GENETICS AND THE EPIDEMIOLOGY OF LEPROSY

I. The Incidence of Leprosy

By S. G. SPICKETT*
Department of Genetics, University of Cambridge

Introduction

Ancient writings describe leprosy either as a highly infectious disease or as an hereditary disease. In more recent times the work of DANIELSSEN and BOECK (1848) gained widespread support for the view that leprosy was an hereditary condition. Hansen's discovery of *Mycobacterium leprae* as the causative organism of leprosy was considered to disprove Danielssen and Boeck's theories.

It is generally accepted that *Mycobacterium leprae* is the causative organism of leprosy, however some authorities have argued that the bacillus cannot produce the disease in all human beings. A variety of factors have been invoked to explain this supposed variation in susceptibility; these include diet, climate, the incidence of debilitating diseases, and factors variously described as innate, inborn, constitutional, familial and hereditary.

AYCOCK (1940; 1941; 1948) considered that there were genetic factors that determined susceptibility to leprosy. Other workers, notably ROTBERG (1937), STEINIGER (1941; 1950) and KINNEAR BROWN (1955; 1956; 1957; 1959), have held similar views to those of Aycock, nevertheless the theory of a dual etiology of leprosy depending upon the coincidence of effective contact from an open case with a genetically determined susceptible individual is not generally held.

It is the object of this paper to make a review of the literature relevant to the problems of genetic mechanisms in the incidence of leprosy, in the hope that this will stimulate workers in the field to provide the information needed if they are to be elucidated.

The distribution of leprosy

The frequency of leprosy is not uniform; variations in incidence are apparent between nations and races. However the distribution of leprosy is not random The social units between which variations in incidence of leprosy may be demonstrated are genetically rather than politically determined; tribes and races show more distinctive patterns of leprosy than do administrative territories. Such observations

*Medical Research Council Scholar.

on the distribution of leprosy suggest that some genetic factor or factors may be of importance in the epidemiology of leprosy.

The concept that the distribution and frequency of a parasitic relationship depends upon the interaction of genetically determined characteristics is not new. It has been shown to hold for several infectious diseases including tuberculosis in man. It is probable that all parasitic associations are controlled in some measure by genetic variability in host and parasite, and it would be surprising if this were not so for the relationship between *M. leprae* and man.

It is difficult to make an accurate assessment of the number of persons suffering from leprosy in a given population, so that data from different populations derived by different methods and gathered by different people cannot be used to make valid comparisons. Some investigators have, however, collected data of different populations by similar methods. MUIR (1927) has given data of the frequency of leprosy in three castes of Hindus cohabiting in the provinces of Bihar and Orissa; Table 1. Each caste forms an inbreeding community, and it is clear that there are considerable differences in the frequency of leprosy between them. The standard of living is different in each group although climate is obviously the same for them all. It has been suggested that hygiene is a factor of great importance in the epidemiology of leprosy, but it is clear that it is not of predominant importance here since the Bowris, who suffer the highest leprosy rate, have a higher standard of living and of hygiene than the more aboriginal Sonthals, but lower standards than the Brahmins.

TABLE 1

Incidence of Leprosy in Different Castes Living in Bihar and Orissa

Caste	*Incidence*
Bowris	145/100,000
Brahmin	28/100,000
Sonthal	29/100,000

GEHR and MUNDAR (1954) have published data relating to the frequency of leprosy in the different components of a multiracial society in Surinam. It is evident from these data: Table 2; that there are significant differences in the incidence of the disease between the various races, since $\chi^2_{(6)} = 435.0169$ and $p \ll .001$.

Similarly, analysis of data from HUMPHREY (1952); Table 3; gives a significant difference between the frequency of leprosy in Australian Aborigines and persons of mixed European and Aborigi-

nal parentage: $\chi^2_{(1)} = 7.91659$, $p < .01 > .001$. WAYSON (1934) has given comparable data of the frequency of leprosy amongst different races from Hawaii: Table 4. It is notable that the incidence in part Hawaiians is approximately midway between that in Hawaiians and that in other races.

TABLE 2

Incidence of Leprosy in Different Races from Surinam

Race	*Population*	*Number with Leprosy*
Creole	89,280	874
Hindu	72,960	254
Indonesian	41,280	135
Bushman	23,040	16
American Indian	3,840	4
Chinese	3,120	6*
European	3,120	4
Others	3,360	0
TOTAL	240,000	1293

TABLE 3

Incidence of Leprosy in Australian Aborigines and in those of Mixed Aborigine European Parentage

Race	*No. Examined*	*No. with Leprosy*
Aborigine	4181	264
Aborigine × European	800	30

TABLE 4

Incidence of Leprosy of Different Races in Hawaii

Race	*Incidence*
Hawaiian	0.850/1,000
Part Hawaiian	0.480/1,000
Japanese	0.019/1,000
Chinese	0.030/1,000

The frequency and distribution of leprosy in North America have been the subjects of reviews by HOPKINS AND DENNY (1929); DENNEY (1933); HOPKINS (1938); MCCOY (1938); AYCOCK AND MCKINLEY (1938); AYCOCK (1940, 1941) and AYCOCK AND HAWKINS (1941), so that the facts need not be detailed here. Aycock has shown that the main concentrations of leprosy in the United States attributable to the immigrant population occur in different parts of the country from the main endemic foci. He has also shown that in those states with the highest incidence of leprosy there are distinct foci in which racial restriction is marked and between which there is no epidemiological relationship.

The leprosy rate may become very high in small inbreeding communities. This is exemplified by the experience of a colony of Bavarians established in Colonia Tovar, Venezuela, over a hundred years ago. 113 of the 1,126 members of this colony had leprosy when examined by CONVIT, GONZALES AND RASSI (1952). This rate of leprosy is far higher than that in the surrounding indigenous population.

Demonstrable differences between the incidence of leprosy in the different groups of a multiracial society have been shown in very many studies. Even in populations which are relatively homogenous racially there is evidence of some degree of limitation to certain breeding groups; See KINNEAR BROWN (1952). COCHRANE (1959a). However, although differences in the frequency of leprosy are found between populations, this does not necessarily mean that these differences are genetically determined.

BADGER (1959) has shown that one of the principle factors controlling the incidence of leprosy is the chance of contact with an open case; he has argued further that this is the predominating factor in the epidemiology of the disease. Also he has shown that the chance of contact with an open case is not dependent upon the frequency of such cases alone but that it depends very largely upon the behaviour and social structure of the community. Evidence has been put forward that strongly suggests that the actual mechanism of transmission of the bacilli from an infected individual to an uninfected individual may involve skin parasites; SPICKETT (1961); and that the relationships of these parasites with both host and bacillus must add further epidemiological complications which may vary between populations. The point at issue is that different populations may vary in a number of characteristics controlling the probability that any individual will come into effective contact with an open case, and therefore that variations in incidence of leprosy between populations may be unconnected with biological susceptibility to *M. leprae.* It would seem very probable that these factors do explain at least in part racial variations in incidence of the disease. BADGER has argued that the differences in incidence between the various races in Hawaii

and in Louisiana are functions of the probability of contact with an open case. If the argument that the predominant reason for differences in racial incidence is the frequency of open cases holds, it would be expected that an immigrant population from a country where leprosy was not endemic would have a lower rate than the native population of the country to which they move if leprosy is endemic in that country. The data of ROTBERG AND BECHELLI (1956) are not in accord with this expectation. In a population of 6,557,423 Brazilians there was a leprosy rate of 0.204/1,000 whereas in an immigrant European population of 815,108 (the majority of whom originated from Italy in which country there was very little if any endemic leprosy) the leprosy rate was 0.303/1,000. This is the reverse of what would be expected if chance of contact with an open case was the controlling factor. BECHELLI and ROTBERG have also made a study of the incidence amongst the contacts of patients in a leprosarium, their data are given in Table 5. The incidence amongst Brazilians of foreign extraction is significantly higher than that amongst native Brazilians ($\chi^2_{(1)} = 12.7303$, p. $< .001$). It is clear that the variation in the incidence of leprosy between populations cannot be explained on the basis of variations in the probability of coming into contact with an open case alone. It must, therefore, be concluded that there is a variation in the frequency and/or degree of susceptibility between populations.

TABLE 5

Incidence of Leprosy amongst Native Brazilians and Brazilians of Foreign Extraction

	Native Brazilians	*Brazilians of foreign extraction*	*Total*
Affected	7,614	4,873	12,487
Unaffected	5,815	3,232	9,047
TOTAL	13,429	8,105	21,534

Although it may be conceded that populations vary in their pattern of susceptibility to leprosy, this does not necessarily mean that these variations are genetically determined; unless "genetic determination" is taken in the broadest sense, including the influence of genetic mechanisms on choice of diet and the like. Several of the environmental factors that have been thought to exert an influence on the incidence of leprosy have already been mentioned. It has been demonstrated that climate is not of itself a factor of overriding

importance nor is hygiene or standard of living, nor is it possible to draw any correlation between diet and the incidence of leprosy. No environmental factor can of itself be shown to be of predominant importance in influencing susceptibility to leprosy, nor can any combination of them be shown to be of great effect in this respect. It is possible that different environmental factors have a different intensity of effect in different populations; however this implies genetic differences between populations relating to susceptibility although their influence may be remote. It may be considered that there must be some factor other than the environment influencing the susceptibility of the body to parasitism by *M. leprae*, and that this factor must be genetic.

Even though it may be concluded that there are genetic effects upon susceptibility to leprosy, there is no indication in the evidence presented so far as to what the nature of the relevant genetic system may be. These effects could be manifestations of known genes; as for example those controlling blood groups; or they could be manifestations of genes hitherto unknown. Furthermore it is not possible, at this stage, to make any hypothesis as to whether the genetic control of susceptibility to leprosy is mediated through one or many genes.

It is apparent from the evidence that has gone before that racial differences in susceptibility are not of the kind that can be used to distinguish virtually all the members of one race or population from virtually all the members of another race or population. This implies that differences between populations with respect to the relevant genetic system, are differences either in gene frequencies or in the manifestations of the gene or genes. The causes of variation in manifestation of gene activity may be manifold and complex. A gene may have no manifestation with regard to a particular character in some individuals whereas it has in others. Such a gene is referred to as being non-penetrant in those individuals, the percentage of individuals carrying the gene who show manifestations of its activity with regard to that character is equal to the penetrance of the gene in that respect. There may be many reasons for lack of penetrance of the gene. It may be due to the presence of other genes modifying its activity or it may be due to environmental variation. Clearly genes controlling susceptibility to *M. leprae* will be non-penetrant if the individual carrying them does not come into contact with the bacilli.

The manifestation of a gene may also vary with respect to the degree to which the character is expressed. For example; in a family reported by LUCAS (1881), some members of whom carried the dominant gene for polydactyly, one person had a normal number of fingers but an extra toe on each foot, whereas another had an extra finger on each hand as well as an extra toe on each foot. This varia-

tion is said to be in the expressivity of the gene, and it may be due to environmental and/or genetic factors. It is obvious that populations may vary in gene penetrance and in expressivity though the latter need not be considered here.

It is possible to summarise the hypothesis as follows; the susceptibility of man to leprosy is influenced by some genetic factor, and human populations vary in the frequency of this factor and in its manifestations, so that its behaviour and significance may vary between populations.

The distribution of leprosy within affected populations is not random, there being a tendency, first noted by DANIELSSEN AND BOECK (1848): see Table 8; for the disease to be limited to certain family lines. This limitation is, as might be expected, more obvious in those populations where leprosy is infrequent than in those where it is common, and has been reported by AYCOCK (1940) from New Brunswick; BRACKEN (1900) from Minnesota; MELSOM (1953) from Norway; BJARNHEDINSSON (1909) from Iceland, MARIANI (1931) from Italy, MUIR (1940, 1943) from Cyprus and Barbados and by STEINIGER (1950) from the Eastern Baltic States. There are many reports from countries with a high rate of endemic leprosy confirming the tendency for limitation to certain families. DENNEY (1917) has shown, with data from the Phillipines, that 33% of children not separated from parents with leprosy showed signs of the disease, and LAMPE has given data from the East Indies that show a frequency of 26% in the children of parents with leprosy. AYCOCK (1941) has quoted details of a study by SAND AND LIE of 2,010 children of 587 couples one or both of whom had leprosy. They found that when the mother alone had leprosy 14% of the children contracted the disease, whereas only 7% did when the father alone was infected, however when both father and mother were infected 26% of the children acquired the disease. The incidence when both parents have the disease is more than the sum of the incidence when the mother alone has the disease and when the father alone has the disease, it is however nearly equal to twice the incidence when the mother alone has leprosy. From this it might be suggested that contact with the father alone is insufficient to give full expression of all the susceptible children, whereas with the mother it is, therefore when both parents have leprosy full expression is gained from contact with the mother, and there is twice the chance of having genes for susceptibility when both parents have such genes as when only one parent does.

Estimates of familial leprosy are usually too low, as has been pointed out by AYCOCK (1941). This is because the index cases do not always have full knowledge of the frequency of the disease in their own families, and moreover, they are often reluctant to admit that a disease regarded as shameful has occurred in their families before. Also studies of the incidence in children involve an under-

TABLE 6

Family relationships between patients with leprosy in St. George's Hospital, Bergen

Total number of cases of leprosy	*In the line of direct descent*						
	Number of cases in the paternal family	*Number of cases in the maternal family*	*Number of cases in both families*	*Series of generations in the lines of both families*			
				1st Generation	*2nd Generation*	*3rd Generation*	*4th Generation*
213	29	40	69	20	40	1	8
	In the collateral line						
	Number of cases in the paternal family	*Number of cases in the maternal family*	*Number of cases in both families*	*Series of generations in the lines of both families*			
				1st Generation	*2nd Generation*	*3rd Generation*	*4th Generation*
	52	64	116	38	58	7	13

estimate since the probability of uninfected children contracting the disease may still be high.

The data show that the tendency for concentration of leprosy in family lines is found in all types of community which have leprosy. However the demonstration of limitation of leprosy to certain family lines while consistent with an hypothesis of genetically controlled susceptibility does not prove it since it is also consistent with a purely contagion theory of the epidemiology of leprosy, and a decision in favour of one theory over the other cannot be made, on this evidence, until much more is known of the epidemiology of leprosy.

DUARTE AND LIMA (1936) examined 9,239 contacts of persons with leprosy and found that 456 of them had leprosy, the relationships of the infected contacts with the index cases are given in Table 7. Unfortunately no data is given of the proportion of each type of contact infected, however the limitation to the family is quite clear. It can be argued that this familial limitation is a function of the greater probability of contact within the family than between unrelated persons rather than a function of heredity. It was found that of the 456 infected contacts 189 did not live in the same house as the index case, this suggests that intimacy of association is not the only factor operable in the limitation of leprosy to certain families.

FERNANDEZ (1948) compared the incidence of leprosy amongst the children of leprosy patients with that in conjugal adults, his data are quoted in Table 8.

These results show that children usually acquire the infection from within the household in which they live, since when susceptible children live in a household with a relatively non-contagious case (tuberculoid) they rarely contract the disease. However the incidence in conjugal adults is not significantly higher in the households in which there are relatively contagious (lepromatous) cases than in those households in which there is a non-contagious case. It is, therefore, clear that child incidence may frequently be underestimated since distinction is not usually made between tuberculoid and lepromatous index cases. Also it is clear that adults leading an active life are as likely to acquire the disease from contacts outside their home as within it. It is, therefore, difficult to explain the limitation of the disease to certain families if it is as freely contagious as these data indicate.

It is rare for an entire family to be affected by leprosy. Several pedigrees have been established in illustration of the very high frequency of leprosy that may be found in certain families. The proportion of wholly affected sibships in all the available published pedigrees is shown in Table 9. These data are derived from: FERNANDEZ (1948), STEINIGER (1942), THIN (1892), GUINTO, RODRI-

TABLE 7

Relationships of Affected Contacts with the Index Case

Relationship of the index case to the affected	*No. affected*	*% of total affected attributable to each relationship*
Father	112	24.6
Brother	83	18.2
Mother	76	15.7
Sister	70	15.4
Husband	30	6.6
Wife	24	5.4
Daughter	16	3.6
Son	10	2.2
Uncle	7	1.6
Grandfather	6	1.3
Sister-in-law	3	0.6
♀ Cousin	3	0.6
Grandmother	2	0.4
Father-in-law	2	0.4
Aunt	2	0.4
Friend	2	0.4

Mother-in-law; Nephew; Niece; Brother-in-law; Employer; Acquaintance; ♂ Cousin and Daughter-in-law; all have 1 affected; that is 0.2% of the total.

GUEZ, DOULL AND DE GUINA (1954), MUKERJEE AND GHOSH (1958), DREISBACH (1954), MELSOM (1953), and NEFF AND SNODGRASS (1930). When it is considered that most of these sibships have been chosen as illustrations of high incidence the proportion of wholly affected sibships would appear to be very low, unless it is allowed that leprosy is very feebly contagious indeed. The data of Fernandez, which has already been quoted, suggests that leprosy is not as feebly contagious as the within family restriction implies. The literature abounds in reports of isolated cases of leprosy which cannot be traced to any known contact which implies that the contact must have been brief. Similarly KINNEAR BROWN (1956) has pointed out that in Uganda the disease must in many instances

TABLE 8

Incidence of leprosy in children and conjugal adults

Type of disease of index case	*Unaffected*		*Affected*		*Total*	
	Conjugals	*Children*	*Conjugals*	*Children*	*Conjugals*	*Children*
Lepromatous	91	184	24	90	115	274
Tuberculoid	59	122	16	4	75	126
Total	150	306	40	94	190	400

originate from a casual contact. Valuable information concerning the communicability of leprosy is available from the work of QUAGLIATO (1956) who followed up a large number of contacts over several years. The majority of cases that occurred in the contacts were detectable within six years of the first contact, this period includes the time between invasion of the new host by the bacilli and the appearance of the first clinical manifestations of the disease. Similar conclusions may be reached from consideration of the data of COCHRANE AND RAJAGOPALAN (1943) and of FERNANDEZ (1948) and of DUARTE AND LIMA (1936). Comparison can be made between the incidence of leprosy in the older and younger halves of affected sibships; such data are given in Table 10. There is no significant difference between them ($\chi^2_{(1)} = 0.470$, $p < .50 > .30$). On the basis of this evidence it seems unlikely that the limitation of the spread of leprosy within families is attributable to the feebly contagious nature of the disease. It must, therefore, be concluded that there is variation in susceptibility to leprosy within families, and, since the effect of environmental factors is minimised within families and no correlation is evident between the order of birth and the frequency of leprosy within sibships, it must be concluded that these intrafamilial variations are genetic and moreover that the evident segregation of the different genes within the family indicates that the appropriate genetic system may well be simple.

TABLE 9

Proportion of Sibships Wholly Affected by Leprosy

Size of sibship	*No. of sibships wholly affected*	*No. of sibships partly affected*	*Total No. of sibships*
2	3	12	15
3	3	9	12
4	—	10	10
5	1	8	9
6	—	4	4
7	—	3	3
8	—	2	2
9	—	2	2
10	—	3	3

There are several requirements that must be fulfilled in the taking of pedigree data for the estimation of genetic ratios, these requirements are discussed in the appendix. The majority of published pedigrees concerning leprosy are very far from satisfying these requirements and cannot, therefore, be used for the elucidation of the

genetic system controlling susceptibility to leprosy. The pedigree shown in Fig. 1 has been taken from STEINIGER (1942) and is from the Acadian French community in New Brunswick. It suggests that susceptibility to leprosy is controlled by a single irregularly dominant gene, that is a dominant gene that is not fully penetrant as a heterozygote. The sibship of 3 comprising III (1, 2, 3) has one parent with leprosy and one without, one of the sibs has leprosy. The sibship of 4 comprising IV (11, 12, 13) also has one parent with leprosy and one parent without and one sib with leprosy. These families suggest that there is a single dominant gene controlling susceptibility to the disease. However neither III 10 nor III 11, both of whom have leprosy, have an affected parent and this suggests that the gene is recessive. The entire pedigree, therefore, suggests that the gene is irregularly dominant and this is in accord with the appearance of other published pedigrees.

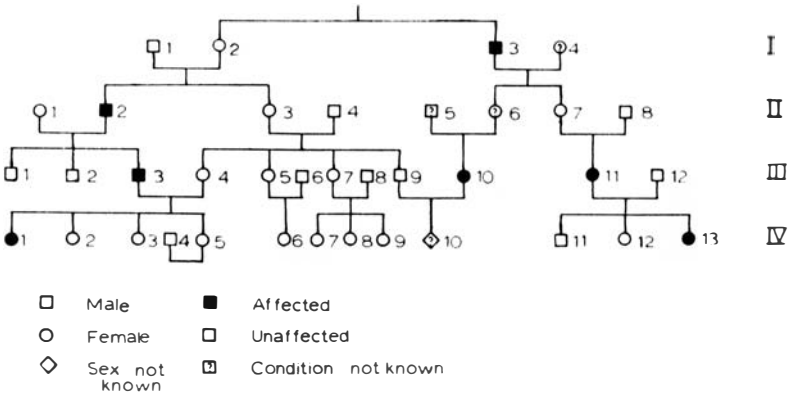

Fig. 1.

A very large pedigree also taken from the Acadian French community in New Brunswick has been given by AYCOCK AND MCKINLEY (1938). It is probable that all the geneological information that can be gained from this community has been published and that ascertainment is complete within these limits. It is, therefore, possible to calculate a value for the penetrance of the gene in this population. Since the frequency of leprosy and by implication the gene frequency, is high, and since the gene is not fully penetrant the most satisfactory value is that to be obtained from a consideration of sibships none of the parents of which had leprosy. It is assumed that where leprosy occurs in a sibship one of the parents must have carried the gene and that the mating is probably of the normal by heterozygote type. If matings of individuals with leprosy by normal individuals were taken there is a higher probability that the mating would be of the heterozygote by heterozygote type or of the homo-

zygote by heterozygote or normal. Data concerning sibships with one or more sibs having leprosy but with parents free from the disease have been abstracted from the pedigree and are given in Table 11.

TABLE 10

The Incidence of Leprosy in the Older and Younger Halves of Sibships*

Age	*Affected*	*Unaffected*	*Total*
Older half	58	59	117
Younger half	63	54	117
Total	121	113	234

* Where the size of a sibship was an odd number the middle sib was recorded as a half in both the older and younger groups.

TABLE 11

Analysis of Pedigree Data

Size of sibships	*No. of sibships*	*Total No. of individuals*	*No. of affected individual*
s	n_s	t_s	T_s
1	14	14	14
2	7	14	13
3	2	6	5
4	2	8	5
5	0	0	0
6	1	6	3
7	1	7	2
8	2	16	5
9	1	9	6
10	0	0	0
11	1	11	3
	n_s	$t_s = T$	$T_s = R$

Since inclusion of a sibship in the data depends upon the presence of an affected propositus within it, the number of affected individuals within each sibship must be reduced by one to give an unbiased proportion of affected individuals.

The penetrance value can be calculated as follows:

Let s = size of sibship.
n_s = number of sibships of a particular size s.
r_s = number of individuals with leprosy within sibships of size s.
T = total number of individuals.
R = number of individuals with leprosy.

Then: $T = sn_s$

and $R = r_s$

The proportion, P, of individuals with leprosy is therefore:

$$P = \frac{R}{T}$$

Making allowance for the bias attributable to the propositi:

$$P = \frac{R - ns}{T - ns}$$

If it is assumed that the matings are all heterozygote × normal then the expected proportion is equal to $\frac{1}{2}$.

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

$$\text{Therefore: Penetrance for heterozygotes} = \frac{P}{\frac{1}{2}} .100\%$$

Substituting in values from Table 11.

$$\text{Penetrance} = 2\left(\frac{56-31}{91-31}\right) 100\%$$

$$= 83.333\%$$

The penetrance value for heterozygotes where neither parent has leprosy is therefore 83.3%. This is a maximum estimate since there is a possibility that some matings may not be of the heterozygote by normal type and the two parents may carry more than one susceptibility gene, in which event more affected progeny would be expected so that the calculated penetrance value would be too high.

It must be emphasised that the penetrance value for homozygotes may be different and also that the value might be higher where one or both parents have the disease. Also it must be emphasised that the penetrance value may well vary in different populations.

Discussion

The evidence strongly suggests that there is a human genetic factor involved in the epidemiology of leprosy. This controls whether or not the bacilli can become established in the human body and would appear to involve a single irregularly dominant gene, which may have a penetrance as high as 80%. There is evidence of a second gene complex that exerts an influence upon the course of the disease, and this will be discussed in a future paper.

It is probable that these genetic systems vary between different populations both in the frequency of the relevant genes and in the extent of their manifestations. It is, therefore, necessary that data should be studied from a wide range of communities. The implication of these genetic systems on the epidemiology of leprosy may vary widely between different populations and attempts to extrapolate from the knowledge of one community to another may be both misleading and dangerous.

The probability of genetic variation in the infecting organism must also be considered, there is some slight evidence that this might be of importance and *a priori* it would be improbable that it is not. It is perhaps appropriate here to draw attention to the risk that strains of bacilli resistant to modern drugs are being selected by the widespread use of these drugs and there is indeed some evidence that this is happening. This possibility might be thought to give an added urgency to the study of genetic variation in human populations with regard to leprosy.

If the problems of genetics as they affect leprosy are to be studied they must, for the reasons that have gone before, be studied on a world-wide scale. Obviously it is of some importance that the considerable effort that will be necessary for such a survey should not be misdirected due to ignorance of the particular requirements that must be fulfilled in the collection of data for purposes of genetical analysis. These problems will be discussed in a future paper.

The main object of this series of papers is to review the evidence that genetic mechanisms may be of importance in the epidemiology of leprosy, and so to stimulate workers in leprosy endemic areas to collaborate in a large scale survey. It is appreciated that many leprosy workers are extremely hard pressed for time and assistance, and it is, therefore, with some hesitation that this appeal is made. Any collaboration will be most welcome and every effort will be made to lighten the task of workers in the field.

Acknowledgements

I wish to thank both Professor J. M. Thoday of the Department of Genetics, University of Cambridge, and Dr. R. G. Cochrane for the advice and encouragement they have given me throughout this work.

Summary

1. A review has been made of variation in the incidence of leprosy in different populations.

2. The evidence suggests that populations vary in their susceptibility to the disease and that this variation is in part due to genetic differences, expressed as differences in gene frequency and manifestation.

3. The evidence concerning familial leprosy has been analysed and a large pedigree has been examined.

4. The evidence suggests that susceptibility of the body to invasion by *M. leprae* is controlled by a single irregularly dominant gene, and in one population this gene has a penetrance of 83.3%.

5. An appeal is made for collaboration in the furtherance of studies on the influence of genetic systems on the epidemiology of leprosy.

References

AYCOCK, W. L. (1940) Familial susceptibility as a factor in the propagation of leprosy in North America. *Int. Journ. Lep.* **8** (2): 137.

AYCOCK, W. L. (1941) Familial susceptibility to leprosy. *Am. J. Med. Sci.*, **201**: 450–465.

AYCOCK, W. L. (1948) A proposed study of conjugal leprosy with reference to contagion and hereditary susceptibility. *Int. Journ. Lep.* **16** (1): 1–8.

AYCOCK, W. L. and HAWKINS, J. W. (1941) Regional, racial and familial relationships in leprosy in the United States. *Publ. Hlth. Rep.*, Wash. **56** (1): 1324–1336.

AYCOCK, W. L. and MCKINLEY, E. B. (1938) The roles of familial susceptibility in the epidemiology of leprosy. *Int. Journ. Lep.* **6**: 169–184.

BADGER, L. F. (1959) Epidemiology. In: Leprosy in Theory and Practice. Ed. R. G. Cochrane. Chapter VI, pp. 51–77.

BECHELLI, L. M., and ROTBERG, A. (1956) Contribuicao para o estudo da herencia da resistencia a infeccao: a lepra no estado da Sao Paulo (Brasil) segundo a naturalidade. *Rev. Brasil. Leprol.* **24** (1–2): 37–47.

BJARNHJEDINSSON, S. (1909) The leprosy in Iceland. *Lepra.* **8**: 367–401.

BRACKEN, H. M. (1900) Leprosy in Minnesota. *Lepra.* **1**: 37.

BROWN, J. KINNEAR (1952) Leprosy in Uganda. Preliminary investigations with special reference to methods of survey. *E. Afr. Med. J.* **29** (12): 493–508.

BROWN, J. A. KINNEAR (1955) The incidence and epidemiology of leprosy in Uganda. *Trans. Roy. Soc. Med. and Hyg.* **49** (3): 241.

BROWN, J. A. KINNEAR (1956) Susceptibility and resistance in leprosy. *Leprosy Rev.* **27** (4): 147.

BROWN, J. A. KINNEAR (1957) The epidemiology of leprosy. *E. Afr. Med. J.* **34** (7): 351.

BROWN, J. A. KINNEAR (1959) Factors influencing the transmission of leprosy. *Int. Journ. Lep.* **27** (3): 250–263.

COCHRANE, R. G. (1959) The history of leprosy and its spread throughout the world. In: Leprosy in theory and practice. Ed. R. G. Cochrane. Chapter I, (11), 1–6. Wright, Bristol.

COCHRANE, R. G. and RAJAGOPALAN, G. (1943) The study of family susceptibility in relation to the epidemiology of leprosy. *Leprosy in India*, **15** (3): 76–81.

CONVIT, J., GONZALES, C. L. and RASSI, E. (1952) Estudios sobre lepra eneel grupo etnico aleman de la colonia Tovar, Venezuela. *Int. Journ. Lep.* **20** (2): 185–193.

DANIELSSEN, D. C. and BOECK, W. (1848) Traite de la spedalskhed. Bailliere, Paris.

DENNEY, O. E. (1917) A statistical study of leprosy in the Philippine Islands. *J. Amer. Med. Ass.* **69**: 2171.

DENNEY, O. E. (1933) Leprosy in the Southern United States. *Sth. Med. J.*, Nashville.

DREISBACH, J. A. (1954) A case of leprosy in a seven month child. *Leprosy Rev.* **25** (2): 81–82.
DUARTE, DO PATEO and LIMA SOLANO (1936) Da frequencia da lepra nos focos familiares estudio epidemiologico. *Rev. Bras. Leprol.* **4** No. espec. 241–259.
FERNANDEZ, J. M. M. (1948) Resultatos del examen de ninos y conyuges convivientes con enfernos de lepra. *Rev. Med. Rosario*, **38**: 780–795.
GEHR, E. and MUNDAR, H. M. (1954) Die lepromin reaktion bei verschieden en volksgruppen in Suriname. *Zschr. Tropenmed.* **5** (3): 379–387.
GUINTO, R. S., RODRIGUEZ, J. N., DOULL, J. A., and DE GUINA, L. (1954) The trend of leprosy in Cordova and Talusay, Cebu province. *Int. Journ. Lep.* **22** (4): 409–430.
HOPKINS, R. (1938) Heredity in leprosy. Tuberculosis and leprosy; the mycobacterial diseases. Symposium Series Vol. 1, *Amer. Ass. Adv. Sci.* pp. 112–118. Lancaster, Pa.
HOPKINS, R. and DENNEY, O. E. (1929) Leprosy in the United States. A statistical study of 700 cases in the National Leprosarium. *Jour. Amer. Med. Ass.* **92**: 191.
HUMPHREY, . . (1952) Leprosy amongst full blooded Aborigines of the Northern Territory. *Med. J. Australia* **17** (1): 570–573.
LUCAS, K. C. (1881) On a remarkable instance of hereditary tendency to the production of supernumary digits. *Guy's Hosp. Rpts.* 3rd Ser. **25**, pp. 417–419.
MARIANI, M. (1931) Otto casi di lebbra familiare a Suzzara. *Arch. Ital. Sc. Med. Colon.* **12**: 654–685.
MELSOM, R. S. (1953) Three new cases of leprosy in Norway. *Leprosy Rev.* **24** (1): 27–33.
MUIR, E. (1927) Some factors which influence the incidence of leprosy. *Indian J. m. Res.* 1927–28, 1–14.
MUIR, E. (1940) Report on leprosy in Cyprus. *Leprosy Rev.* **11** (1): 70–74.
MUIR, E. (1943) Report on leprosy in Barbados. *Leprosy Rev.* **14**: 18–24.
MUKERJEE, N. and GHOSH, S. (1958) Familial leprosy. *J. Ind. med. Ass.* **31** (3): 129–131.
MCCOY, G. W. (1938) Communicability of leprosy and application of control measures. *Arch. Derm. Syph.* N.Y. **37**: 169–174.
NEFF, E. A. and SNODGRASS, R. J. (1930) Leprosy. An unusual case of family infection. *J. Exp. Med.* (*Hyg.*) Lond. **32**: 137.
QUAGLIATO, R. (1956) Contagio familiar da lepra entre os communicantes da I.R. de Campinas. Imortancia dos exames periodicos par o despistamento dos casos indiferenciados. Vinte anos de observacao (1934–1954). *Sessao da Soc. Paulista Leprol. Em.* 19–3, 1956.
SPICKETT, S. G. (1961) A preliminary note on *Demodex folliculorum* Simon (1842), as a possible vector of leprosy. *Leprosy Rev.* **32** (4): 263–268.
STEINIGER, F. (1941) Die erbliche disposition bei der entstehung der lepra. *Zschr. menschl. vererbungs-und Konstitutionslehre* **25** S 245–272.
STEINIGER, F. (1950) Die lepra im. Ost- und Nordseeraum. *Zschr. f. tropenmed de parasit.* **2**: 175–193.
THIN, G. (1892) Origin and spread of leprosy in Parcent in Spain. *Lancet*, **1**: 134.
WAYSON, N. E. (1934) Leprosy: Observations on its epidemiology in Hawaii. U.S. Treasury Department, Public Health Service Bulletin, No. 212.