumarate-grown organisms. Acetate was oxidized by disrupted bacterial preparations. The evidence seems to suggest the existence of fumarate and acetate permeases, though less clear-cut in the case of the adaptive acetate permease.

The impermeability of mycobacteria cannot be ascribed solely to the high lipid content of the outer layers of the cell and specific permeability factors should be considered.

*Reacción Leprosa: Su Tratamiento con Cloroquinas. (Lepra Reaction: its Treatment with the Chloroquines.)* E. MACOTELA. Rev. Mexicana Dermatología, 3, 3: Sept., 1959, pp. 238-242.

The author discusses the types of lepra reaction and the treatment, which is the commonest accessory therapy for leprosy. A drug which is effective in all cases and without disadvantages for the patient has still not been found. The *antimonials* have been used for some time and continue to be used, and the results in general are good. There is little danger in their use but there are cases which fail to respond. *Transfusion* of small quantities of whole blood may give rapid improvement especially when the reaction is chronic or with grave deterioration of the general condition. The *corticosteroids* are powerful, but their use demands constant medical supervision because of the dangers of ulcers, diabetes, etc., and on stopping the treatment there may be a rebound reaction as intense or more than the original reaction. The *chloroquines* were reported on by Gonzalez Prendes and co-workers in 1955, who gave 25 reacting cases a daily dose for 7 days of 300 mgm. of Atebrin, with favourable result especially on fever and cutaneous lesions after the failure of other treatments. Merklen and Riou used Nivaquin in 14 cases in 1957. This also had a good effect, in doses of 600 mgm. orally daily for 5 to 14 days, with progressive decrease to 200 mgm. daily for several weeks. Germain and other workers have had similar good results. Merklen, Germain, and Riou think that the chloroquines not only have an action on the acute reactional episodes but are an adjuvant to the sulphones in the sense of increasing the tolerance of the patient to the sulphones and finally reinforcing their action. The chloroquines are worth trial in grave reactional states. At the beginning of treatment the intramuscular route may be better tolerated in many patients.

*Terapeutica Actual de la Lepra. (Present Treatment of Leprosy.)* M. MALACARA. Rev. Mexicana Dermatología, 3, 3: Sept., 1959, pp. 247-250.

The author quotes Chaussinand as saying that the number of leprosy patients in the world is about 10 millions, and about 600,000 of them receive adequate treatment. Because this disease is ancient the list of medicaments used for it is long, and many of them have no action or even make the patient worse. There is a sharp division between the two epochs, before the sulphones, and after the sulphones. In March, 1941 the first sulphone was used by Faget in Carville, U.S.A. DDS was first made synthetically in Germany in 1908, and in 1937 it was used with good results in streptococcal infections in animals. A little later the first sulphone derivative (Promin) was used in tuberculosis of guinea pigs, and a little later Cowdry and Ruangsiri used it in murine leprosy. This caused Faget



and his colleagues to think it could be useful in human leprosy, and they gave it to 10 patients, first by mouth and then intravenously, as the oral route seemed too toxic. By October, 1945 they found that 71.4% had improved after 6 months. By 1948 Cochrane and Lowe had shown that DDS itself could be used orally in moderate dosage. In Mexico, Latapí and colleagues first used Promin and in 1950 the use of DDS was established. The good results of the sulphones are slow, so new drugs have also been studied in the hope of getting more effect in less time. These newer drugs have either been those with an anti-tuberculous effect or successful in murine leprosy. Streptomycin and Dihydrostreptomycin were used on a dosage of 1 g. daily and found to have effect, but the danger of toxicity has inhibited their general use. TB-1 or thiosemicarbazone in a dose of 100 to 150 mgm. has good results which fade out and some authors advise against it. INH at 4 to 7 mgm./kg. daily is useful in some acute manifestations but is not recommended in general as a routine treatment. PAS has been found to have no action against leprosy. DDSO or diamino-diphenyl sulphoxide has a similar action to DDS, but in later stages of treatment is apt to be toxic. Antigen Marianum in intradermal injections of 0.1 ml. once a month for 6 months causes severe local and general reactions on account of which it should not be used. Diethyldithiolisophthalate (Etisul or ETIP) is applied by inunction. It has a marked antibacterial action from 3 weeks onwards, and has a disagreeable odour, and resistance is reported at 3 months. Cycloserine has been given at 500 to 700 mgm. daily and most report a good result, sometimes better than the sulphones. It deserves wider investigation. The author thinks that the diphenylthiourea Ciba 1906 has given the best results of the newer drugs. The dose is 3 g. daily in the adult and 1.5 g. in children. Davey has reported that it is perfectly tolerated, there is a marked improvement with its use which is as good as the sulphones and better and it is especially useful in severe neuritis. Kanamycin and Griseofulvin are worth trying in leprosy. Kanamycin is given by injection and has been shown to be effective in murine leprosy. Griseofulvin is given orally for fungal skin infections and might possibly be useful in leprosy. At the moment the sulphones continue to be the basic treatment for leprosy.

*Cultural Determinants in Placebo Reaction.* WM. A. SODEMAN, Jr.  
Texas Reports on Biology and Medicine, **18**, 1: 1960, pp. 18-24.

The placebo effect of a drug may provide a major portion of its action, and may vary with the different cultural heritages of the people on whom it is used. It may also modify the drug's action, or have little or no effect on this. Placebo effect of a therapy may so alter subjective and objective symptoms without changing the basic disease state that both patient and doctor are lulled into a sense of

false security. The placebo effect can well apply to the inert substance given as a 'placebo' in drug trials, for toxic reactions have been reported by Wolf (1954) to occur from such an inert substance. Placebo effect is as old as therapy and in peoples of varying cultural heritage presents different patterns which act through neural and humoral systems, and there are groups in any culture who are placebo reactors or placebo non-reactors. There are both individual and cultural determinants of placebo action. The technique of the administration of the drug, rather than the drug itself, may elicit the effect in some peoples. In any case the drug concerned must fit into the group concept of disease or be reconcilable with it in order to have a placebo effect, and any individual recipient of the treatment must believe that it has a part to play in the alleviation of his disease state. It is worth while studying the disease concepts of every primitive and civilized group, so as to understand the working of placebo effects, which penetrate into therapeutic practices everywhere. Hillis (1952) tested several drugs with these points in mind, and found that by removing the placebo reactor group he obtained a truer assessment of the pharmacological effect of aspirin as an oral analgesic, compared with morphine and codeine. A drug with little or no pharmacological potency, if applied with a logic of treatment based on the patient's concept of disease, may prove successful. Treatment, both physical and pharmacological, as we know it, ever contains an unknown quantity of placebo action in its effect. The pharmacological effect may be denied, permitted, potentiated or added to. Dramatic therapeutic successes or failures should always be interpreted with regard to the placebo effect in individuals and cultural groups all round the world.

*A Concurrent Comparison of Home and Sanatorium Treatment of Pulmonary Tuberculosis in South India.* WALLACE FOX and colleagues, Tuberculosis Chemotherapy Centre, Madras. Bulletin of the World Health Organization, **21**, 1959, pp. 51-144.

This report is of great interest to leprosy workers, as it gives experience of a year's study of sanatorium and domiciliary therapy on balanced groups of about 96 patients in each category. It was found that the results of domiciliary chemotherapy approach closely enough to the results of sanatorium treatment, namely rest, diet, nursing, and supervised administration of the medicines, but there are also disadvantages, such as the disruption to family life. The standard of medical care during this study was very favourable, but it is thought that similar good results would be obtained from a domiciliary service if it is operated from a tuberculosis clinic, and if there is a satisfactory supply of anti-tuberculosis drugs, and if there is enough staff (including a public health nurse and a social worker). Adequate transport should be provided, including an

ambulance, and a small number of beds for special cases, an efficient appointment system, a system of surprise checks on the co-operation of the patients in taking their medicines, reliable smear examinations for tubercle bacilli in sputum, and a welfare fund for especially needy patients.

*Griseofulvina en Micosis Cutaneas Profundas. (Griseofulvin in Deep Cutaneous Mycoses.)* F. LATAPI, P. LAVALLE, J. NOVALES, and Y. ORTIZ. *Rev. Mexicana Dermatología*, 3, 1: Jan.-Mar., 1959, pp. 34-41, 8 figs. on plates.

The new antibiotic Griseofulvin has been shown by many authors, and also in Mexico, to have good activity as an oral treatment of superficial dermatomycoses. The authors now give a preliminary report on a trial in 2 cases of deep mycoses, one of mycetoma due to *Nocardia brasiliensis* and the other of Sporotrichosis due to *S. schenckii*. There was rapid and marked clinical response in both cases, and further observation is needed before a final assessment.

*La Dexametasona en la Lepra Reaccional. (Dexametasone in Reactional Leprosy.)* A. J. MELAMED, I. SIMONOVICH, J. GANOPOL, E. FUHRER, and M. MELAMED. *Rev. Asoc. Med. Argentina*, 73, 11: Nov., 1959, pp. 1-9.

The authors describe 13 cases of leprosy in reaction who were given the corticosteroid Dexametasone, and studies were made of their proteinograms by paper electrophoresis and the Landis test for capillary permeability. It was found that there were great changes in the capillary permeability for the serum and proteins of the blood, and intense dysproteinaemias. All these changes modified favourably or unfavourably according to the stage of the evolution of the reaction. Although these tests are valuable in the study of each individual, the study suggests that the greatest value lies in the appreciation of the successive variations in repeated tests in different clinical and therapeutic conditions. From this point of view it is possible to classify the patients studied in this investigation into (1) Toxic or co-ordinated, with a good prognosis. (2) Atoxic or unco-ordinated, with a bad prognosis. The functional capacity of the vessels (arterioles, capillaries, and venules) in leprosy and in the leprosy reaction may explain the different evolutive types of the disease and the varying results of the corticosteroid medication. Dexametasone showed an action on lepra reaction similar to drugs of the same nature used previously, but with much more activity and less of secondary effects.

*Results of Investigation for the Physically Handicapped in Leprosy.*

J. MIZUOKA and I. OYAMA. *La Lepro*, **28**, 5: Sept., 1959, pp. 183-191.

A study was made of 1209 leprosy patients (755 lepromatous and 454 tuberculoid). Crippled in some degree were 940 cases (77.7%). Of these 591 or 48.8% were mutilated in the upper and lower extremities, 295 or 24.4% in the upper extremity only, 54 or 4.4% in the lower only. Claw hand, wrist-drop, and lack of opposition in the thumb were common. Visual disturbance was frequent in lepromatous cases. Total amount of handicapping was 68.8% of those examined.

*The Value of Thiacetazone (TB-1) in Leprosy.* A. M. ALONSO. *Internat. J. of Lep.*, **27**, 4: Oct.-Dec., 1959, pp. 321-327.

The author thinks that Thiacetazone has not been properly appreciated for its value in the treatment of leprosy. Since 1951 he has used it on 220 patients and assesses it as a drug of the first rank. He gives by mouth 100 to 150 mgm. daily, in tablets of 25 or 50 mgm. two or three times a day. In lack of toxicity it is superior to the sulphones. There have been no toxic or side effects in 220 patients. Any form of the disease responds well to it, and for neural disturbances it seems better than the sulphones. The effect on the bacillary index is similar to that of the sulphones, and there were a few cases where negativization was attained in shorter periods than usual, e.g., 12 months, 20 months, 24 months.

*Treatment of Lepromatous Leprosy by a Combination of DDS and Sarsaparilla. (Smilax Ornata.)* R. ROLLIER. *Internat. J. of Lep.*, **27**, 4: Oct.-Dec., 1959, pp. 328-340, 11 figs. on plates.

Sarsaparilla has been traditionally used by Moroccans in the treatment of leprosy. Two of the varieties used, *Smilax ornata* and *S. japicanga* were examined by Vaillant and Bernard and Cottet and the saponisides studied, and Rollier and colleagues in 1950 to 1957 studied the action in leprosy. Weak aqueous extracts were first used, and later tablets containing 240 mgm. of the extract of *S. ornata*. Rollier now reports on two groups of lepromatous patients observed over 3 years. The first group of 111 cases were given DDS in progressive doses from 25 mgm. to 150 mgm. and the sarsaparilla 4 to 10 tablets daily in the first week and remaining at 10 tablets for a minimum of 6 months and a maximum of 1 year, thereafter on DDS alone at 150 mgm. daily. In the second group of controls DDS was given in doses similar to the first group. With both groups the treatment was given 6 days a week. Activity on the part of sarsaparilla was indicated by significantly greater bacterial negativization after 12 months, compared with DDS alone. The author thinks that the

treatment of leprosy by a combination of red sarsaparilla (*Smilax ornata*) and DDS represents the best therapy at the present time, and is a therapeutic association such as will avoid drug resistance.

*Health Services in the U.S.S.R. Public Health Papers No. 3, WHO, Geneva.*

This is an interesting report on the health organization and medical care in the U.S.S.R., arising from a visit in October 1958 of an international team of 23 medical specialists and health administrators. There is a reference to leprosy on page 23 as follows: "The following diseases occur only sporadically or as isolated outbreaks: trachoma, typhoid fever, leprosy (6,000 cases only in the whole of the U.S.S.R.), malaria (5,000 cases only during 1957 in the whole U.S.S.R.)".

*Control of Leprosy in the U.S.S.R.: Participation of Local Medical and Prophylactic Institutions.* N. A. TORSUEV and P. S. GREBENNIKOV. *Indian J. of Dermatology*, **4**, 4: July, 1959, pp. 95-99.

These workers of the Rostov-on-Don Experimental and Clinical Leprosarium describe the process of integration of the anti-leprosy work in the U.S.S.R. into the broad medical and public health network of the country. Skin and V.D. clinics, health and epidemiological stations, and rural medical services all play their part, and the leprosaria existing (number and location not given) are to be fitted into the plan. (The number of known cases of leprosy in the U.S.S.R. is not stated. From other sources, particularly the WHO visit, the number is given as 6,000. EDITOR.) Care is being taken to include the instruction and training of health workers, rural medical aids (feldshers), doctors and students, and the search for and registration of contacts is not forgotten. In short, in Russia they are in the stage of modernising and improving their anti-leprosy work, and making it widespread.

## REPORTS

*Annual Report of the Medical Dept., Uganda Protectorate, 1958, Vol. 2.*

This report on pages 43–45 contains summarised figures for leprosy work by districts and provinces, and figures for those in treatment villages. In the four provinces of Uganda the intake of leprosy patients had reached 62,003 by December 1958. The total of discharged cured was 5,217 in December 1958. Total absentees were 19,682, and the estimated number attending was 32,217 at December 1958. The Treatment Villages in the 4 provinces were 76 in number, with accommodation for about 4,414 patients. Three have been closed. Leprosaria are 5 in number, with a total intake to December 1958 of 14,852 and total discharges of 2,612 to that time. The total absentees were 5,512. The estimated number in attendance in 1958 was 3,302.

*Report of Pakistan Leprosy Relief Association, Karachi Branch, from May, 1957 to December, 1958.*

The President of the Association is Mr. N. M. Khan, C.S.P., who is the Chief Commissioner, Karachi. The Chairman is Mr. Muzafar Husain, C.S.P., the Hon. Treasurer, Mr. M. A. Mirza, and the Hon. Secretary, Mr. Sarfaraz Khan. This is the first report, for the Pakistan Leprosy Relief Association, Karachi Branch, came into being in May 1957. Its first task was to take over the running of the Manghopir Leprosy Hospital. There was much to be done, and they started with a credit of Rs. 23/- (about £1 14s. 0d.), but generous donations were given and much voluntary service, and it has been possible to improve the hospital greatly. There are 200 inpatients and more are asking for accommodation. It is proposed to build to receive a further 100 inpatients and to provide an outpatient clinic in the city. The latter is estimated to cost 100,000 rupees (£7,500). Mendicancy of leprosy patients is a problem in the city.

*Annual Report of the Medical Department, Tanganyika, 1958, Vol. 2.*

On pages 20 and 21 are statistics of leprosy inpatients and outpatients. There are 19 leprosaria, in which there were 4,700 patients resident at the end of November 1958, mostly on sulphone therapy. There were 1,500 patients admitted during 1958 and 778 discharged. Leprosy outpatient clinics are 344, with a total of 28,727 cases under treatment, including 7,071 new cases during 1958. The total under sulphone treatment is 25,902.

*Annual Report of the Calcutta School of Tropical Medicine, 1957–58 (issued 1959).*

On pages 122–126 Dr. N. Mukherjee reports on the work of the Leprosy Department.

There were *autoradiographic studies* on DDS tagged with S<sup>35</sup>, which showed a higher concentration around hair follicles, sweat glands, blood vessels, nerves, and cellular exudate.

*Electron and phase microscopy* of *M. leprae* revealed a glea-like substance around each bacillus and especially around a globus. Under sulphone treatment bacilli from patients showed no obvious changes in the first 6 months but later the cell membrane became ragged, cytoplasm disintegrated, mitochondria often broke up into smaller granules, the cell wall disintegrated and partially absorbed in some, and glea material disappeared.

In *immunology* studies continued on Dharmendra refined lepromin and Kedrowsky antigen on 1,015 subjects. The reactions were very similar, but the Kedrowsky antigen often produced a smaller zone of erythema and rather more induration at the site of injection. The lepromin reaction was studied histologically. In the lepromatous cases there was only slight oedema and tissue destruction. In the tuberculoid there was marked oedema and slight infiltration with polymorph neutrophils, lymphocytes, histiocytes, and eosinophils. Later after 48 hours the lymphocytes and histiocytes increased in number.

Studies in *experimental transmission* were on young Syrian hamsters and hybrid black mice, by intraperitoneal route of inoculation. There was some success.

*Histopathological* studies were carried out on leprosy lesions. In tuberculoid lesions some of the histiocytes and macrophage cells were found to contain ester phosphatides, especially in reacting tuberculoid lesions. In lepromatous lesions histamine content was found not higher than in healthy tissue. A study was also made of hypopigmented macular lesions in 9 cases. Bacteria were found in some, and a weak positive lepromin test in some.

In *therapeutic studies* Acidomycin was used by intradermal injection of the lesions, 0.25 ml. rising to 1 ml. on alternate days for 9 months, in 2 tuberculoid cases. The lesions subsided completely, but without recovery of sensory perception. For lepra reaction Sandosten calcium and Irgapyrin were tried in 5 cases. The first drug gave moderate improvement. Irgapyrin also gave a moderate improvement. Chlorpromazine (Largactil) was tried unsuccessfully for relief of joint pains and disturbed sleep in one case.

*The East African Leprosy Research Centre.* p. 10, The East African Council for Medical Research, Annual Report, 1958-59, pub. by Government Printer, Nairobi.

This Centre has been in existence 5 years. The staff at present comprises the Director, Dr. John Garrod, a biochemist, Mr. G. E. Ellard, M.Sc., and Mr. R. Rhodes-Jones, laboratory technologist, and Mrs. Rhodes-Jones (photographer). The Centre carries out

medical supervision of 6 leprosy clinics in Uganda and 4 in Kenya, and on retirement of Dr. Harden-Smith as medical officer in charge of the Leprosarium to which the Research Centre is adjacent, Dr. Garrod has taken over this work. Dr. Garrod records appreciation of the generous financial support by the British Leprosy Relief Association to the Centre, by a contribution which amounts to nearly one half of the running expenses, and for a recent grant of £4,000 for mains electrical connection to the Centre. In the scientific work of the Centre, Mr. Ellard has used the ferric chloride method, previously developed in the Centre, for studies of the absorption and excretion of the drug SU 1906, (diphenylthiourea), and its metabolite. He has found that for maximum absorption and effect the dose need not exceed 1.5 g. at a time and preferably should be given daily at least. About one-tenth of the oral dose is absorbed and metabolized. Attempts to isolate the metabolite are making some degree of progress. Dr. Naylor of Makerere College has begun work on radio isotopes in their uptake by bacilli. Three years' experience of the drug trials with Ciba 1906 confirms that it is a valuable alternative line of treatment, with absence of toxic effects, and less of unpleasant reactions and their sequelae. Etisol or diethyldithiolisophthalate by inunction is also being tried. Progress is 3 to 4 times as fast as with standard treatment, and any drug resistance is avoided by its use in combination with standard drugs, and there are some hopes that a fully lepromatous case may reach bacterial negativity within a year of starting treatment. Clinical progress runs closely parallel to progress in bacterial counts and histology. There is an odour associated with the use of the drug. This does not upset the patient much but causes some ostracism from his associates.

Dr. Garrod records that as a result of the work in the 10 outpatient clinics, more lepromatous cases are found.

*The German Leprosy Relief Association. (Deutsches Aussätzigen Hilfswerk.), 4 Dominikanerplatz, Würzburg.*

Dr. I. Nowicki of the Medical Department of the German Leprosy Relief Association has kindly provided information about this new Association. It was founded in 1957 and began as a work of relief and aid to a leprosarium in Ethiopia, on finance provided by voluntary contributions from the public. It next gave support in medicaments and instruments to other leprosaria and constructed its own leprosarium in Bisidimo near Harar in Ethiopia. It now also aids 2 leprosaria in Korea, 1 in Indonesia, 1 in India, 3 in Tanganyika, and others in Paraguay, Chile, Brazil, Argentina, and Colombia, and has extended aid to 3 centres in Ethiopia besides Bisidimo, and others in Ghana and Angola. The Association also gives scholarships to 12 medical students from India and Indonesia, who might become medical officers of leprosaria in these countries, and proposes



to establish a research centre under the guidance of Dr. G. Klingmüller (who is Vice-Director of the Würzburg University Hospital for Skin Diseases).

*Rajah Sir Charles Brooke Memorial Settlement, Chunking, Sarawak : Report for 1959.*

Dr. J. D. Finlayson and Mr. Hamish MacGregor, O.B.E., report a good year. The number of patients on the roll was 384 at the beginning of the year and 388 at the end. New admissions were 82, and 69 were discharged symptom-free. Tuberculosis seems to be the most important intercurrent disease, for during the year 46 cases were treated. Of great interest are the remarks in the report on their experiences in the treatment of leprosy. Most patients are given bi-weekly oral DDS tablets, 1 to 3 tablets, and their efficacy has been shown by the number of discharged patients. Also for patients who do not make good progress or show themselves intolerant to the DDS, some 45 patients received weekly intramuscular injections of *Sulfon U.C.B.*, which is a combination of sulphones and hydno-carpus oil. This treatment has proved very helpful. *Ciba* 1906 and *Etisul* have also been tried:

*Ciba* 1906 (*DPT*, or *diphenylthiourea*) was given in daily oral dosage to 10 patients for 21 months. With 2 exceptions the bacillary index improved greatly and 4 became negative and remained so. Eight of the 10 still have reactions and new nodules so the clinical state lags behind. Another 7 patients have the *Ciba* 1906 for periods of 3 to 9 months and are improving but still subject to reactions. Another 3 patients admitted in December were given *Ciba* 1906 and *Etisul* is to be given later. The usual dose of *Ciba* 1906 has been 3 tablets daily, as the patients do not seem to tolerate more. Reactions are milder on the whole.

*Etisul* (diethyl dithiolisophthalate) has been given by inunction in 3 groups of patients and a reduction in the bacillary index was obtained of 56% over a period of 11 to 15 weeks (this would take 6 to 12 months or more on standard treatment). Of the 13 cases on trial, 6 became negative and 2 relapsed. Combination with DDS and other drugs will now be tried.

*Mission to Lepers: The Present State of the Leprosy Work in Korea, 1960.*

Dr. N. D. Fraser, Medical Secretary of the Mission to Lepers, 7 Bloomsbury Square, London, has kindly provided the following information.

Rev. C. M. Lloyd and Mrs. Lloyd and Miss Grace Bennett, S.R.N., S.C.M., arrived in Korea in 1956. In 1959 they were joined by Dr. Gerald Wilson and Miss M. Butterworth, S.R.N., S.C.M. Rev. Lloyd reports that the first 10 months were spent in Pusan, from

whence they visited various concentrations of leprosy patients who were voluntarily segregated on the outskirts of towns and villages and in more remote places. These groups were independent and tried to administer themselves, and did not seem likely to respond to any new approach, so Pusan area did not give scope for the formation of a new modern centre. Mr. Lloyd therefore decided to move to Taegu, right in the centre of an area heavily affected by leprosy. Here he found Koreans had a much more alert interest and active concern, and in the Provincial Health Dept. Patients soon came forward and a small weekly clinic was formed, helped by Dr. S. R. Choi of the Government Mobile Clinic who at that time was conducting a leprosy survey. Soon the Presbyterian Mission Hospital provided more suitable premises for the clinic and the women of the Church in Korca raised funds. By 1960 the outpatient clinic work in Taegu moved to premises in the grounds of the Government Medical College Hospital, and 11 other clinics had been set up in rural areas within a radius of 50 miles of Taegu; the total registry of patients reached 1,000, with 20 to 30 new patients monthly. Regular attendance is 500 to 600 patients. These clinics may be in the open air and roadside, or in simple accommodation. It soon became evident that a centre of hospitalization was necessary, and has been begun by a four-bed unit in the Taegu Medical College Hospital opened in December 1959, and surgical and X-ray facilities have been given. It is hoped that a larger and more permanent leprosy hospital will develop from this. There is a Government leprosarium, Ae Sang Wan, some 10 miles from Taegu where the medical team visits and spends one day a week, and where their work is welcomed and appreciated. This leprosarium has a Korean full-time medical officer, a laboratory technician, and a trained nurse, and 800 patients, who are now being examined for the purpose of classification, with a view to bringing emphasis on the admission of infectious patients by preference. Also there have been great strides in the administration of Sorok Do, an island off the south coast of Korea where there are 5,000 to 6,000 patients. The Mission has given help to the Government Preventorium in Taegu, where Miss Bennett runs a clinic for health supervision of the 200 children. There is also good work which the Mission helps at Andong Colony, 80 miles north of Taegu, which is a refuge for mutilated and crippled patients founded by Mr. Kim Dae Bal, who is also in charge of Ae Sang Wan. The Korean Minister of Health has publicly expressed the sincere appreciation of the Ministry for all the help given by the Mission to Lepers and the hope for its continuance.

## REVIEWS

### Book Review

*The Handbook of Diseases of the Skin*, 6th Edition, 1959, price 8s. 6d. net, H. O. MACKEY: London, Macmillan & Co., 263 pp., 203 illustrations black and white.

This *Handbook of the Diseases of the Skin* is meant for students as a practical guide to diseases of the skin and as such is very good value. It is interesting to note that it includes two pages for the description of leprosy, with six illustrations. This is in line with the natural position of leprosy as a section of dermatology, and will do something to bring to the mind of the student an awareness of this disease, which, because of the greater movements of the peoples of the world, can provide examples even in European practice. There are about 300 cases known in England at the present time. The description of leprosy given is necessarily brief and because of its impact on the student perhaps the author will not mind introducing a few corrections. On page 177 in the first paragraph, he states that it ends "usually with a fatal termination from involvement of the viscera or from intercurrent diseases". This is misleading; it would be better to say "usually not with a fatal termination from the leprosy *per se* but from intercurrent diseases". On page 178 in the description of nodular leprosy it is unwise to leave out the information that lepromatous leprosy can appear, and often does, not only in the face but in the whole body. A useful addition would be the sentence added to the first paragraph as follows: "Nodules, or raised macules, or diffuse infiltration, may appear symmetrically disposed over the whole body". In symptoms, first signs are given as a husky voice and nasal discharge. In fact, these are apt to be in the late stage and it would be truer to say that the first signs are usually seen in the appearance of raised macules, or nodules, or infiltration of the skin. Later the author states "the malarial type of fever with wasting and diarrhoea is common". It would be better to state for the student's information that there is a reactional form of leprosy associated with fever and arthralgias and neuritis and swelling of the existing lesions in lepromatous leprosy, and that there is also a reactional tuberculoid leprosy. On page 179 in the third line, the term 'leper claw' is better rendered as 'claw hand'. In diagnosis the author states that it is made by finding the bacilli, which is perfectly correct but he misses a very good opportunity as a dermatologist by failing to add "and by careful clinical observation of the lesions and of the associated interference with nerve sensation". In treatment of leprosy he states that "sulphone J-51 is a rapid non-toxic antibiotic", but the term 'antibiotic' is out of place as J-51 is a chemotherapeutic agent. Under treatment it would be useful to mention that the severe nerve pains of leprosy call for the

use of chlorpromazine in conjunction with analgesics such as aspirin and pethidine and that leprosy reactions which are so troublesome can be treated with the antimalarial drugs, such as chloroquine and mepacrine, and the corticosteroids are of great value.

*Transactions of the 7th International Congress of Leprology, Tokyo, November, 1959*, published by Tofu Kyokai, Tokyo, Japan, 1959, 518 pages, over 200 illustrations.

This very attractive clearly-printed volume is a worthy record of the unique 7th Congress. The papers are given in English, French and Spanish, and Japanese authors have very courteously given their papers in English. There is an interesting and valuable record of discussions, and indeed of all the extracurricular social activities of the Congress, visits to leprosaria, and research centres, etc. The Technical Resolutions of the Congress are presented on pp. 457-490. Hearty congratulations are due to the Tofu Kyokai on the production of these Transactions, and many will understand the amount of hard work behind it, and express their gratitude.

*Variações em Torno de um Mesmo Tema. (Various Addresses on the Same Theme.)* by Dr. Orestes Diniz, Director of the National Leprosy Service, Brazil, Rio de Janeiro, 1959, 195 pp.

These various speeches and papers of Dr. Orestes Diniz have been gathered together and are worthy of being studied carefully in full, as they show the bases of the present anti-leprosy campaign in Brazil and explain the programme and plan of the future work. There are 20 articles, beginning with *Leprosy Makes 5,000 New Victims Annually*, and including *How to Intensify the Antileprosy Campaign*, *The National Antileprosy Campaign*, *New Phase in the Fight against Leprosy in Brazil*, *Conquering the Leprosy Endemia by Chemotherapy*, *Organization of the Leprosy Control Programme and its Integration in the General Public Health Services*, *Prophylaxis of Leprosy in Brazil*, *Training of Personnel for the Work of the Antileprosy Campaign*, etc.

*Expert Committee on Leprosy, Second Report; WHO Technical Report Series, No. 189*, Geneva, 1960, pp. 27.

Five of the 29 members of the WHO Expert Advisory Panel met by arrangement of WHO in Geneva on 3rd to 8th August, 1959. These were Dr. J. A. Kinnear Brown, Dr. Orestes Diniz, Col. P. Laviron, Dr. H. W. Wade, and Dr. R. V. Wardekar. From the Secretariat were Dr. W. Bonne, Dr. J. M. M. Fernández, Dr. J. Gay Prieto, Dr. V. Martínez Domínguez. The Committee elected Dr. H. W. Wade as Chairman, Col. P. Laviron as Vice-Chairman and Dr. J. A. Kinnear Brown as Rapporteur (i.e., Recorder).

The Committee first considered the *Infectivity and Mode of Spread of Leprosy*. They thought that lepromatous cases are not the only source of infection; borderline, reactional tuberculoid, and some indeterminate cases have a certain degree of infectiousness. Truly polar tuberculoid cases are not normally infectious. Leprosy, even in the lepromatous form, does not seem to be able to infect the majority of individuals. The natural susceptibility of the host seems to play an important part. This is greatest in childhood, but in a few it does not diminish with age. Regarding the *Lepromin Reaction* the committee defined integral lepromin, bacillary lepromin, Dharmendra antigen, and leprolins. The latter elicit only the early reaction and do not themselves sensitize. For routine lepromin testing the Mitsuda-Hayashi type of lepromin is recommended, preferably using the technique introduced by Wade. Dilutions should be studied further including multipuncture tests with depot lepromin. A method of standardization is still being sought. Hanks' method of actual counting after declumping may well be the solution of the problem. In the reading of the reactions the question of the lower limit of positivity should be left open pending further histological studies of the reaction lesions.

*Leprosy Prevention:* the two chief methods suggested to protect contacts are BCG vaccination and prophylactic chemotherapy. Though the benefit of BCG is not as yet proved, it does no harm and there is no objection to its being used in leprosy campaigns. The Committee discussed the protocol of trials of BCG as a prophylactic against leprosy and gave a general outline of such an experiment. As regards prophylactic use of the sulphones the evidence so far is not convincing enough.

In *Leprosy Control* the Committee developed the ideas of preliminary investigation, case-finding programme, epidemiological survey, pilot project in a pilot area, and mass campaigns, with an attack phase, a consolidation phase, and an integration phase. They also discussed the personnel of leprosy campaigns and the assessment of results of leprosy campaigns. The question of personnel lies at the very heart of success in these campaigns.

In *Therapy* the Committee reaffirmed the value and dependability of the sulphones, considering that DDS is the best drug for mass campaigns, and mentioned rules for evaluation of progress during treatment, but did not outline the criteria of cure. Trials of new drugs should have a control group on a treatment of proved value, such as DDS. The Committee recommended that WHO assist in controlled chemotherapeutic investigations, which should be conducted simultaneously in several centres in various parts of the world, and that a protocol for trials should be prepared by WHO.

The Committee discussed the importance and principles of *rehabilitation* and gave a scheme of classification of deformity,

mostly in 5 grades, and asked for research in deformities and rehabilitation. Rehabilitation was considered a function of leprosy institutions.

*Teaching and Training in Leprosy and Health Education* were considered. Training of paramedical personnel was now of great importance, as these are the basic personnel of the mass campaign.

*Classification of leprosy* was thought to be in a stage of marking time until more facts are known. Lepromatous, tuberculoid, indeterminate, and borderline can be accepted for the time being.

*Revista de Leprologia; Fontilles, 4, 8; July-Dec., 1959, pp. 653-786.*

Volume IV of the Fontilles Review of Leprology contains 8 interesting articles.

Drs. J. Terencio and F. Contreras Rubio describe *a case of Laennec cirrhosis in a leprosy patient*, in which necropsy showed that the cause could not be attributed to leprosy. Alcohol, malaria, toxic action of the sulphones have been discarded as causes, but there may have been a possible virus origin, helped by nutritional deficiency. Drs. J. Terencio and J. Tarabini report on *the action of dexametasone in the treatment of leprosy reactions*. This synthetic steroid, which is 9-alpha-fluormethylprednisolone (Millicorten-Ciba) they gave in doses never exceeding 4 mgm. daily by mouth, and found it the best so far used, with absence of danger and without the relapses so common with other corticosteroids. The same two doctors also report on *histochemical investigations of the amorphous fundamental substance* in old cases, and Dr. Tarabini describes the *bacteriology of leprosy and visceral leprosy*. The two doctors again together report on a case of *the brown line in a leprosy patient*: this was a frontal dyschromia in a patient associated with schizophrenic attacks. Drs. F. Contreras, J. Terencio and J. Tarabini describe a case of *calcification of the cubital nerve*, and Drs. J. Terencio and J. Guillén of *paroxysmal haemoglobinuria in a leprosy patient*: there was a syphilitic history and a cure with penicillin.