FACTORS INFLUENCING THE SPREAD OF LEPROUS INFECTION

By E. MUIR, M.B., F.R.C.S. (Edin.)
Working under the Indian Research Fund Association, and the School of Tropical Medicine, Calcutta
and
K. R. CHATTERJI
Bankura Leprosy Investigation Centre

IN this paper certain definite hypotheses are set forth. Evidence is brought forward in their support based chiefly upon two grounds : the leprolin test, and careful investigation into the histories of affected families at the Bankura Leprosy Investigation Centre.

Our hypotheses may be summarized as follows :—

1. Most healthy human adults possess (perhaps in varying degree) natural resistance to leprosy.
2. Subliminal infections with *Mycobacterium lepræ* tend to increase resistance to the disease.
3. Resistance to leprosy is lessened by three main factors :—
   (*a*) *The age factor*—in young children resistance to leprosy is lowered.
   (*b*) *The debility factor*—any disease, habit, physiological condition, or anything else which debilitates the patient, lowers the body resistance to leprosy during the period that debility lasts.
   (*d*) *The hyperinfection factor*—the multiplication of Hansen's bacilli in the body beyond a certain amount lowers the resistance to leprosy, even though the patient may otherwise enjoy excellent health.

The leprolin test

If an autoclaved suspension of ground-up leproma, containing large numbers of Hansen's bacilli, is injected into the human skin, certain reactions take place which may be studied clinically and histologically. A standard suspension (Hansen's leprolin) is used and 0.2 c.cm. is injected intradermally.

Clinical appearance.—A weal about 10 millimetres in diameter is raised which disappears in a short time and may be followed by the appearance of an area of slight erythema, wider in diameter than the weal; this also disappears after a day or two. If the reaction is positive, there appears after a period varying from 4 days to 2 or 3 weeks a slightly raised, erythematous area round the point of inoculation. On picking up the affected skin between the finger and thumb an indurated nodule is felt varying in thickness from 3 to 10 millimetres. This induration generally reaches its maximum about the third or fourth week, and then gradually subsides, though it may take several months before it entirely disappears. In some cases necrosis takes place at the centre and a small pustule appears and discharges, this being followed by more rapid resolution of the nodule.

The indurated nodule described above is caused by Hansen's bacilli, and the reaction is the same whether the suspension injected is first subjected to heat or not. A similar reaction is caused in healthy adults by other acid-fast bacilli such as rat leprosy bacilli, tubercle bacilli or saprophytic acid-fast bacilli. For a reason which will appear later, in carrying out the test we generally use as a control a suspension of rat spleen and liver, taken from a rat inoculated several months previously with *Mycobacterium lepræ muris*. This suspension (rich in Stefansky's bacilli and generally called Stefansky's leprolin) is standardized so that 0.2 c.cm. produces, in a healthy, non-leprous adult, at the end of the third week, an indurated nodule of approximately the same size as is produced by the same amount of Hansen's suspension. The end of the third week is chosen as in many cases the reaction to *Mycobacterium lepræ* suspension (Hansen's leprolin) takes place more slowly than that to the control; but at the end of the third week the former has generally caught up on the latter. The degree of reaction may be conveniently read by picking up the nodule between the finger and thumb and measuring it in millimetres with a pair of sliding calipers (figure 1). The test should always be carried out in the thin skin of the medial side of the arm.

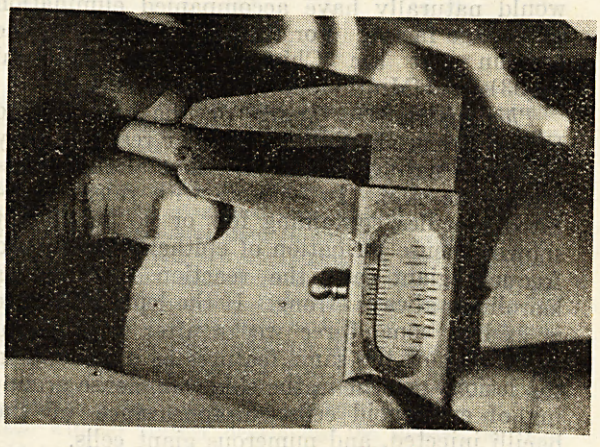

Fig. 1.—Measuring leprolin nodule with sliding calipers.

So far we have considered the leprolin reaction in the healthy adult. We shall now study the variations in leprous patients :

1. In patients who have been in contact with infectious leprous patients and have received subliminal infections the reaction to Hansen's leprolin tends to be enhanced, while that to Stefansky's leprolin remains the same. This is true whether or not visible lesions are present.
2. In patients in whom hyperinfection has taken place, *i.e.*, in whom bacilli have multiplied to more than a certain concentration, the

reaction to Hansen's leprolin is less, and in C-2 or C-3 cases no indurated nodule forms. Provided however that the patient is an adult and in good health the control reaction to Stefansky's leprolin is positive as in healthy non-lepers.

3. In young children, especially in the first year of life, the reaction to both Hansen's and Stefansky's leprolin is reduced or negative. An exception to this is sometimes found in children who have had slight contact with a highly infectious case, or more close and prolonged contact with a less infectious case, and have thus acquired subliminal infections; in these children one may find the reaction to Hansen's leprolin stronger than that to Stefansky's.

4. In debilitated patients the reaction to both forms of leprolin is reduced or may be clinically negative. Debility in the sense referred to may be caused by various diseases, dietary deficiency, climatic and many other conditions; even such physiological conditions as pregnancy and lactation must often be included.

5. Any two or all of the three factors which lower resistance may exist together and enhance each other, or they may follow each other successively. Thus a child in contact with a highly infectious mother may on account of the age factor acquire a high infection during its first few months or years. Later, as the child grows older, the hyperinfection factor comes into play and prevents the increase of resistance which would naturally have accompanied elimination of the age factor. For further references to the leprolin test *see* Chiyuto (1932), Hayashi (1933), and Muir (1933, 1934 and 1934*a*).

The histological study of the reaction to Hansen's leprolin shows a cellular response very similar in nature to that of lesions already present in the skin. In patients with raised indurated macules containing few or no bacilli but showing dense formation of epithelioid cells and frequent giant cells, the reaction to Hansen's leprolin is always strong. If the leprolin nodule is excised some three weeks after inoculation, sections show the same features as are found in the lesions present in the skin, *viz,* dense grouping of epithelioid cells, disappearance of the bacilli injected, and numerous giant cells.

In contrast to this we take a C-2 case and, choosing a region of the skin where bacteriological examination fails to show any acid-fast bacilli, inject Hansen's leprolin. Clinically there is no reaction. Sections taken two or three weeks later show either no cellular reaction or only a comparatively loose and mild cellular response causing slight thickening of the capillaries; the injected bacilli have almost all entirely disappeared, having apparently been removed by the lymph flow.

Discussion.—At the beginning of this paper we put forward the hypotheses that resistance to leprosy is present in different degrees in the majority of healthy adults; that this resistance is enhanced by slight (subliminal) infections, but is diminished by heavy infection, by all conditions of debility and in early childhood. These hypotheses are based primarily upon a careful clinical study of large numbers of leprosy cases, but these are confirmed by the results obtained with the leprolin test.

There appears to be no doubt that the leprolin test gives a reliable indication of the degree of resistance to leprosy. It is strongly positive in cases which all leprosy workers are agreed in regarding as resistant cases, *viz,* those in whom there are a few limited, indurated, highly anæsthetic lesions, chronic in nature, with few or no acid-fast bacilli and with little or no tendency to increase in size or number. There is much reason to believe that lesions showing a strong, compact epithelioid reaction, often with numerous giant cells, as found in sections both of the natural lesions and of the leprolin nodule, may be rightly regarded as a sign of high systemic resistance to leprosy.

In contrast with this is the strong, healthy, adult leper (C-2 or C-3 type), with a negative leprolin test; cellular response to the injected bacilli is comparatively weak. Similarly in young children and in debilitated persons the cellular response to Hansen's leprolin is low and the bacilli are not rapidly destroyed at the site of inoculation. It is justifiable to consider that these three factors render the system non-resistant to leprosy.

It is well known that conspicuous swollen leprous lesions often disappear during acute febrile fevers, and in other conditions which produce rapid debility. During convalescence however these lesions reappear in their former sites, generally extended in size and often accompanied by new lesions of similar appearance. The explanation of this phenomenon is that during the period of debility cellular reaction to the bacilli lying in the skin is held in abeyance, though the bacilli, undeterred by tissue response and phagocytosis, multiply rapidly. During convalescence the power of the cells to react is gradually restored, marked cellular response to the bacilli in the skin once more takes place, and hence lesions reappear larger and greater in number.

All authorities on leprosy are in agreement that while conjugal infection from infected wife or husband is comparatively uncommon (given variously as from 2 to 4 per cent), infection of children by leprous parents is exceedingly common, averaging round about 40 per cent. It is generally found (note cases described below) that, in a family where young children, older children and adults are in contact with an infectious case, the younger children tend to develop a generalized form of the disease, at first inconspicuous, but later showing itself in multiple lesions of the cutaneous or non-resistant type. On the other hand those who have passed their tender years when infectious contact first takes

place tend (if the disease appears at all) to develop fewer lesions, and these are more of the resistant, neural type. These facts corroborate the evidence that the resistance in young children to leprous infection is lower than that in adults.

Spread of infection.—The practical bearing of our hypotheses on the nature of the spread of leprosy may be made clear by presenting it in diagrammatic form (figures 2 and 3).

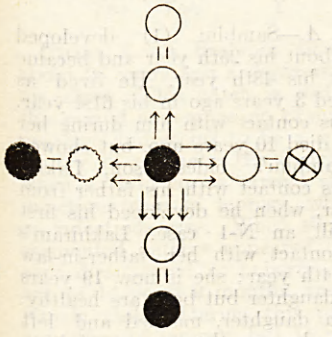

Fig. 2.

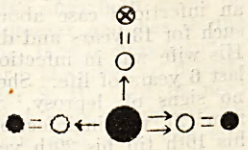

Fig. 3.

The key to the diagrams is as follows:—large disc = adult; small disc = child; white disc = non-leper; crossed disc = non-infectious leper (resistant type); black disc = infectious leper; smooth-margined disc = non-debilitated; wavy-margined disc = debilitated; arrows = degrees of infectious contact; = indicates the result of this infectious contact. Degree of infection depends on the closeness and length of contact and on the grade of infectiousness of the transmitter of infection.

It will thus be seen that, on the basis of the arbitrary standard that we have adopted, two degrees of infection are not sufficient to induce the disease in the healthy adult, but three degrees produce a non-infectious or resistant case, and four degrees an infectious case. On the other hand three degrees of infection are sufficient to make a debilitated adult into an infectious case. In the case of young children, however, one degree of infection may turn a healthy child into a non-infectious case of leprosy, and two degrees a healthy child into an infectious case, while one degree may be sufficient to make a debilitated child into an infectious case.

Leprosy investigation centre evidence

The truth of these hypotheses can only be checked by careful study of the spread of infection in families and communities. Investigations which are being carried out at the Bankura Leprosy Centre furnish considerable confirmatory evidence. The following six charts with explanatory notes illustrate the nature of this evidence.

In the case of healthy individuals the disc of the sex symbol is white, in infectious lepers black, and in non-infectious lepers crossed. The numbers above each sex symbol indicate (from above downwards) year of birth, year of first clinical signs, year of becoming an infectious case, and year of death. If any of these is not known, a ? is inserted; if any has not yet occurred, a dash is inserted. The century figures are omitted as far as possible to save space, 1920 being written 20. If other families have been infected by the original family the contact is indicated by a dotted line, the year when contact began being marked along this line. When there is more than one case in a family, each case is marked by a serial number in brackets.

CHART I

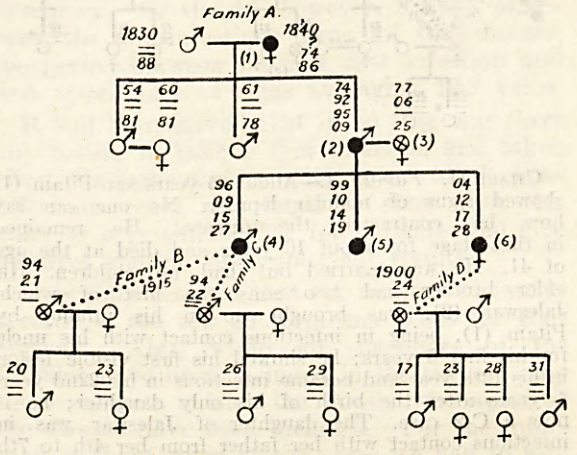

CHART I. *Family A.*—Gendu (1) when 34 years of age became an infectious case of leprosy after the birth of her third son, Prananath (2). At that time her first son had married and was living in his father-in-law's house, and her second son was about 13 years old; the latter died in his 17th year without any sign of leprosy. Gendu remained an infectious case for another 12 years and died in her 46th year. Prananath (2) the third son of Gendu (1) had infectious contact with his mother from birth. He showed his first visible lesion in his 18th year, one year after his marriage. Three years later he became a nodular case and remained in that condition for 14 years, dying in his 35th year. Prananath's wife (3) was 18 years old when her husband became an infectious case; she developed a few patches in her 29th year, but died in 1925, without further developing the disease, in her 48th year. Jati (4), the first son of Prananath, was in infectious contact with his father from birth; his first visible lesion appeared when he was 13; he became an infectious case in his 19th year and died at the age of thirty-one. Mati (5), the second son of Prananath, was likewise in infectious contact with his father from birth. He showed an initial lesion when 11 years old, became infectious in his 15th year and died in his 21st year. Prananath's third child Gati (6) was a daughter; she also was in infectious contact with her father from birth onwards; her first visible lesion appeared in her 8th year; she became an infectious case when 13 years old and died as such in 1928 in her 24th year.

Family B.—Paran, a friend of Jati (4) of family A, was in infectious contact with Jati from his 21st year. His first lesion appeared in his 27th year and still persists. He is now 40 years of age and an N-1 case. His wife and two children show no sign of leprosy.

Family C.—Bibhuti, likewise a friend of Jati, was in infectious contact with him from his 21st year; his first lesion appeared in his 28th year. He is now 40 years old and an N-1 case. His wife and 2 children show no sign of the disease.

Family D.—Charubala, a friend of Gati (6) of family A, was in infectious contact from her 17th year of life. Her first visible lesion appeared at the age of 24 after the birth of her second child. She is now a widow, aged 34, and has four children none of whom show signs of leprosy. She is still an N-1 case.

CHART II

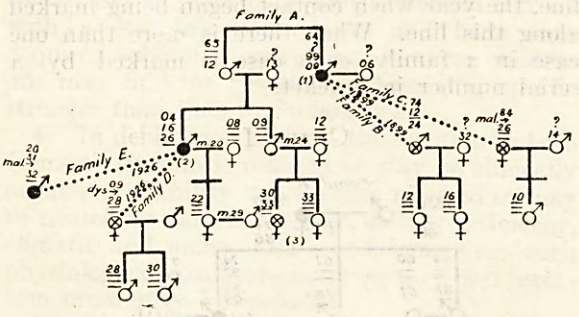

CHART II. *Family A.*—About 35 years ago Pitam (1) showed signs of nodular leprosy. No one can say how he contracted the disease. He remained in that stage for about 10 years and died at the age of 41. He was married but had no children. His elder brother had two sons the first of which, Jaleswar (2), was brought up in his infancy by Pitam (1), being in infectious contact with his uncle for his first 5 years; he showed his first visible lesion in his 12th year and became infectious in his 22nd year, 4 years after the birth of his only daughter; he is now a C-2 case. The daughter of Jaleswar was in infectious contact with her father from her 4th to 7th year when she was separated by marriage. She is now 12 years old, living separately in another village and showing no sign of leprosy. The brother of Jaleswar was born after the death of Pitam (1). He was in infectious contact with his brother from his 17th year onwards. He is now 25 years old and yet free from any sign of leprosy. He has two daughters, the older (3) of which was in contact with Jaleswar from birth and developed the first visible lesion at the age of 3½ years; she is now 4 years old. The age of the second daughter is only 8 months. Jaleswar's wife and brother's wife have been in infectious contact with him from their 18th and 14th years respectively; they are still free of signs of disease.

Family B.—Sreenath, a friend of family A, showed signs of neural leprosy in his 37th year and died in that state in 1924 at the age of 49. His wife died 2 years ago without any sign of disease. They have left behind two widowed daughters who are still free from any sign.

Family C.—Khiroda a cousin of Pitam was in infectious contact with him during her 15th year and then was separated. After an attack of malaria she developed an anæsthetic patch in her 42nd year; this patch still persists. Now at the age of 50 she is an N-1 case. Her husband and son show no signs of leprosy.

Family D.—Narayan, aged 25, is a neighbour of Jaleswar with whom he had infectious contact during his 17th year. At that time he also suffered from dysentery. In his 19th year he showed a neural leprous patch which is still present.

Family E.—Balai, aged 14, is also a neighbour of Jaleswar with whom he had infectious contact from his 6th year; the first visible lesion appeared in his 11th year; after a protracted malarial attack he developed within a year into an infectious (C-1) case.

CHART III

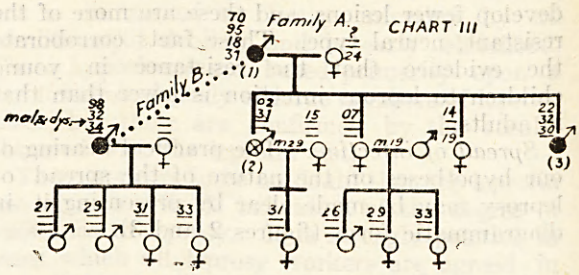

CHART III. *Family A.*—Sambhu (1) developed the first sign of leprosy about his 25th year and became an infectious case about his 48th year. He lived as such for 13 years and died 3 years ago in his 61st year. His wife was in infectious contact with him during her last 6 years of life. She died 10 years ago, but showed no signs of leprosy. Sambhu's oldest son, Lakhiram (2), was in infectious contact with his father from his 16th till his 29th year, when he developed his first visible lesion. He is still an N-1 case. Lakhiram's wife was in infectious contact with her father-in-law for two years from her 14th year; she is now 19 years old and has a 3-year-old daughter but both are healthy. Sambhu's second child, a daughter, married and left home when 12 years old; she was thus separated from her father after being in infectious contact for only one year; she is now 27 years old and has three children all of whom are healthy. Sambhu's third child died at the age of five, after one year's infectious contact, without signs of leprosy appearing. The fourth child was a son (3); he had infectious contact with his father from birth; his first visible lesion appeared when he was 10 years old, and now at the age of 12 he is an infectious case.

Family B.—Gara, a nephew of Sambhu, had infectious contact with his uncle for 13 years beginning when he was 20 years old. He developed his first visible lesion when 34 years old and within the last 2 years he has become a highly infectious (C-2) case. He has been suffering from repeated attacks of malaria and dysentery during these two years. He has two sons and two daughters all below the age of ten.

CHART IV

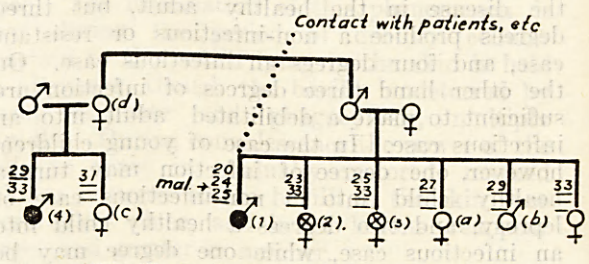

CHART IV. Parimal (1), aged 14, used to play about with cotton swabs from leprous cases, he also used to drink milk supplied by an infectious leprous woman who herself milked the cow; the first sign of disease appeared when he was 4 years old; after repeated attacks of malaria he became an infectious case when 5 years old, and is now a C-3 case at the age of fourteen. His sister (2), aged 11, had infectious contact with her brother from her second year; her first lesion appeared when 10 years old; she is still an N-1 case. Another sister (3), aged 9, also had infectious contact from birth; she first showed signs of leprosy when 8 years old and has now four hypopigmented, anæsthetic patches; she is thus an N-2 case; her leprolin test shows increased resistance to leprosy. Parimal's cousin (4), a boy of five years, had infectious contact from birth; 6 months ago he developed a lesion which is positive on bacteriological examination.

CHART V

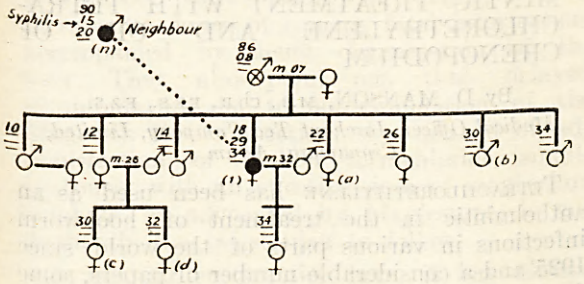

CHART V. A Brahmin, now aged 48 years, noticed about 26 years ago a depigmented anæsthetic patch on his chest. This patch is still present and has during this period undergone no change. It is bacteriologically negative and seems to be a scar. He gives no definite history of contact. His daughter S. B., aged 16, used when a child to be carried about by a neighbour, an infectious case of leprosy, who is still alive and still an infectious case. When she was 11 years old, hypopigmented patches appeared on her body, which however disappeared at puberty. She was married at the age of 14 years 9 months, and 13 months later bore a female child. During this period she was free from any signs of leprosy, but 1½ months after the birth of her child a number of bacteriologically-positive thickened patches suddenly appeared in different parts of the body, including the sites of former lesions. The leprolin test shows slightly increased reaction in the near relatives marked (b), (c) and (d).

CHART VI

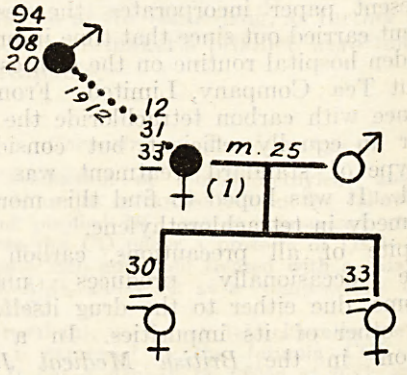

CHART VI. Fulkumari (1) was in contact from her birth up to the age of 8 years with her cousin, an infectious case of leprosy who used to carry her about in his arms. She was married at the age of 13. In her 19th year after the birth of her first daughter, she developed two anæsthetic patches which however disappeared during her second pregnancy. But three months after the birth of her second daughter, many erythematous thickened patches appeared all over her body. She is now 22 years old, a C-1, N-2 case.

We have used the terms 'infectious' and 'non-infectious' for lesions according to whether they were found positive or not on routine bacteriological examination.

Discussion.—We find that, out of the 17 cases which had infectious contact beginning from birth or before the sixth year of life, 10 have already become infectious cases; the average period between their first possible infectious contact and their becoming infectious was 14.7 years. Of the remaining 7 cases one is only 4 years old, and she has already developed a non-infectious lesion. The remaining 6 are all of one household; one child is already an N-1 and another an N-2 case; in this household the source of infection was a boy who was known to be suffering from leprosy and was kept partly isolated; moreover, in this family the average period between first possible infectious contact and the present time is 5.5 years, or a little more than one-third of the average period required to produce infectiousness in the 10 cases mentioned above which have already reached this stage.

Of the remaining 16 cases, whose first infectious contact occurred at ages varying from 11 to 25 years, only one has become infectious; and there was in his case a very distinct history of marked debility due to malaria and dysentery. Of the 16, however, 8 have developed the non-infectious type of the disease, the period between possible first infection and first appearance of signs averaging 10.5 years.

It will be observed that in no case was there any reason to believe that infection had taken effect through contact with a so-called *non-infectious case;* this tends to show that this name is a justifiable one for patients who give negative routine bacteriological results.

It is fully realized that the number of family records is too few to form any basis for conclusions. Also, while all members of the families have been included in the survey, only those contacts outside the family who acquired the disease have been included. For the information about some of the cases we had to rely almost entirely upon the results of cross examination of villagers; but, as far as we are aware, no data were entered which were not at least approximately correct. Those 6 families have been selected as typical of many others, and we have recorded them fully in order to show a method of investigation which may usefully be taken up by other workers. As statistics based upon such surveys accumulate the hypotheses put forward will be thoroughly tested.

The present records, as far as they go, tend to confirm our hypotheses, at least regarding the nature of the factors which raise and depress resistance to leprosy.

Two points are brought out clearly by those family records: (*a*) the importance of the infectious case in transmitting leprosy within the house and among neighbouring contacts; and (*b*) the importance of the child who within the first few years of life comes into close and prolonged contact with an infectious case. For this child not only acquires the disease, but generally develops it in the cutaneous and infectious form, and thus becomes the transmitter to the next generation. Although adult contacts sometimes become cutaneous or infectious cases, especially if exposed to some severe and lasting source of debility, this occurrence

is comparatively rare; and there is reason to believe that if in any community all infectious cases could be effectively isolated from children under 10 years of age, leprosy would disappear from that community in one, or at most in two, generations.

Summary

1. Most healthy adults are naturally resistant to leprosy. This resistance is increased by small infections, but it is low in young children, and is decreased in debilitated persons and in those who have become hyper-infected with *Mycobacterium leprœ*.

2. Evidence in favour of the above is found in the leprolin test, the use of which is explained.

3. Similarity is found between the clinical and histological appearances of a patient's leprous lesions, and those of the nodule produced by the leprolin test when this test is carried out in the same patient.

4. The factors influencing the spread of leprosy are given in diagrammatic form.

5. The histories of six typical leprous families are examined in detail. These tend to confirm the above hypotheses concerning the spread of infection.

REFERENCES

Chiyuto, S. (1932). The Leprolin Test. *Philippine Health Service Bull.*, Vol. XII, p. 300.

Hayashi, F. (1933). Mitsuda's Skin Reaction in Leprosy. *Internat. Journ. Leprosy*, Vol. I, p. 31.

Muir, E. (1933). The Leprolin Test. *Leprosy in India*, Vol. V, p. 204.

Muir, E. (1934). Some Factors Influencing the Nature of Leprous Lesions. *Ibid.*, Vol. VI, p. 12.

Muir, E. (1934*a*). A Suggested Descriptive Notation of Leprosy Cases. *Ibid.*, Vol. VI, p. 72.

DENTAL MYIASIS

By D. N. ROY, M.D., D.T.M. (Cal.)

Assistant Professor of Medical Entomology, School of Tropical Medicine, Calcutta

A CASE of dental myiasis in a person with a badly carious tooth was reported by Strickland (1929).

We have now received maggots from a second case, notes of which have been sent by Dr. Chakrabarty, assistant medical officer, Ambootia Tea Estate, Kurseong, as follows :—

'A patient had inflammation of the gum which went on to abscess formation. Pus was noticed round the tooth, the tooth itself not being carious. It was extracted and a large number of fly maggots emerged and were collected. The patient made an uneventful recovery'.

Evidently the odour of pus had attracted a fly which deposited its eggs in the vicinity of the peri-dental abscess while the patient was

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A COMPARATIVE RECORD OF ANTHELMINTIC TREATMENT WITH TETRACHLORETHYLENE AND OIL OF CHENOPODIUM

By D. MANSON, M.B., Ch.B., F.E.S., F.Z.S.

Medical Officer, Jorehaut Tea Company, Limited, Cinnamara, Assam

TETRACHLORETHYLENE has been used as an anthelmintic in the treatment of hookworm infections in various parts of the world since 1925 and a considerable number of papers, some favourable and some adverse, on its efficiency and toxicity have been published by research workers, mainly in the United States of America, since that date.

Articles on its use have appeared in this journal (Maplestone and Chopra, 1933, and Maplestone and Mukerji, 1929 and 1933); in these were embodied the results of researches conducted at the Calcutta School of Tropical Medicine. In the last of these articles a careful résumé of the effects of treatment with tetrachlorethylene was given; the workers concluded that tetrachlorethylene was safer than, and at least as efficient as, carbon tetrachloride.

By the courtesy of the workers at the Calcutta School of Tropical Medicine, I was furnished with a quantity of tetrachlorethylene (Parke, Davis and Co.) in December 1933 and the present paper incorporates the result of treatment carried out since that time in ordinary tea-garden hospital routine on the estates of the Jorehaut Tea Company, Limited. From past experience with carbon tetrachloride the necessity for an equally efficient, but considerably safer type of standard treatment was clearly realized. It was hoped to find this more suitable remedy in tetrachlorethylene.

In spite of all precautions, carbon tetrachloride occasionally produces untoward symptoms, due either to the drug itself, or to one or other of its impurities. In a recent quotation in the *British Medical Journal*, carbon tetrachloride is indicted as the offender and the chemical impurities are exonerated from blame.

One fairly definite fact is that carbon tetrachloride is apt to produce symptoms of toxæmia in cases of severe roundworm infection. Its use in alcoholic subjects has also been arraigned and there is a large mass of evidence that this charge is a true bill.

(*Continued from previous column*)

asleep. The eggs hatched out and the maggots led to the further trouble.

The larvæ were identified as those of a species of chrysomia, probably of *C. bezziana*.

REFERENCE

Strickland, C. (1929). A Case of Myiasis of a Carious Tooth. *Indian Med. Gaz.*, Vol. LXIV, p. 386.