Lep. Rev. (1968) **38**, 1, 49-56

Some Genetic Aspects in the Epidemiology of Leprosy

(Study of Multiple case families)

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'No scientific investigation is final; it merely represents the most probable conclusion which can be drawn from the data at the disposal of the writer. A wider range of facts, or more refined analysis, experiment and observation will lead to new formulae and new theories. This is the essence of scientific progress.'
—PEARSON (1898).

INTRODUCTION

Leprosy is generally believed to be a disease of antiquity, with some historians claiming evidence of it in Egypt as far back as 4000 B.C. and in India and Japan probably earlier than 1500 B.C. Biblical references to the disease are legion, but there is considerable doubt today whether leprosy mentioned therein is the same disease that we now recognise. Though Hansen, a Norwegian physician, discovered the leprosy bacillus in 1872, until today all attempts at laboratory culture have been unsuccessful. Only limited success has been achieved in the field of animal inoculation. The exact means by which leprosy is transmitted—how the bacillus actually enters the body still remains a debatable point. However, it was generally believed that it is communicated only after prolonged and intimate contact with a patient, which is vague in itself. All those who now instinctively hold their breath when they pass a leprosy patient will be surprised to learn that it is classified only as a 'mildly communicable' disease. Indeed many medical men believe it is the least communicable of all communicable diseases. Although it is universally accepted that *M. leprae* is the causative organism of leprosy, it became apparent that the bacillus does not produce disease in all human beings with whom it comes in contact. A variety of factors has been invoked to explain this supposed variation in susceptibility and these include diet, climate, age, sex, incidence of other diseases and factors variously described as innate, inborn, constitutional, familial and hereditary.

Rotberg (1937), Aycock (1940, 1941, 1948, 1962), Steinigar (1941) suggested genetic factors in determining the susceptibility to leprosy. Kinnear Brown (1950, 1956, 1957, 1959) and Spickett (1962, 1963, 1964) have also supported the hypothesis that there is a genetic factor in determining the susceptibility to leprosy. Although several authorities have supported the concept that leprosy may only be manifest in those who are genetically susceptible to it, the hypothesis is not generally accepted.

Two different opinions

Leprologists all over the world are confronted with the problem of finding a clue regarding the aetiology of leprosy. There are two different opinions regarding how the disease is caused.

1. It is due to bacillary infection and the infection is caused by intimate and prolonged contact with a leprosy patient.
2. It is the genetic susceptibility in presence of bacilli and the intimate and prolonged contact that cause the disease.

If leprosy is an infectious disease, then all or at least the majority of the individuals who had

intimate and prolonged contact should have developed the disease.

Noordeen and Mohamed Ali (1964) studied 579 families each of which had more than 1 leprosy patient in the family. They found that occurrence of multiple victims in the same family was not strictly governed by the law of contagion. Particulars of these 579 multiple leprosy patient families are given below:

TABLE 1

Showing the population particulars of multiple leprosy patient families

Total No. of families	579
Total population	3382
Total No. of leprosy patients	1296
Average size of the family	5.84
Average No. of leprosy patients per family	2.24
Percentage of affected population	38.4

It is but natural that no other individual can have a more intimate and prolonged contact than between the members of the same family. If leprosy is an infectious disease and the infection is caused by intimate and prolonged contact with a patient, most, if not all those living in close contact should develop the disease. But it is seen that only 38.4% of the population contracted the disease. It is difficult to explain this apparent immunity of certain individuals to leprosy and this is taken to be due to the natural resistance the individual possessed. When it is the genetic susceptibility that is in operation he must inherit it from one or other of his parents. In such a patient it should be in accordance with the laws of inheritance. Let us analyse the various findings in the study of these multiple leprosy patient families and see if the occurrence of patients follows the laws of inheritance in any recognised manner.

Familial Aggregation

On looking into the family history of the different families, we find patients with varying degree of duration of the disease. The duration of the disease is the period between the age of onset of the disease and age of the individual at the time of survey. The individual having the longest duration of the disease in a family is taken as the source responsible for spreading the disease to the other members of his family and he is named the source patient.

In the population which provided the 579 multiple patient families we have thus 579 source patients as the source of infection. The total number of patients in these families was 1296; deducting source patients we have (1296—579)=717 patients who developed the disease by living with a source patient in intimate and prolonged contact and these 717 patients are termed secondary patients.

All the individuals who live with a patient in the same family are not affected. From this, one cannot escape postulating that infection alone cannot explain the incidence of the disease and may be that the individual susceptibility genetically governed has some say in the matter.

An analysis of the source and secondary patients arising from the source patient is given in Table 2:

It will be seen from the table that when parents are source patients, only sons and daughters (not all of them) were affected in spite of many other persons living with them in close contact. Secondly, when brothers and sisters are source patients, only their brothers and sisters were affected. When grandparents are source patients, only their grandchildren are affected and, lastly, when the paternal uncle was a source patient, his brother's children became affected. Thus whoever may be the source patient, only his blood relations were affected and not the others. Again when the husband was a source patient, some wives became affected. In the instance where spouses and in those when daughter-in-laws were affected, it was found that marriages generally took place among those families where there is a history of leprosy and among close relatives. All these things suggest that the disease is concentrated on family lines.

Genetic mechanism

At present there are different opinions regarding the role of genetic factors in determining the susceptibility to leprosy. They are:

TABLE 2

Showing the classification of source and secondary patients

Type of source patients

Secondary patient in relation to source patient	Source Patients	Head or Father	Mother	Son	Daughter	Brother	Sister	Wife	Grand-father	Grand-mother	Paternal Uncle	Others
Sons		161	73									
Daughters		67	38									
Wife		109										
Brother						66	14					
Sister						21	13					
Grandsons									9	9		
Granddaughters									2	5		
Brother's Son											6	
Brother's Daughter											3	
Mother				8	2							
Father				3								
Daughter-in-law		5	2									
Husband								10				
Son-in-law		1										
Others												90
Total		343	113	11	2	87	27	10	11	14	9	90

(1) based on a single dominant gene (Dominant inheritance);

(2) based on a single recessive gene (Recessive inheritance);

(3) based on a single irregularly dominant gene (Incomplete dominant inheritance);

(4) based on the influence of a number of genes (Polygenic inheritance).

Let us assume that a single gene A is responsible for susceptibility to leprosy. A gene is said to be dominant when it produces its effect if it is present on either one or both the pairs of chromosomes, and a gene is said to be recessive when it produces its effect only if it is present on both the chromosomes of the pair. In the case of dominant inheritance we expect the ratio between the affected and unaffected in the progeny to be 3 : 1 and in the case of recessive inheritance we expect the ratio to be 1 : 1. But our data do not conform to either of these categories.

Now let us assume incomplete dominance. Here the phrase 'incomplete dominance' needs some explanation. Incomplete dominance means a dominant gene which is not capable of fully penetrating as a heterozygote. In the case of incomplete dominance all the heterozygotes are not capable of producing the disease; only a few of them will penetrate and cause the disease.

We have from our data, 579 families, each family having a source patient who is considered as the source of infection to the other family members. All the 579 members who are source patients are suffering from leprosy, and therefore should possess the alleles either AA or Aa. (Here 'A' is the abnormal gene responsible for the susceptibility to leprosy and 'a' the normal gene.) We cannot rule out the possibility of some heterozygotes getting affected and this is in accordance with principle of incomplete dominance and their number may be small when compared to the homozygotes. Thus the source patients must be either homozygous to A or heterozygous to A and not homozygous to 'a' which indicates a normal person. In the course of life he or she (source patient) might have married an individual who is homozygous to A (AA) or heterozygous to A (Aa) or homozygous to a (aa) the normal. From this we can work out the expected type of progeny as a result of marriages between the above types of individuals.

Type of marriages	*Type of progeny*			
1. AA × AA	AA	AA	AA	AA
2. AA × Aa	AA	Aa	AA	Aa
3. AA × aa	Aa	Aa	Aa	Aa
4. Aa × AA	AA	AA	Aa	Aa
5. Aa × Aa	AA	Aa	Aa	aa
6. Aa × aa	Aa	Aa	aa	aa

These are the six possible types of marriage and as a result of such marriages we expect the progeny as:

AA : Aa : aa .. 9 : 12 : 3

or AA : Aa : aa .. 3 : 4 : 1

Now all the individuals possessing either AA or Aa are susceptible to leprosy, i.e., 87.5% of the progeny are susceptible to leprosy. But how many of them get the disease by living in contact with an open patient depends upon the rate of penetrance of the gene. Susceptibility and getting the disease are two different things. A heterozygous susceptible individual may not sometimes get the disease even by an intimate contact with a patient because of his having only 'Aa' and the necessary environmental factors. But we can certainly expect a homozygous person (AA) to get the disease earlier when compared to a heterozygous individual (Aa) because he is more prone to the disease by having 2 genes; probably this might be the reason for finding people getting affected with the disease at different ages though they are living with a patient in the same family under similar conditions. The susceptible individual getting the disease may also depend upon environmental conditions. As one of the studies conducted at the Central Leprosy Teaching and Research Institute (Dharmendra, 1961) showed that leprotic patches in children are often evanescent ones and therefore our findings in a survey might not have been the correct picture in the case of many children. Such cases may be heterozygous individuals who are susceptible to leprosy and by virtue of their susceptibility get a patch or two that disappear soon. Thus:

(1) All the heterozygous susceptible individuals may not contract the disease even by living with a patient. The same might be true with some homozygous susceptible individuals also by virtue of their having only a casual contact with a patient, but these may be small.

(2) Unless we know the penetrance rate in the population it is not possible to pronounce more precisely about how many heterozygotes will get affected.

Now let us see how far the observed things in our present study are in agreement with the projected hypothesis. For this, only those familes where parents were source patients and the secondary patients their children were considered. The total number of children in these families and the number affected in different cases are given in the following Table 3.

TABLE 3

Showing affected and not affected children with parents as source patients

Source Patients	Secondary Patients	Sons		Daughters		Sons and daughters	
		Total	Affected	Total	Affected	Total	Affected
Father	.. .. ..	479	161	287	67	620	228
Mother	.. .. ..	141	73	69	38	356	111
Total	.. .. ..	620	234	356	105	976	339

With the help of the above data an attempt has been made to test how far the proposed hypothesis is in agreement with the observed facts. From the available records we observed that the average age of the different secondary patients under consideration was 13.4 years. Since they were living in close contact with a patient for a considerable length of time we

expect many of the homozygous susceptible individuals to develop the disease during this period. To test this hypothesis the X^2 test has been applied and the results are shown below.

1. Sons and Daughters taken together (3 : 4 : 1) i.e. (3 : 5)

	Affected	*Not affected*	*Total*
Observed	339	637	976
Expected	366	610	976
Difference	—27	27	

$$X^2 = \Sigma \frac{(Obs—Exp)^2}{Exp}$$

$=3.01$

X^2 from tables at 5% level is 3.84.

X^2 on 1 d.f. is insignificant at 5% level.

2. Sons (3 : 4 : 1) i.e. (3 : 5)

	Affected	*Not affected*	*Total*
Observed	234	386	620
Expected	233	387	620
Difference	+1	—1	

$$X^2 = \Sigma \frac{(Obs—Exp)^2}{Exp} = \text{less than 1}$$

X^2 on 1 d.f. at 5% level is insignificant.

3. Daughters (3 : 4 : 1) i.e. (3 : 5)

	Affected	*Not affected*	*Total*
Observed	105	251	356
Expected	133	223	356
Difference	—28	28	

$$X^2 = \Sigma \frac{(Obs—Exp)^2}{Exp} = 9.4$$

The X^2 is significant at 5% level. The hypothesis that all the homozygous susceptible individuals will contract the disease when they are allowed to have an intimate contact with a leprosy patient is true in the case of (1) sons and daughters taken together (2) only sons and (3) in the case of daughters it was not true. In the case of these daughters our information is incomplete because generally daughters after marriage go to their husband's houses. Some of them must have developed the disease when they are living as wives. This may be the reason for finding a large number of wives as secondary patients, with the head of the family as the source patient. According to the theoretical ratio 3 : 4 : 1, we are having 87.5% of the progeny as genetically susceptible individuals (7 out of 8). These include homozygous as well as heterozygous individuals. Out of these genetically susceptible individuals only those who are homozygous to A got infected and showed the signs and symptoms of the disease and this is quite in agreement with the observed numbers as revealed by the tests of significance. The individuals who are homozygous to A will develop the disease earlier when compared to the individual who is heterozygous to A, under similar conditions of living. Because of greater susceptibility the majority of the homozygous individuals are sure to develop the disease when they are in contact with a leprosy patient and only a few may not develop the disease because of environmental factors. Some of the heterozygous individuals will also develop the disease and how many of them develop the disease depends upon the penetrance rate of the gene in the population. At present, in India, data are not available to work out the exact penetrance rate in the population. If we know this rate, in the population, then we can predict the number of individuals who are likely to develop the disease in future. In the absence of information on the penetrance rate in the population, the only way of finding the number of individuals who are likely to become infected in course of time is by keeping the family members under prolonged observation.

Penetrance Value

Penetrance value is the rate at which heterozygotes penetrate and develop the disease in the individual. Since the frequency of leprosy is high, the gene frequency also will be high and since the gene is not fully penetrant, the most satisfactory value of the penetrance rate may be obtained from a consideration of the

progeny, none of the parents of which had leprosy. The exact method of calculating the penetrance rate is to take the pedigrees of the affected families. But in the absence of such data, we will do the second best, viz., to consider the present generation in obtaining a value for the penetrance rate in the population.

In the study of conjugal leprosy (Mohamed Ali, 1965) conducted at the Central Leprosy Teaching and Research Institute information is available on the progeny where none of the parents had leprosy. We have information on 106 couples who were not affected with leprosy before marriage. After they got married they had children and some of the children developed the disease. The analysis of the progeny of these 106 couples gives us the following Table 4.

TABLE 4

Showing the distribution of children according to the size of the sibship

Size of sibships	*No. of sibships*	*Total No. of individuals*	*No. of affected*
0	5	0	0
1	22	22	5
3	21	42	8
3	26	78	17
4	12	48	4
5	11	55	11
6	5	30	1
7	4	28	2
	106	303	48

The observed proportion of affected individuals $= \frac{48}{303}$

The rate of penetrance is given by:

$$\frac{\text{Observed proportion}}{\text{Expected proportion}} \times 100$$

The expected proportion of affected individuals depends upon the type of mating. Here in our case we have 6 types of matings and we can calculate the expected proportion of heterozygotes in these 6 types of matings. The following Table 5 gives us the expected proportion of heterozygotes and the corresponding penetrance rates in the case of different types of matings.

It can be seen that the rate of penetrance changes with the type of mating and it takes the maximum value 31.7%. This happens in the case of matings between:

1. Homozygous vs Heterozygous individuals
2. Heterozygous vs Normal individuals

and it takes the minimum value in the case of mating between a homozygous vs normal individuals.

From this we observe that the maximum penetrance of heterozygotes is 31.7% and if they are allowed to live under similar conditions we expect 31.7% of the heterozygous individuals to become infected (in course of their average lifetime). In our problem we have 488 (4 out of 8) heterozygous individuals who are living with one or more patients and the number of in-

TABLE 5

Showing the penetrance rates in the different matings

Sl. No.	Type of mating	Proportion of heterozygotes	$\frac{\text{Observed proportion}}{\text{Expected proportion}}$	Penetrance rate
1	AA × AA	0	—	—
2	AA × Aa	$\frac{1}{2}$	$\frac{48}{303} / \frac{1}{2}$	31.7
3	AA × aa	1	$\frac{48}{303} / 1$	15.8
4	Aa × AA	$\frac{1}{2}$	$\frac{48}{303} / \frac{1}{2}$	31.7
5	Aa × Aa	$\frac{3}{4}$	$\frac{48}{303} / \frac{3}{4}$	21.1
6	Aa × aa	$\frac{1}{2}$	$\frac{48}{303} / \frac{1}{2}$	31.7

dividuals who are likely to become infected if they are allowed to live under similar conditions is given by:

$$\frac{488 \times 31.7}{100} = 155 \text{ (approximately)}$$

These are the total number of individuals whom we can expect altogether to get the disease in the course of their life. After knowing the number of individuals who are likely to get infection the next step is to know when they are likely to get the disease. From a contact survey conducted in the Institute (1963-66) we have got information on the attack rate in multiple patient families (Report in print). The attack rate per year during first contact survey period (22 months) is 1.60 and it is 2.19 during second contact survey period (12 months), the weighted average being 1.81 per year per 100. At this attack rate we expect

$$\frac{488 \times 1.81}{100} = 9 \text{ (approximately)}$$

9 heterozygous individuals to get infection in a time interval of 1 year. On this, we can say during the course of about 17 years from now $\left(\frac{155}{9} = 17\right)$ we expect all the heterozygous individuals are likely to develop the disease because of their genetic susceptibility provided we observe them under similar conditions of living. All these things are valid only if we disregard the effect of environment which may have some influence in the development of disease.

After working out the penetrance rate that is operating in the population and the expected number of heterozygous individuals to get affected every year, the next thing would be to see how far the observed things are in agreement with the calculated one. There are altogether 976 sons and daughters with father or mother as source patient. Out of this, 958 were examined at the time of the general survey. Assuming that the genetic ratio:

AA : Aa : aa .. 3 : 4 : 1

holds good in the population, the age distribution and the respective number of individuals in different classes are given in Table 6.

Though it is clear that the homozygous individuals will contract the disease earlier compared to the heterozygous individuals we cannot rule out the possibility of a few heterozygous individuals developing the disease. Also those homozygous individuals whose age is less than the probable incubation period of the disease may not develop the disease. Thus the 339 individuals who were affected at the time of the general survey include heterozygous individuals also but their number will be much smaller compared to the homozygous individuals. Many of the studies so far done on the incubation period shows that the period varies from 3 to 15 years. The long incubation

TABLE 6

Showing the age distribution of the sons and daughters with parents as source patients

Age	Son	Daughter	Total	AA	Aa	aa
0—4	78	72	150	56	75	19
5—9	137	86	223	84	112	27
10—14	124	117	241	90	120	31
15—19	74	51	125	47	63	15
20—24	92	14	106	40	53	13
25—29	42	11	53	20	27	6
30—34	25	4	29	11	15	3
35—39	13	5	18	7	9	2
40—44	6	2	8	3	4	1
45—49	1	1	2	1	1	0
50—54	3	0	3	1	2	0
Total	595	363	958	360	481	117
Average Age			13.4	13.4	13.5	

period in certain individuals may be due to heterozygosity of the individual. It will be seen from the table that the average age of the homozygous individuals is 13.4 years and that of the heterozygous individuals is 13.5 years. Taking the average maximum incubation period as 9 years it is clear that most of the homozygous individuals will have developed the disease. In the case of heterozygous individuals the disease takes a long time to develop the signs and symptoms, generally more than 9 years. The average age of heterozygous individuals being 13.5 years we cannot expect an appreciable number of heterozygous individuals to get affected. From this we can presume that almost all the affected individuals are homozygous individuals.

During the first 2 contact survey periods, i.e., during an interval of 3 years, we observed 49 patients among these sons and daughters. From the table, it will be seen that there are 360 homozygous individuals in the population, out of whom 339 were already affected. There are 21 homozygous individuals left unaffected at the time of the general survey. According to the calculated penetrance rate which is operating in the population, we expect 9 heterozygous individuals to get affected in a period of 1 year, thus giving 27 during a period of 3 years. All the homozygous individuals who were living with patients and not affected at the time of the survey may get affected during this interval and thus the total expected number of individuals who are likely to get infected during this interval of 3 years is $21+27=48$, and the actual number observed is 49. It is indeed a very striking coincidence of the observed with the expected.

CONCLUSIONS

(i) The data relating to the multiple patient families supports the theory that the disease leprosy may be determined genetically.

(ii) A genetic ratio exists between the affected and non-affected progeny under the assumption of incomplete dominance.

(iii) Penetrance rate has been calculated for the population under study with the help of which we can predict something about the prevalence of the disease in future.

It is clearly worthwhile to plan a genetic study in this population which enables us to pronounce more definitely about the factors operating in the spread of the disease.

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ACKNOWLEDGEMENT

We wish to express our thanks to Major-General P. N. Bardhan, Director, Central Leprosy Teacihng and Research Institute, for scrutiny and permitting us to publish this paper, and to Mr. P. Sirumban, Statistical Assistant, for his help in the compilation of data.