SUSCEPTIBILITY AND RESISTANCE IN LEPROSY

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Infection with leprosy as a result of contact with a patient is not necessarily the whole story, because:—

(a) Conjugal infection is relatively uncommon.

(b) Only a fraction of the children of infected parents develop leprosy.

(c) The majority of people living in constant relationship with patients do not develop the disease; others do so after contact so brief or trifling as to pass unnoticed.

(d) Some of the evidence suggests that a child can infect a parent who had hitherto failed to contract the disease.

In illustration of (d) *P.N.* is an intelligent woman now in the employment of a leprosarium in Uganda. Her circumstances are well known to the authorities. She is aged 41, married with one child—a boy born when she was 22. Her husband has never had leprosy. None of the grandparents had leprosy. There is no history of leprosy in the family. She and her husband lived in a typical East African house, separated by farms from their neighbours. There were a few cases of leprosy in the district but none was obviously lepromatous. The nearest patient had tuberculoid

leprosy and lived more than 100 yards away. When the boy was 8, he developed hypopigmented macules on the forearms and the backs of the hands, which disappeared without treatment after two or three years. One year later a tuberculoid macule appeared on the mother's right cheek. This was confirmed by biopsy. A year later, when the boy was 13, he was admitted to the settlement with widespread lepromatous leprosy.

There are various alternatives—none of them easy:

A. *The boy's original macules were leprotic* and the boy infected his mother, or the mother infected the boy before she had any signs of tuberculoid leprosy.

B. *The original macules were not leprotic* and the mother infected her son with lepromatous leprosy from a bacteriologically negative tuberculoid patch, or before her patch appeared.

C. *Both mother and son were infected by the same source* but any contact was trivial and not remembered, and no different from what the mother and her neighbours normally experienced—e.g. seeing an occasional patient in the market.

" C " is quite feasible, but why in the same environment should the mother not have been infected before when she was younger? It is more probable that the boy's macules were lepromatous and that his presence in the family made all the difference. Both mother and child were susceptible, but the boy more so than his mother.

This is not the only case where the child has appeared to bring the infection into the house. In some instances the parent has shown the first signs several years after a son or daughter has developed leprosy. It is not always easy to delve into the history of patients as deeply as one would wish, but most of the anomalies listed above are explicable on the basis of inherited susceptibility or resistance.

Susceptibility and its converse, resistance, presuppose a factor *X*, the presence or absence of which decides whether the disease will develop and what form it will take.

If " A " is the descendant of a marriage where both parents have *X*, and " B " of a marriage where neither have *X*, " A " can be represented by *XX* and " B " by *OO*. If " A " and " B " marry, their children will belong to one of the groups *XX*, *OO* and *XO*—i.e. there will be resistant and susceptible children and others at a " neutral " point *XO* somewhere between.

(i) *If XX and XO marry,* the majority of their children
Will be resistant (*XX*);
Some will be " neutral " (*XO*);
None will be susceptible (*OO*).

(ii) *If OO and XO marry,* the majority of their children
Will be susceptible (*OO*);
Some will be " neutral " (*XO*);
None will be resistant (*XX*).

(iii) *If XO and XO marry,* the pattern will be the same as if *XX* and *OO* married—
Some will be resistant (*XX*);
Some will be " neutral " (*XO*);
Some will be susceptible (*OO*).

Where people of the Resistant group (*XX*) are in the majority and, therefore, marry only Resistants (*XX*) or Neutrals (*XO*), casual contact may take place in each of several generations without producing clinical leprosy. When, however, two Neutrals (*XO*) marry, a susceptible child is possible who will develop leprosy, and the more serious type, after only a brief exposure to infection. If this susceptible child escapes because it is not exposed to any risk, and eventually marries a person who has become susceptible by the same process or even an individual belonging to the Intermediate or Neutral group, a family may be created with a bias towards susceptibility, and the infection of one member may rapidly lead to leprosy in some of the others producing " Household Infection."

In endemic areas where marriages follow the brother and sister pattern, or are confined within a small tribal group because of language and cultural differences, the incidence of leprosy may be higher.[1] Under such circumstances, the probability of the pairing of Neutrals or Susceptibles is greater. As the marriage circle extends the chances are less, especially if " *X* " is not a single factor or gene, but a combination of several.

It is known that a negative lepromin can be converted to positive by BCG. It is thought that sensitization to tubercle may protect against leprosy, but a positive lepromin does not protect against tubercle. It is improbable that " *X* " is anything but a compound factor.

Suppose that *O* represents the absence of one component related to leprosy;
,, ,, *X* ,, the presence of that component;

,, ,, *T* represents the absence of one component related to tuberculosis;
,, ,, *Y* ,, the presence of that component.

The possible combinations of *O*, *X*, *T* and *Y* are much greater than when only *O* and *X* are considered. If *OXTY* is paired with *XXYY*, the following may result:—

(a) *OXTY* " neutral " to leprosy and tuberculosis;
OXYY " neutral " to leprosy but resistant to tuberculosis;
XXTY resistant to leprosy but " neutral " to tuberculosis;
XXYY resistant to both.

Similar patterns may be worked out for other combinations, e.g.—

(b) *OXTY* and *OXYY* one neutral to both diseases, the other neutral to leprosy, resistant to tuberculosis.
OOTY susceptible to leprosy but neutral to tuberculosis;
OOYY susceptible to leprosy but resistant to tuberculosis;
OXTY neutral to leprosy and tuberculosis;
OXYY neutral to leprosy but resistant to tuberculosis;
XXTY resistant to leprosy but neutral to tuberculosis;
XXYY resistant to leprosy and tuberculosis.

(b) *OXTY* and *OXTY* are paired—both neutral to both diseases they may produce:—
OOTT susceptible to leprosy and tuberculosis;
OOTY susceptible to leprosy, neutral to tuberculosis;
OOYY susceptible to leprosy, resistant to tuberculosis;
OXTT neutral to leprosy, susceptible to tuberculosis;
OXTY neutral to both diseases;
OXYY neutral to leprosy, resistant to tuberculosis;
XXTT resistant to leprosy, susceptible to tuberculosis;
XXTY resistant to leprosy, neutral to tuberculosis;
XXYY resistant to both diseases.

To obtain a complete picture one would have to include any other components that may behave genetically, such as the blood group, the hormone pattern, the susceptibility to disease in general. There may indeed be others. It would be necessary also to know what the relationship is between the various immunological tests and the different genes, whether direct or indirect, specific or non-specific; what is the effect of small or massive infections, and what

causes conversion in the absence of infection or vaccination. There are benign cases of leprosy which have a very positive lepromin suggesting marked resistance but producing progressive and severe deformities; there are others in which bacilli may come and go and the lepromin reaction fluctuate round the ± level, whilst the disease runs a more hectic course but leaves less permanent damage in its trail. One sees tuberculoid patients with briskly positive Mantoux and lepromin reactions, and similar patients with a negative Mantoux and a strongly positive lepromin. On the other hand, there are the lepromatous patients with negative lepromins, some of whom are Mantoux positive, but others negative. The infiltration and ulceration following injections of lepromin also vary widely in patients who appear clinically to be almost identical.

These notes are put forward not as a complete solution but because it is believed that along such lines it may be possible to harmonise the various types of leprosy and their frequency, their different immunological reactions, the influence of other infections, and to explain why, and by what method, leprosy disappears from some communities after changes in the sex, age and type incidence.

(N.B.—The word " neutral " is not used to suggest that the resistant gene inherited from one parent is cancelled by the absence of that gene in the other parent. It is used only in an attempt to simplify what is probably a difference in degree.)

REFERENCE

(1) J. A. KINNEAR BROWN, 1955. *Trans. Roy. Soc. Trop. Med. & Hygiene*, 49, 3.