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FACTORS INFLUENCING THE TRANSMISSION OF LEPROSY [1]

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This review is based on seven years' work in East Africa and more than one hundred surveys. The majority have been in Uganda but some in adjacent parts of Kenya. Details of most have already been reported (Kinnear Brown). From these it is concluded that susceptibility or lack of resistance plays a more decisive role than has been attributed to it. The argument can better be advanced by considering some of the more traditional views about the prevalence and transmission of leprosy. For convenience they are listed as follows:

i. Leprosy is a disease of hot humid climates.

ii. The prevalence of leprosy is influenced by overcrowding and the extent to which people mix.

iii. Leprosy is more common among males.

iv. Leprosy is a disease of childhood, susceptibility decreasing with age.

v. Non-lepromatous patients are non-infectious.

vi. Prolonged intimate contact is necessary for infection.

Evidence can be advanced in support of all but much of it is circumstantial and some of it misleading.

THE INFLUENCE OF CLIMATE

If what is known of leprosy is plotted on a map the disease appears to belong to those countries which lie in the tropics and which have a fairly heavy rainfall. One cannot have leprosy, however, without people, and there are not many people where there is little rain. The map today might be different from one drawn five hundred years ago when leprosy was prevalent in countries from which it has now disappeared, and the most malignant forms of the disease today are not concentrated within or limited to the tropics.

[1] Reprinted, verbatim, with permission, from the *Transactions of the Royal Society of Tropical Medicine and Hygiene* **53** (1959) 179-189. The references, however, have been filled out, as in the author's original manuscript.

Uganda is a compact country, half the size of Spain, slightly less than the area of the British Isles. It includes large areas of open water and swamp, and sits on the Equator on the northern shores of Lake Victoria, an inland sea with an area of 26,000 square miles. The lake and most of the land are at an altitude of 4,000 feet. The climate is tropical, but with greater temperature variations than occur at sea level. It is influenced near the Lake in the direction of greater humidity by the vastness of the expanse of water and the storms it precipitates. Inland, people are found living at lower and higher levels; in forest and by the Nile River at 2,000 feet, at 7,000 feet on the unsheltered slopes of Mount Elgon and the Ruwenzoris.

Within the greater part of the lake area the prevalence of leprosy is less than 10 per 1,000. At the same altitude but inland where there is less rain it is often three or four times higher. In the hills of Eastern Uganda the incidence is low; at a similar altitude in the west it is high, as high as in the thick forest 2-3,000 feet below. At all levels, in open country or forest, similar rates occur. There is no correlation with temperature, humidity or altitude.

In Liberia, in the same latitude as Uganda but at sea level, with a rainfall of 160 inches at the coast, 96 inches inland, a relative humidity of 80 per cent. for 7 months of the year and a mean temperature of 77° to 80°F., the incidence is of the order of 1 per 1,000 (Poindexter, 1951). In Netherlands New Guinea, with a similar wet tropical climate the coastal incidence is about the same but with inland values as high as 55 per 1,000 (Leiker and Sloan, 1954). In Southern Nigeria in 1930, within the same belt of rain forest and oil palm there were the greatest variations between individual villages. In 1942 Davey recorded a range of 15 to 129 per 1,000.

Any influence which the climate exerts must, therefore, be secondary or incidental. It is insufficient to override factors which keep the prevalence rate low. It is not strong enough to prevent the disease from changing its type or even from disappearing altogether. It is probably of some significance also, that in the Uganda surveys no obvious difference was observed in the frequency of the disease or the type of disease among those who were habitually overclothed and whose skin was thereby enveloped in a humidity of 100 per cent., and those who, because they wore little or no clothing, were constantly exposed to the sun and the air.

DENSITY OF POPULATION, OVERCROWDING AND MIXING

There are no villages in Uganda, and towns are a modern development. The family is the unit of society and the population is segregated in family groups. Five and a half million people occupy 80,000 square miles of land, an average of 70 to the square mile which holds over large areas. Elsewhere a hundred people would crowd into a village of a few

acres in the middle of their farms. In this country they spread over the whole area, each family isolated by its land. Leprosy is seen, therefore, as a rural disease uninfluenced, until recently, by artificial conditions.

The same fluctuations occur in the prevalence rate, however, as anywhere else. In one locality, with 925 people to the square mile, it was 26 per 1,000; in another with 17 to the square mile it was 41. The same rates were found under different conditions. In the densely populated areas the natural segregation neutralizes the worst effects of overcrowding, but in others, where the dispersal is greater, it may still limit but be unable to prevent a high rate of infection.

The more people mix the more infectious disease spreads unless, of course, there has been successful vaccination. The higher prevalence rates for leprosy did not occur in commercial centres or where there was the most movement. They were often in the backwaters where there was little communal life. Usually, of course, the more vigorous engage in commerce and travel, and amongst them one would expect a lower rate of infection, but this is not the complete explanation. Natural segregation provides a defence for the community. There must be another defence, however, that is more individual, that is able to withstand indiscriminate mixing and is even stimulated or strengthened by it. In its absence, that is, in the susceptible, leaving the protection of the family group may be disastrous.

SEX DISTRIBUTION; LEPROSY IS COMMONER AMONG MALES

It is still taught and believed that leprosy is characteristically commoner among males, but some of the figures produced need to be seen against their background. Nearly twice as many men attend hospitals in this country as women, but there are not twice as many men nor are they sick twice as often. The women are simply less mobile. The population is divided equally between males and females. The proportions in the surveys were the same. The patients were divided equally between the sexes.

Country	*Lepromatous rate*	*Proportion of male to female patients*
1. Triangulo Mineiro	75%	2:1
2. Netherlands New Guinea	43%[a]	6:5
3. Philippines 1933	60%	2:1
Philippines 1948	30%	11:9
4. Uganda	9%	1:1

[a] The authors believe this is a little higher than the actual.

The over-all lepromatous rate was 9.1 per cent, but significantly more males had lepromatous leprosy, and more females tuberculoid or non-lepromatous leprosy. In view of the male predominance reported elsewhere, one is led to ask whether the disease is different in Uganda or whether everywhere there is an underlying relationship between the sex and the type. The preceding comparisons are interesting:[2]

Where leprosy is more common among males, the lepromatous type predominates; where the tuberculoid type is more common, more females are infected. This was the experience in Southern Nigeria. It is true of Uganda and of parts of Kenya. As there was a swing from the lepromatous to the non-lepromatous types in the Philippines (see 3 above) the sex ratio altered correspondingly, and Littann (1953) has shown that the decline of the disease in northern Europe was accompanied by a similar change.

Somewhere there must be an endocrine link, lepromatous leprosy being the "masculine type" and tuberculoid leprosy the "feminine type," with a number of patients who are not definitely either, but are, at various stages, between. The same or a related endocrine influence may be associated with the higher male and lepromatous ratios which exist at the present time among races whose skins are less pigmented than the Africans.

The sex-type distributions may thus indicate the stage and trend the disease has reached. They may be the consequence of endocrine adaptation, the method or result of successful defence. The differences in the disease patterns are characteristics not of the disease any more than they are superficially of the race, but of a particular group of individuals within the race. The adaptation which takes place is probably a long-term process whereby a less infectious type of disease is produced, a form of natural selection.

LEPROSY AS A DISEASE OF CHILDHOOD; SUSCEPTIBILITY DECREASES WITH AGE

The child rate is thought to indicate the severity of the disease. The average in this country was 18.6 per cent, but it varied. In the north, 25 per cent of patients were children; in the south, only 9 per cent. In the north the child population was bigger, 49 per cent of the whole; in the south it was only 27 per cent. The greater the number of children —which means the larger the families—the greater was the proportion infected.

If all children were susceptible the size of the family should make little difference to the child rate. Because it varied, one has to think of possible explanations. The following appear the more likely

i. Susceptibility is a recessive character. Generations of small families restrict the number and proportion of recessives.

[2] These figures were extracted or calculated from the following authorities: (1) Diniz and Da Cunha, 1950; (2) Leiker and Sloan, 1954; (3) Guinto *et al.*, 1954; (4) Kinnear Brown.

ii. Large leper families in one tribe may contain more susceptibles because it is the practice for patients to marry patients. Where this happens promiscuity is often more common. In another tribe public opinion may limit such marriages and infection dissolve them.

Where the child rate was high, the adult rate was low; where it was low, the adult rate was high. The total incidence was usually unaffected. Susceptibility is not, therefore, something one is certain to grow out of. The age of infection depends very much on opportunity and the child rate should be examined from this angle.

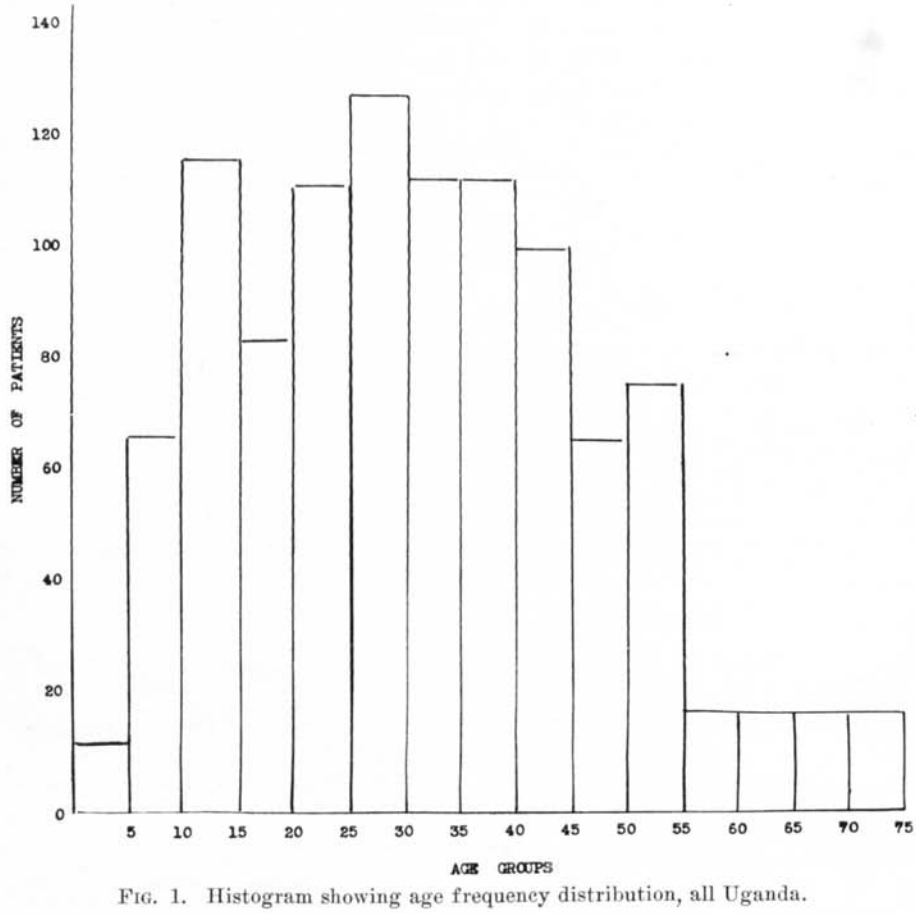

FIG. 1. Histogram showing age frequency distribution, all Uganda.

Unless the disease is changing, the age frequency should indicate the time of infection and onset. Less than 20 per cent were children; as many were in or over middle age; 60 per cent were between 15 and 45. Leprosy can hardly be called a children's disease at the present time. The histogram emphasizes the large number of patients who are adults, but it has an interesting depression in the 15-19 age-group which is followed by a rise to the maximum in the following 10 years. The

form is identical with that which can be derived from figures obtained by Ross Innes (1950) in two widely separated districts of Uganda some years previously.

This picture is not peculiar to this country. In Netherlands New Guinea (Leiker and Sloan, 1954) 60 per cent of patients are between ages 20 and 49 (Uganda 60 per cent); 42 per cent are between 30 and 49 (Uganda 37 per cent) and there is the same fall in the 15 to 19 age-group. Comparable figures from other countries lead to the same conclusion, that childhood is not the only time of danger, and control measures focussed simply on the child will have limited success.

The explanation of the depression in the 15-19 group is that in this country opportunity for infection occurs at two periods separated by

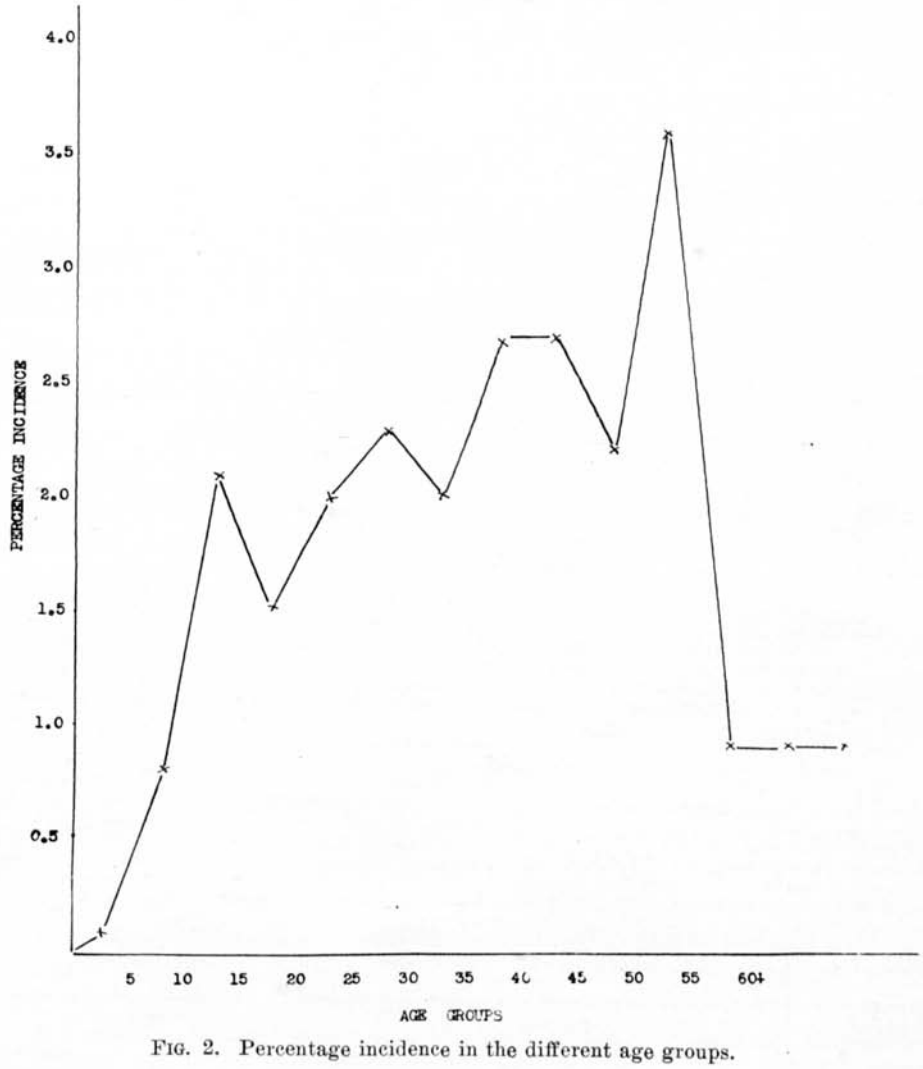

FIG. 2. Percentage incidence in the different age groups.

an interval during which losses by death are not replaced by new cases. The first period is childhood and involves principally the susceptible children within the household of a patient. The natural segregation of the population protects all but a minority of the children in other families. The second period occurs when a new group becomes exposed, the susceptible adolescents of healthy families, who begin to leave the isolation of their homes and, for the first time, to encounter infection. These are the individuals to whom mixing freely is dangerous; they are probably the only ones.

The graph shows the incidence in each 5-year group. It rises steadily, falls between the ages 15-19, then rises again irregularly until the peak is reached about age 55. This could hardly mean that leprosy is a cause of longevity! The other possibilities are that people are not now being infected, that the incubation period is lengthening, and that many are attacked irrespective of age.

There are reasons for believing that the disease is on the decline, a feature of which may be a lengthening of the incubation period, that is, the period between infection and final breakdown of whatever resistance there is. Both may be producing an effect, but a sufficiently large proportion of patients are known to have shown the first signs in middle life to support the view that under natural conditions leprosy is not a children's disease. Artificial conditions such as the crowding of people into compounds and villages may make it appear so by bringing everyone into contact with infection in infancy.

THE INFECTIOUS PATIENT

From the view that all patients were infectious and the general interest needed their segregation, the pendulum swung almost to the opposite extreme. Believing that interference with the liberty of the individual was justified only in exceptional circumstances, an attempt was made to treat as out-patients all who were bacteriologically negative and to allow them complete freedom of movement. From this it was an easy step to regarding the lepromatous or open case as the only source of infection. This view could have put the clock back considerably where it guided administrative policy because there is evidence that it is mistaken. Fortunately, the introduction of modern chemotherapy has helped to neutralize the danger.

Where the lepromatous rate is high and the people live in close proximity there may be a patient of this type within the orbit of every person. Where it is low and the people scattered, it requires more than a little imagination to attribute all the leprosy in a large area to the odd lepromatous subject who is already virtually segregated.

In one survey after another, where the prevalence rate was 20 or more per 1,000 not one lepromatous patient was discovered and the inclusion of one or two unrecognized open cases would not have affected

the issue, unless the important concession is made that the majority are open at some time or another. In the accompanying plan the homes of a number of patients have been plotted to show the distance in miles between them. There was no evidence that any were lepromatous, and there were no other patients in the area. Where two occupied the same house they had married after infection.

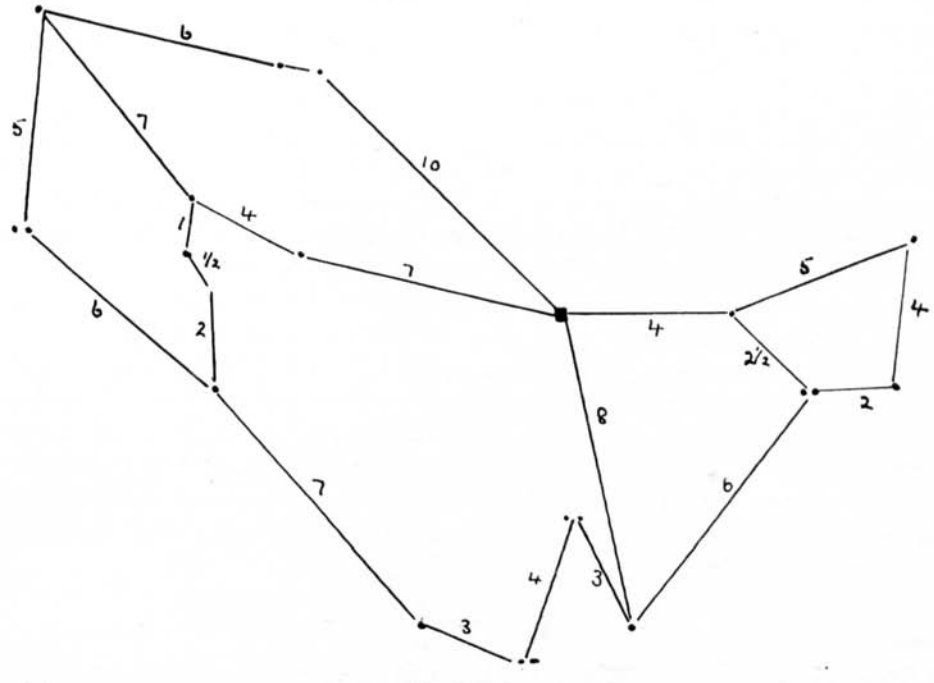

FIG. 3. Diagram showing distance in miles between the homes of the only patients in the area around the Igaru Health Centre in Kenya. Single dots signify single patients; double dots signify man and wife, but married after contracting leprosy; solid square indicates Health Centre.

Tuberculoid patients have tuberculoid children; occasionally their children are lepromatous. In either case, by whom are the children infected, by the negative parent within the house or a lepromatous patient 10 miles away?

Tuberculoid lesions that have always been negative suddenly react and are found to be positive. Even the so-called burnt-out non-lepromatous patient, who had always been negative, can suddenly develop bacteriologically positive nodules. From where do the masses of bacilli suddenly come, from a new infection in a hitherto resistant patient by release from a focus that had not been discovered, or were they there before but for some reason did not take up the stain?

It has been estimated that it takes a minimum of 10,000 tubercle bacilli per c.c. of sputum before the ordinary direct smear can reveal enough for any given specimen to be considered positive (Wade, 1954).

Tissue concentration and newer methods of staining reveal bacilli in lesions that had been regarded as negative. Surely a negative result only means, "Bacilli not found." There is little quarrel with the belief that the lepromatous patient with his skin and mucous membranes teeming with bacilli is the more grossly infectious, but it is ignoring facts to maintain that he is responsible for every case of leprosy, mild or serious, found within miles of his home. The question, "Who is the infectious patient?" should really be, "What is an open case?"

PROLONGED INTIMATE CONTACT

Everyone within a patient's home must have prolonged intimate contact with him; but that does not prove it is necessary for infection. Any contact with a patient outside the home must be deliberate if it is prolonged and intimate, or casual when it may be forgotten or even not recognized. Many a patient in this country is the first in his immediate family. Infection was from outside, where the natural segregation favours such contacts, being more accidental than in a village. Not every patient is wrong when he says he has never had prolonged and intimate contact. There may only be one or two patients known to him, and they a mile or two from his house. As an expression, "prolonged intimate contact" epitomizes a difficulty, something we do not understand about the transmission of the disease. Using it does not solve the difficulty. Some form of intimate contact is reasonable, but how intimate and why prolonged?

THE DISTRIBUTION OF LEPROSY

The prevalence rates in the different surveys varied from 0 to 43 per 1,000. The sample average was 17 per 1,000. Using the relevant figures to estimate the number of patients in each district, there are about 70,000 patients in Uganda with a general average of 13 per 1,000. Of these 6,500 are lepromatous (9.1 per cent). The map illustrates the distribution.

The most striking feature was the occurrence of the higher rates in the smaller, more isolated tribes, the isolation being due to language and custom as well as to geography. This is more understandable on the assumption that susceptibility is a recessive characteristic. Until recently marriage within the tribe was inevitable. This, together with the custom of brother and sister marriages—a man from one clan could only marry a girl from another if a man from the second clan married a girl from the first—must have led to some degree of inbreeding whereby any recessive characteristics would be maintained or disappear more slowly.

The distribution of the disease between the Lwo and Bantu tribes is of particular interest. The parent tribe of the Lwo peoples who are Nilotics is in the north. At one point there was a large migration to the

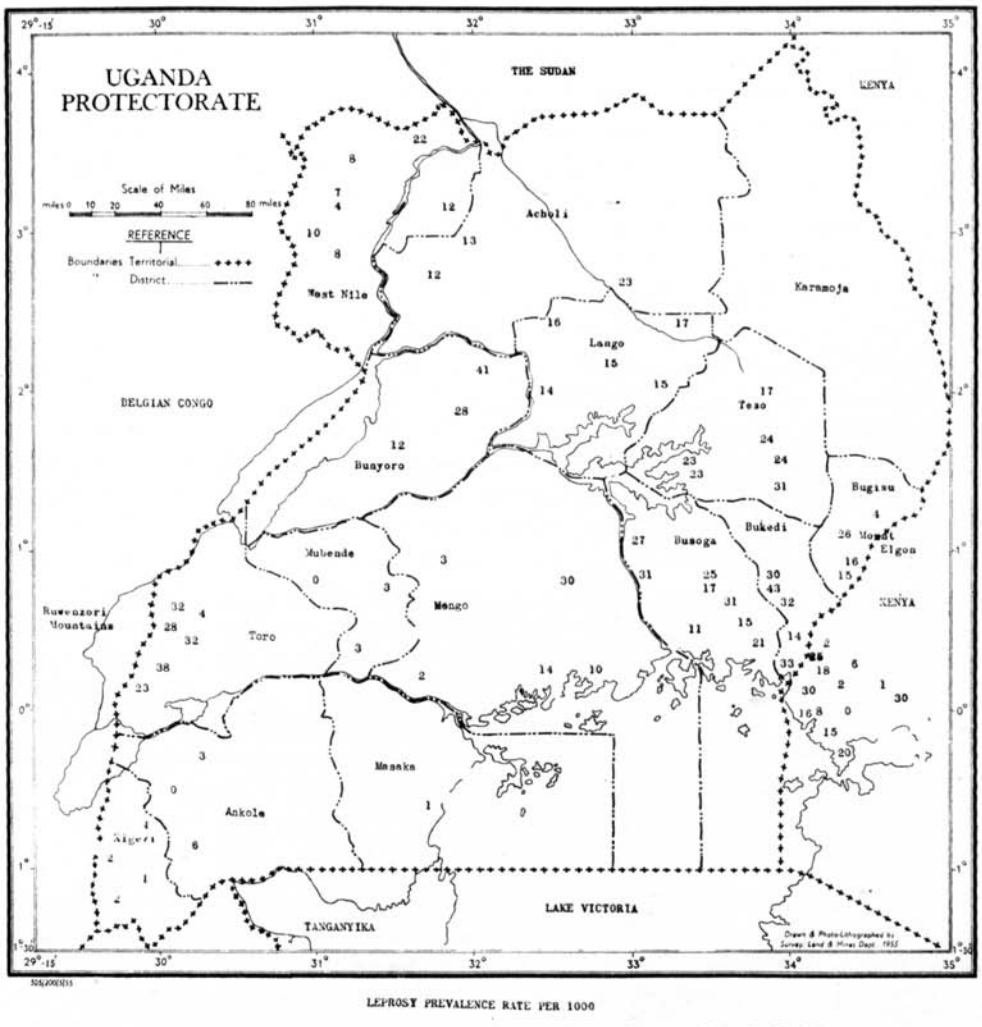

FIG. 4 Map of Uganda showing prevalence rates per thousand in individual surveys.

south and a large settlement in Kenya. In both these tribal groups the incidence of leprosy is about 10 per 1,000. A small unit, however, was left behind in eastern Uganda and, being surrounded by Bantu peoples, has become known as the Badama. The incidence of leprosy in these Nilotics isolated among the Bantus varies between 30 and 43 per 1,000. Among the Kenya Lwo, however, the position is reversed; the higher prevalence rates are in one or two small Bantu units surrounded by Nilotics.

The Bakonjo and the Baamba were left behind by the various Bantu movements and have remained secluded in the mountains and forests of Western Uganda. The prevalence of leprosy among them is more than 30 per 1,000. Their more numerous neighbours, the Batoro of the

same Bantu stock, move and mix freely beyond the natural confines of the tribe. Their prevalence rate is no more than 4 per 1,000.

Where the Banyoro, Batoro and Baganda are immediate neighbours, and there is no barrier to their mixing freely, the incidence is low among them all. Among a small section of the Banyoro, however, that is more scattered and geographically isolated, the incidence is much higher, 30 per 1,000. Sandwiched and isolated between this group of Banyoro and the River Nile are the Chopi, a small remnant of Lwo stock. The incidence among them is even higher, 41 per 1,000.

These variations are not due to external influences such as climate, over-crowding or even diet nor to something peculiar to the tribe, but to a factor which may be present to a greater or less degree in any tribe, a factor which behaves genetically and reflects the history of the tribe and its customs. Leprosy is practically non-existent in Germany, yet in South America in the Colonia Tovar is a colony of immigrants from the Black Forest who settled there in the middle of the last century. They have maintained their isolation and their culture by keeping their stock pure. They number 1,126 of whom 113 have leprosy, a prevalence rate of 100; 43 per cent are lepromatous (Convit *et al.*, 1952). Various reasons have been put forward for the disappearance of the disease from Great Britain. It could quite easily have been due to the opening up of the country and the expansion of the marriage circle. A man no longer had to marry in his own or the neighbouring village; the Londoner married in Tyneside and the English married the Scot.

ANOMALIES

Wherever the prevalence of leprosy is investigated, certain anomalies are encountered. The rate of conjugal infection ought to be high, it is surprisingly low. All the children born to patients should contract the disease; many of them do not. There should be a high rate of infection among those who are in daily contact; it is far lower than one would expect. Occasionally a parent develops the disease after his child has introduced it to the home. Other anomalies have already been referred to. If infection depended only on contact with an open case they could not happen. The exceptions prove the rule, some people are easily infected, some cannot be.

DISCUSSION

Thirty years ago the soil was regarded at least as important as the seed. Since then concentration has been less on the host than on contact with the bacillus, the bacillus that could be found rather than the one that had to be assumed. Theories of transmission have sometimes been moulded away from the facts because the disease was not seen other than in an artificial environment. It is not difficult for the atten-

tion to be diverted from the picture to the frame; what appears to be characteristic of the disease may be quite misleading.

In recent years the host has had rather more attention. It is believed that those who do not react positively to the lepromin test lack something essential to resistance. The knowledge that many who are negative in childhood become positive in later life, or after B.C.G. vaccination—but not all—has increased interest in the host. What the relation of induced lepromin positivity is to resistance or susceptibility is not fully known. It is important, however, that the host is coming more into prominence. The emphasis on the bacillus and the open case has left gaps in schemes of control because the host has been forgotten, as a result of which he has suffered. The susceptible individual needs to be found and protected against every possible source of infection, not just from those which are obvious.

Susceptibility and resistance are not new ideas but they have not been given the prominence they deserve. Rotberg (1937) referred to the N factor without which some individuals are inherently incapable of reacting; Fernandez (1943) suggested that a protective allergy could only be evoked in the presence of an unknown constitutional factor. Wade and Ledowsky (1952) drew attention to the considerable proportion of cases in the Nauru epidemic that were infected in adult life, and to the contrast between the high susceptibility of the people to infection and their resistance to the progression of the disease, evidenced by the mild form it took in most patients. They believe that some other inherent and fundamental factor is involved, and that resistance to attack is distinct from resistance to the progression of an already engrafted disease.

Keil, writing about hereditary factors in leprosy, gave several instances of twins, some believed to be identical, both of whom or neither of whom developed the disease. Some time ago it was reported that there had been twins (thought to be identical) in one of the Uganda leprosaria, with lepromatous leprosy. They had then returned to their home 200 miles away where, unfortunately, all trace was lost. Identical twins with tuberculoid leprosy were discovered, however, the only patients among nine surviving children of non-leper parents (Kinnear Brown, 1958).

The suggestion made here is that susceptibility behaves genetically, but not that it is a single gene. A number of influences may be involved, some or all of which behave genetically. It is probably their permutations and combinations that produce quantitative differences in the immunological status of different individuals. These permutations may be responsible for those manifestations which are classified rather too rigidly into groups, phases and types.

It would be very convenient to have a limited number of pigeon holes into one of which each patient could automatically be placed. The

predominating forms of the disease vary, however, from one people to another. They represent the immunological progress which has been made by a process of selection throughout successive generations but the different races have started at different times, each with a different heritage. They have progressed at different rates because the customs which influence inheritance have been dictated by different circumstances. As far as is known, there is only one bacillus but there are many hosts, patterns of disease are recognizable but their borders are often vague and ill defined and in time evolution brings mutation. Classification as a form of analysis or comparison is a useful exercise, but only the widest classification will embrace all experience, and the wider the system the less simple it will be and less applicable in the clinic or the field.

CONCLUSIONS

1) Climate, density of population and overcrowding are of secondary importance.

2) Under natural conditions leprosy is not a children's disease. The age of onset is determined by opportunity for infection.

3) Individual susceptibility or lack of resistance decide the issue whenever there is contact with infection.

4) Lepromatous cases are grossly infectious but they are not the only, nor always the most important, sources of infection. Most patients, at some time or other, may be infectious to susceptible individuals. Prolonged intimate contact is not necessary.

5) Susceptibility is a compound factor. Some or all of its components behave genetically.

6) Susceptible individuals belong to a race within the race. They remain undiscovered until they react ineffectively to infection.

7) The response of the host determines the form of his disease and, whilst there are strong resemblances between certain predominating patterns, not all fall easily into a simple classification.

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