GENETICS AND THE EPIDEMIOLOGY OF LEPROSY

II. The Form of Leprosy

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Introduction

Leprosy is made manifest in a variety of forms and the classification and relationships of these forms are matters of controversy. There is, however, wide agreement that communities vary in the relative frequencies of the different forms of the disease and, furthermore, it is accepted that the symptoms within a particular form of the disease may vary in different populations.

It has been shown in an earlier paper, SPICKETT (1962); that there is a very great weight of evidence to support the hypothesis that susceptibility to some form of leprosy is controlled by a single irregularly dominant gene. However in view of the characteristic forms of leprosy found in different populations it seems possible that there might be a genetic control over the form of the disease. This paper is an attempt to see whether published records can support this possibility.

Data concerning the incidence of forms of the disease have been published by several authors using a variety of methods and terminology of classification. Since the relative validities of the different schemes does not affect the present argument the terms used by the original authors have been used, rather than attempt to reclassify the data according to one system.

Variations between the form of leprosy in different populations

Differences in the manifestations of leprosy between the constituent races of a multiracial society were first noted by COCHRANE (1935). He pointed out that Africans living in the West Indies showed those forms of the disease characteristic of Africans living in their native land. Similarly Indians and Chinese showed forms of leprosy found in the native populations of India and China. Lowe (1938) has also pointed out that in a multiracial society the different races may differ in the relative frequencies of the different forms of leprosy. Comparison was made between Burmese and Indians living in Assam. A random selection of 100 patients of each race was taken from an outpatients clinic and from a leprosarium; the data of incidence of the different forms of the disease are given in Table 1.

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GENETICS AND THE EPIDEMIOLOGY OF LEPROSY

TABLE 1

Incidence of the different forms of leprosy amongst Indians and Burmese in Leprosaria and at leprosy clinics in Assam

		Lepromatous	Tuberculoid
	Burmese	75	25
Leprosaria	Indians	39	61
	Burmese	56	44
Clinics	Indians	31	69

There are significantly more lepromatous cases amongst the Burmese than the Indians both in the clinic ($\chi^2_{(1)} = 12.714$; p < .001) and in the hospital ($\chi^2_{(1)} = 26.160$; p < .001).

Variation in the relative frequencies of lepromatous and tuberculoid leprosy in Central African populations have been reported by MUIR (1940 a, b, c). These data are given in Table 2. They are not suitable for statistical analysis, but it is quite clear that there are striking differences between the populations.

TABLE 2

Incidence of certain forms of leprosy from different populations in Africa

Form of leprosy	Population					
	Barotseland	Belgian Congo	Central and Eastern Rhodesia	Nyasaland		
Tuberculoid	60%	36%	22%	12%		
Lepromatous	11%	22%	28%	35%		

MUIR (1940 d) also found that of the 102 patients of a South African leprosarium there were 92 Bantu of whom 23 were lepromatous and 12 Europeans all of whom were lepromatous. The high incidence of lepromatous leprosy amongst Europeans was again noted by MUIR (1940 e) who reported that the lepromatous rate in Cyprus was 98%. Although the actual data upon which this percentage is based are not given it is clear from other data in the same report that the sample could not have been smaller than 200.

Although the differences between the incidence of different forms of leprosy in various populations are obvious it may be argued that environmental differences between populations may be sufficient of an explanation.

BECHELLI and ROTBERG (1956) have published data from which it is possible to make a comparison between native Brazilians and the children of the predominantly European immigrants. There is a significant difference between the two populations ($\chi^{2}_{(2)} = 24.0153$; p < .001). These data are given in Tagle 3.

TABLE 3
Incidence of the different forms of leprosy in Native Brazilians and
in Brazilians of foreign extraction
(After ROTBERG and BECHELLI)

	Form of Leprosy			
Population	Lepromatous	Indeterminate	Tuberculoid	Total
Brazilians Brazilians of foreign	3431	1958	935	6324
extraction Total	2090 5521	946 2904	497 1432	3533 9857

AZAVEDO (1936) has made a similar study to that of Bechelli and Rotberg, also comparing Brazilians with the children of immigrants, but using a different system of classification. The analysis of his data reveals no significant difference between the two populations $(\chi^{2}_{(2)} = 1.4608; p < 0.7 > 0.5)$. The data are quoted in Table 4. The inconsistency between the results of these two investigations emphasises the difficulties raised by the use of different systems of classification.

TABLE 4

Incidence of the different forms of leprosy in Native Brazilians and in Brazilians of foreign extraction

	Рорг			
Form of Leprosy	Native Brazilians	Children of Immigrants	Total	
Mixed	2117	1318	3435	
Nervosa	2085	1350	3435	
Tuberosa	490	337	827	
Tuberculosa	9	2	11	
Total	4701	3007	7708	

(After AZAVEDO)

Much data concerning the incidence of the different types of leprosy to be found in individual populations has been published, e.g. LITTAN (1953) from Spain; BJARNHEDDINSON (1909) from Iceland; MOISER (1934) from Southern Rhodesia; CONVIT, GONZALES and RASSI (1952) from Venezuela; LEIKER and SLOAN (1954) from New Guinea; HUMPHREY (1952) from Australia; and MAXWELL and KAO (1952) from Eastern China; however for the reasons stated comparisons between these data are unlikely to be useful. It has been noted by RYRIE (1948) that in Malaya one third of the cases of leprosy occurring amongst Chinese are tuberculoid whereas three quarters are tuberculoid amongst Indians. Malays have a tuberculoid leprosy rate approximately midway between that in Chinese and Indians. Furthermore, it has been found that the symptoms relating to any particular form of the disease vary between the different races. For example, severe lepromatous reactions are much more common amongst the Chinese than amongst the other races.

Variation in the symptoms associated with particular forms of leprosy have been described by Ross (1948). He found that in Gambia the lesions were more extreme in both tuberculoid and lepromatous forms of the disease than in Nigeria; he also found other differences that need not be elaborated here.

The population of the Fiji Islands is multiracial. AUSTIN (1948) made comparisons in the lepromatous rates between the Indian and Melanesian populations and found a significantly higher lepromatous rate in Indians than in Melanesians ($\chi^{2}_{(1)} = 131.390$; $p \ll .001$). The data is given in Table 5. Austin also found that although the Indian populations had the higher lepromatous rate the prognosis was more hopeful amongst lepromatous Indians than amongst lepromatous Melanesians.

TABLE 5

Relative frequency of lepromatous and non-lepromatous leprosy in Indians and Melanesians

	Form o		
<i>Population</i>	<i>Le promatous</i>	Non-lepromatous	<i>Total</i>
Melanesians	181	148	329
Indians	168	72	240
Total	349	220	569

In addition to the published data there are many reports by authorities who have stated on the basis of wide experience, that different forms of leprosy predominate in different races. For example, COCHRANE (1947) states that Europeans and Mongoloids are more likely to contract the lepromatous form of the disease than are Indians or Africans.

There is no clear understanding of the relationship between the results of the lepromin test on healthy subjects and the form of leprosy to which they are liable. However, it is agreed that variation in the results of the lepromin test is indicative of potential variation in the reaction of the body to invasion by *M. leprae*. Variation in the distribution in the results of the lepromin test between populations are, therefore, indicative of variations in the incidence of the different forms of leprosy between those populations.

GEHR and MUNDAR (1954) have given data of the results of the lepromin test as applied to several populations, of these two had had no contact with the disease; the data relating to these two populations are given in Table 6. There is a significant difference in the proportion of positives between the two populations; in total ($\chi^2_{(1)} = 38.223$; p < .001) and in adults ($\chi^2_{(1)} = 8.920$; p < .01 > .001) and in children ($\chi^2_{(1)} = 16.193$; p < .001).

TABLE 6

		Results of lepromin tests				
Population			±	+	++	+++
Adult males	Hindus Bushmen	9 13	8 5	8 46	1 22	
Adult females	Hindus Bushmen	10 17	4 39	14 36	$\begin{vmatrix} -1\\ 32 \end{vmatrix}$	5
Male children	Hindus Bushmen	34 6	5 12	$\begin{bmatrix} -7\\25 \end{bmatrix}$	6	
Female children	Hindus Bushmen	27 17	4 24	12 16	$\begin{vmatrix} -3 \\ 13 \end{vmatrix}$	

Results of lepromin test on Hindu and Bushman populations

It has been suggested by FERNANDEZ (1943) that the capacity to give a positive lepromin reaction needs to be evoked by prior contact with antigens derived from M. leprae. While this cannot hold absolutely, since Gehr and Mundar have demonstrated positive reactions in populations that have not been exposed to leprosy (it is probable that related organisms can bring about the effect), there is no doubt that the reaction does become stronger after repeated tests. There is variation in the development of the reaction in different individuals. IGNACIO, PALAFOX and JOSÉ (1953) subjected 47 children who had been separated from their parents (at least one of whom had had leprosy) at birth. Of these children 74% were positive at the second test. Fernandez found that 73% of the children of affected parents gave a positive reaction at the first test. LARA (1940) also found that 73% of the children of parents with leprosy gave a positive reaction at the first test. Fernandez found that those who did not give a positive reaction at the first test gave only a feeble reaction after six tests, whereas those that gave a positive reaction at the first test gave a very strong reaction by the sixth test. These observations suggest that there is a polymorphism within populations with regard to reactions to lepromin, and this reaction may indicate a type of allergic response that determines the form that the disease will take.

Variations in the form of leprosy within families

At the family level there is very little evidence indeed applicable to the problem of genetic variation affecting the form that leprosy will develop if contracted. The few published pedigrees in which the form of the disease is detailed have usually been selected to illustrate a particular point of view and as such do not form a representative sample, so that they are of little value. However they do show that within a family there may be wide variations in the form of the disease although more commonly the disease takes a similar form within a family. Differences within a family indicate that variation in form of the disease is not principally due to variation in the bacilli since the cases within a family may be assumed to be epidemiologically related and derived from the same strain of bacilli.

DANIELLSEN and BOECK in this classical study of leprosy in Norway, found that of the 68 people who had had anaesthetic leprosy and had been patients in the hospital of St. George, Bergen, 58 bore relationships with others suffering from the same form of the disease, and of the 145 who had had tuberculoid leprosy 127 had relatives suffering from this form of the disease. This evidence suggests that the form of leprosy is under the influence of some genetic system of the host.

KEIL (1939) and KINNEAR BROWN and STONE (1958) have published some observations on leprosy in twins. These and other accounts provide the source of the data in Table 7. Although these data are too few to enable a test of significance to be made, the degree of concordance between identical twins as compared with that between fraternal twins is highly suggestive of a genetic influence on the form of the disease.

TABLE 7

Similarities and dissimilarities in the form of leprosy in identical and fraternal twins

	Similar	Dissimilar Tota		
Identical twins	6	0	6	
Fraternal twins	4	3	7	

Discussion

The evidence for the existence of a genetic system controlling the form of leprosy is suggestive but not conclusive. Differences in the forms of leprosy prevailing in different races might be due to environmental variation, but the existence of such differences even in well integrated multiracial communities indicates that environmental variables are not the most important factors involved.

Genetic variability in Mycobacterium leprae could be responsible

for part of the variation between forms of leprosy. If this were so it might be expected that there would be a higher degree of concordance between contacts than the random expectation. Unfortunately there are no data available that relate to this.

It is probable that any genetic influence of man upon the forms that leprosy may take will be multifactorial. The different factors may exert their effects upon different aspects of host immunity and function. Alternatively there may be a complex of genes of similar effect so that it is the relative frequency of the two alleles that influences the predisposition of the individual to particular types of leprosy. It is, however, difficult to regard the variation in leprosy as a simple continuous variation, which is what such a theory implies, and moreover, it would not be possible to explain satisfactorily why some populations have symptoms of leprosy unique to them. If however there are many factors of different effect fixation of one allele of one locus in a population will cause the spectrum of forms of the disease in that population to differ from that in a population where the alternative allele is fixed. It follows from this that there may be genetic explanations for the fact that different systems of classification are appropriate for different populations.

The data discussed here have referred to a variety of systems of classification. The different systems used by AZAVEDO on the one hand and BECHELLI and ROTBERG on the other have yielded contradictory results. It is not relevant to enter into any discussion of the relative validities of particular systems of classification in this paper, but it is clear that the forms of leprosy described by one system may be better phenotypic descriptions than the forms described by another system. It is possible that a system of classification based on the phenotypes of different genes whilst not superseding other systems may provide a means of reference whereby the relationships of these systems may be more clearly understood.

Similar considerations may apply to the genetic variation in *M*. *leprae*, so that the wide variation in the manifestations of leprosy could be due in large measure to the interaction between genetically different types of human individual and genetically different types of bacilli.

It is clear that the investigation of genetic variability in man and in M. *leprae* is a task of great importance, it is equally clear that it will be a task of great complexity. However it is probable that there is sufficient recorded information for many of these problems to be solved if it were made available.

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Summary

1. Expatriate races show forms of leprosy more similar to those prevailing in their native lands than those amongst the natives of the land in which they live.

2. Different groups in multiracial societies vary in the ratios of the different forms of leprosy and in their detailed manifestation.

3. Quantitative comparisons between populations of the frequency of different forms of leprosy varies according to the methods of classification used.

4. Populations are polymorphic with regard to their reactions to lepromin; this may indicate genetic variation.

5. Affected individuals within families tend to suffer from similar forms of leprosy.

6. The evidence suggests that there is a genetic system in man which affects the form that leprosy might take.

7. There is a possibility that genetic variability in the *M*. leprae influences the manifestation of leprosy.

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