Downloaded from rstb.royalsocietypublishing.org

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Implications of Genetics for the Epidemiology and Control of Leprosy

P. E. M. Fine

Phil. Trans. R. Soc. Lond. B 1988 **321**, 365-376
doi: 10.1098/rstb.1988.0097

References

Article cited in:
http://rstb.royalsocietypublishing.org/content/321/1207/365#related-urls

Email alerting service

Receive free email alerts when new articles cite this article - sign up in the box at the top right-hand corner of the article or click **here**

To subscribe to *Phil. Trans. R. Soc. Lond. B* go to: **http://rstb.royalsocietypublishing.org/subscriptions**

This journal is © 1988 The Royal Society

Downloaded from rstb.royalsocietypublishing.org

Phil. Trans. R. Soc. Lond. B **321**, 365–376 (1988)
Printed in Great Britain

Implications of genetics for the epidemiology and control of leprosy

By P. E. M. Fine

Department of Tropical Hygiene, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, U.K.

This paper reviews the rationale and history of genetic studies related to leprosy, and considers their implications for the epidemiology and control of the disease. A long tradition of genetic studies in leprosy was initiated by early impressions that the disease clusters within families. Investigations were first motivated by an attempt to understand population patterns, and the focus shifted from investigations of racial differences to investigations of families, of twins and ultimately of genetic markers. The strongest evidence for genetic influence has come from studies of HLA segregation patterns within families, and this has led to elegant *in vitro* work demonstrating the role of HLA-DR alleles in mediating T-cell reactions in conjunction with antigens of *Mycobacterium leprae*.

The epidemiological implications of this work are not yet clear. The emphasis on family-segregation studies may have given a biased impression because of their requirement for multi-case families. There is evidence that the genetic mechanisms underlying leprosy differ within and between populations. One possible application of the current work would be the use of HLA-DR-specific reactions to identify epitopes of *M. leprae* which should be excluded from future vaccine preparations.

Introduction

No disease has a longer and richer debate on the possible role of genetics in determining individual differences in susceptibility than does leprosy. The idea of hereditary influences in leprosy doubtless has its roots in the impression, common to many who have worked on the disease, that cases of leprosy cluster in particular families. The question of whether such clustering is real at all and, if so, whether it reflects clustering of genetic factors predisposing to or regulating the infection, or whether it reflects shared environmental factors or just the facility of infection transmission within the intimacy of the home, has exercised many workers. It is the intention of this paper to trace the history of this argument, with particular reference to how changing views on genetic influences have related to changing views on the control of the disease.

Leprosy is an unusual disease in many respects (Hastings 1985). Superficially it may be defined as a disease of skin and peripheral nerves attributable to infection with *Mycobacterium leprae*. The mode of transmission and course of the infection are still unknown. There is some evidence for respiratory transmission from lesions in the upper respiratory tract; however, how this leads to invasion of peripheral nerves is not understood. The most important clinical manifestations are associated with the loss of sensory and motor function of affected nerves, leading to anaesthesia, contractures, loss of the pain reflex, and ultimately to ulceration and gross deformities particularly of the hands and feet. Though the disease is today confined largely to tropical regions, it was once widespread in Europe, and was endemic within the last century as far north as the Arctic Circle (Irgens 1980). The progressive disappearance of

The Royal Society is collaborating with JSTOR to digitize, preserve, and extend access to *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences.* www.jstor.org

Downloaded from rstb.royalsocietypublishing.org

leprosy from northern latitudes over the past several centuries is a subject of many speculative hypotheses. Among these has been, inevitably, the genetic hypothesis: that northern populations have somehow been selected for resistance to the leprosy bacillus. Such a hypothesis is of questionable testability, and it seems unlikely as an explanation for the best documented disappearance: more than 8000 cases of leprosy were registered in Norway between 1850 and 1950, but not a single case has appeared there since. Environmental influences seem more likely to provide an explanation for this relatively rapid disappearance of a disease than do genes.

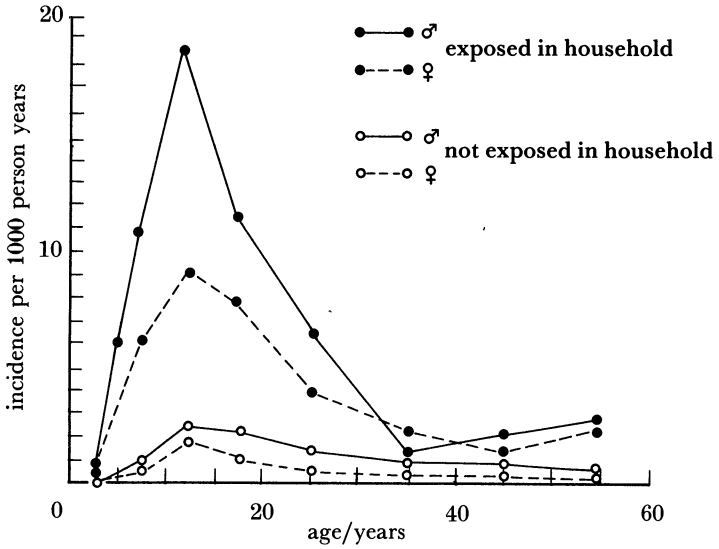

FIGURE 1. Incidence rates of leprosy (per 1000 person years) by age, sex and household contact status, as estimated by Doull *et al.* (1942) in Cebu, Philippines.

Figure 1 shows incidence rates of leprosy in an endemic population on the island of Cebu in the Philippines. The pattern is typical of that in many leprosy endemic regions. It should be appreciated that leprosy is 'a rare disease even where it is common': 1% is a high prevalence rate, and one per thousand is a high incidence rate of this disease. It is clear that age and sex are important correlates of the disease. In addition, we see that household contact is a risk factor. Several cohort studies have shown that individuals living in household contact with a known leprosy case have a risk of developing clinical leprosy which is from two to eight times that of individuals lacking household contact (Doull *et al.* 1942; Martinez Dominguez *et al.* 1980). The only other well-documented determinant of risk is a history of Bacille Calmette–Guérin (BCG) vaccination, which has been found to reduce the risk of leprosy by 20–80% in different populations (Fine 1985). Several other risk factors have been suggested, such as pregnancy and poor nutrition, but these have yet to be demonstrated convincingly (Fine 1982). For this paper, I shall concentrate on the household contact factor, as this is intimately related to the issue of family clustering and the possibility of genetic influences.

Three features of leprosy pose particular problems for family and genetic studies. The first is our ignorance of the relation between infection and disease. Though the leprosy bacillus was identified long ago, there is still no sensitive or specific tool for identifying infected individuals (Burgess *et al.* 1988). The organism still has not been cultured *in vitro*. Thus the pattern of infection in endemic communities is not known. Similarly, the proportion of infected individuals who go on to manifest disease is not known, though several lines of argument – for

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

example analogies with tuberculosis – suggest that it is small, perhaps as low as 10% (Newell 1966; Fine 1982). The fact that the incubation period is extremely long and variable – ranging from months to decades – increases the difficulty of studying this problem. Just what determines whether or not an infected individual will manifest disease is unknown, but some would argue for genes.

A second major difficulty facing leprologists is the variety in its clinical manifestations. Clinical leprosy takes several forms, classically described as occurring along a spectrum from 'tuberculoid' to 'lepromatous' disease. The tuberculoid pole is characterized by few discrete lesions, very few detectable bacilli, a minimal humoral antibody response, but a strong specific cell-mediated response as manifested in granulomatous histopathology, positive lymphocyte transformation assays and delayed type hypersensitivity to certain skin tests employing antigens of the leprosy bacillus. At the other end is lepromatous disease, characterized by the opposite features of many diffuse lesions, very many bacilli, a strong humoral antibody response and an absence or anergy of any specific cell-mediated immune response (Bryceson & Pfaltzgraff 1979). There are also intermediate or 'borderline' types of disease between these two poles. The pattern and determinants of the various clinical forms are important for several reasons. Lepromatous individuals are in general the most seriously affected clinically, they require the most prolonged and careful therapy and they are responsible for shedding a disproportionate number of *M. leprae* into the environment, predominantly in nasal secretions. The factors that determine the type of disease manifested by an individual are still unknown, but may include genetical determinants of the host.

A third feature of leprosy relevant to the subject of genetics and disease control is that of stigma. Leprosy has traditionally been among the most stigmatizing diseases of man, as reflected in the continued overtones of the word 'leper' today. Though the nature and extent of the stigma of leprosy has varied between societies, it has often been associated with hereditarian views. It has been a strong force influencing social attitudes towards the disease, to the extent of affecting marriage patterns and hence affecting family distributions of the disease. And it has influenced theories and strategies on leprosy control.

Historical background

The lingering social implications of the word 'leper' reflect its origins in words used to describe several deforming and frightening diseases. Over time the word came to be applied specifically to just one of these diseases, that which we now attribute to infection with *Mycobacterium leprae*. The early prominence of hereditarian thinking in leprosy is illustrated by comments such as the following, written a century and a half ago: 'few facts in the history of... leprosy seem to be more universally admitted by all writers on the disease, both ancient and modern, than the transmission of the predisposition to it from parents to offspring' (Simpson 1841). The first textbook on leprosy, published in 1848 by two Norwegians, Danielssen and Boeck, claimed heredity to be the most important factor underlying the disease. These views reflected traditional interpretations of observed family clusters of the disease. What is more, they lent scientific authority to traditional beliefs that families of leprosy cases were somehow tainted, and thus were to be segregated and stigmatized with the diseased individuals themselves. The fears, ostracism and social disruption that affected individuals and families caught in the web of leprosy were, in many societies, severe.

Given this background of strong hereditarian belief, it is ironic that the leprosy bacillus,

Downloaded from rstb.royalsocietypublishing.org

Mycobacterium leprae, should have been the first bacterial infectious agent of man to be discovered, in 1874. It is of even greater irony that this discovery was made by the Armauer Hansen, himself son-in-law to Danielssen, the foremost authority and upholder of the hereditarian view of leprosy. A controversy arose between those who emphasized heredity and those who emphasized environmental determinants of infection in the aetiology of the disease. The irony of the situation was extended when Hansen (a contagionist) and S. W. Boeck, Danielssen's colleague and a staunch hereditarian, both travelled to the U.S.A. to test their views by studying the pattern of leprosy in Norwegian immigrants. Boeck noted that the only secondary cases were in children of immigrant cases, which reinforced his belief in hereditary causes, whereas Hansen noted that the disease disappeared in the second generation, which he saw as confirming his view of the environment as the major determinant (Lie 1938). It is a good example of researchers observing what they wish to observe.

The discovery of the leprosy bacillus had an important impact on the strategy for controlling the disease. Apparent family clusters came to be interpreted as reflecting transmission of infection within the home, and the view arose that 'prolonged and intimate contact', such as would occur within a family, was somehow essential for transmission of the leprosy bacillus. The infectious aetiology theory justified efforts to segregate leprosy cases in institutions and thus supported popular fears of the disease. The family clusters thus seemed to have been explained, and the leprosy literature went silent on the subject of heredity for half a century.

The issue of possible genetic influences in leprosy came to life again about 1950. This coincided with the introduction of dapsone, the first effective drug against the leprosy bacillus. Because of its low cost and low toxicity, dapsone rapidly became the basis of leprosy control programmes throughout the world. Enthusiasm was so great that some people and organizations even spoke of the possibility of eradicating leprosy, if only a high enough proportion of infectious – in particular lepromatous – cases could be ascertained and treated. Part of the strategy towards this goal was a conscious effort to reduce the stigma of leprosy, in order to encourage cases to reveal themselves rather than hide their disease. Thus the policy of segregating cases in leprosaria was abandoned in most countries, and efforts were oriented towards case-finding and ambulatory treatment in the community. And a changed view of the disease was espoused. Leprosy somehow even appeared in the Guinness Book of Records as the 'least infectious' disease, reflecting reassuring voices that cases need not fear nor be feared (McWhirter 1981). Many control programmes took to active propaganda against traditional views of the disease, as by vehicle banners declaring 'leprosy is not hereditary', in an attempt to reassure not only cases but also families of cases. Genetics came to be viewed as an enemy of leprosy control.

Despite such propaganda, the irony continued. Just as leprosy control workers were busy trying to stamp out stigma and associated hereditarian views of leprosy, research workers accumulated increasing evidence that genes might be playing a role, after all.

Evidence for genetic influence

Serious attempts to demonstrate that genetical factors were operating in leprosy began about 1950. Tracing the history of these studies is interesting as it illustrates the evolution of more and more rigorous methods for discovering genetic influences in a human disease. The first studies focused on population patterns of the disease, the same features that had originally led to

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

hereditarian views of leprosy. Initial arguments were hardly more than circumstantial, suggesting that different patterns of disease observed in different races might be due to different genetical characteristics. A frequently cited example is the proportion of tuberculoid disease, which has been reported to be much more frequent in African than in Oriental or Caucasian populations. It has been suggested that this might reflect a more powerful local cellular response in dark-skinned individuals, perhaps mediated by dermal Langerhans cells which have been shielded by skin pigments from the adverse effects of ultraviolet radiation. On the other hand, races differ in many characteristics other than just their genes. And the apparent higher proportion of tuberculoid disease in dark-skinned people might just reflect differences in ascertainment. A hypopigmented patch, typical of tuberculoid disease, is more easily identified against a dark than a light background.

Studies of family clusters proved equally unconvincing (Fine 1981). Several authors attempted to demonstrate clustering by statistical analysis of household survey data. This proved a difficult problem in that the data sets related to households, rather than to families. Moreover, households differ in size and age distribution, and a collection of old individuals is more likely to contain multiple leprosy cases than is a collection of young individuals (Beiguelman 1972). Beyond that, any apparent clusters, even if they passed formal tests of statistical significance, might be explained equally well by social forces tending to aggregate leprosy patients, or by shared environmental factors, as by genes. Another problem with the family cluster argument is that it has become circular. The widespread belief in family clustering has tended to influence the diagnostic suspicion of fieldworkers once an initial case is detected in a family. Such families are typically placed under special surveillance and examined more closely. But the harder you look for something, the more you're likely to find it, and so family clustering becomes a self-fulfilling prophecy. This bias is more easily avoided in theory than in practice, given the realities of field diagnosis of this disease. Only one study, the Medical Research Council-funded BCG trial against leprosy in Uganda, has attempted to break down household data by both genetic relationship and degree of contact (White *et al.* 1978). Interestingly enough the incidence rates appeared to be higher among first degree than more distant relatives of leprosy cases, but this trend disappeared when the data were stratified by proximity of contact, as measured by dwelling or compound of residence or visiting status (table 1). Thus the increased risk was explained as well by intimacy of contact as by closeness of genetic relationship.

TABLE 1. INCIDENCE RATES OF LEPROSY (PER 1000) AS OBSERVED IN MEDICAL RESEARCH COUNCIL TRIAL OF BCG AGAINST LEPROSY IN UGANDA (WHITE *ET AL.* 1978)

(Rates standardized for age, tuberculin and vaccination status at intake, lepromatous and multiple contact.)

degree of contact	degree of genetic relationship					
	1	2	3	4	5+	All
dwelling contact	(24.6)[a]	—	—	—	—	24.6
compound contact	14.4	13.2	9.7	19.4	14.1	13.5
visiting contact	—	12.4	13.5	12.8	10.1	11.4

[a] 89% 1st degree relatives had dwelling contact.
5% 2nd+ degree relatives had dwelling contact.

Taking family studies one step further, several authors have tried to collect and analyse pedigrees of families with leprosy, and to fit single or multiple gene models to them. The single-gene models have in general suggested dominant inheritance with incomplete penetrance

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

(Belknap & Hayes 1961; Spickett 1962). This is consistent with the recognized high risk among children of known cases; but could merely reflect confounding by contact status, as shown in table 1. Not surprisingly, multiple-gene models have been found to give a better fit to such data than do single-gene assumptions (Sergeantson *et al.* 1979). None of the models have been validated on independent data sets, however, and their inherent flexibility makes them unconvincing alone. Thus this approach has not proved particularly useful.

Somewhat stronger evidence was drawn from studies of twins, in particular a large series of 102 pairs of twins in India, each with at least one case of leprosy (table 2) (Chakravartti & Vogel 1973). The concordance rate for clinical leprosy was significantly higher among monozygotic (37 out of 62) than dizygotic (8 out of 40) pairs, suggestive of a genetic influence. But the series was obviously heavily biased, with more monozygotic than dizygotic pairs overall (only about a quarter of all twins born are monozygotic) which suggests a bias in favour of similarity and hence overestimation of implied genetic effect. On the other hand, the data show a similar proportion concordant for clinical type between monozygotes (32 out of 37) and dizygotes (6 out of 8), and the series includes five monozygotic pairs discordant for clinical type. Both of these observations suggest that any genetic effects may be more important in determining the appearance of disease than in determining the clinical type of disease.

Table 2. Summary of results of Chakravartti & Vogel's (1973) study of leprosy in twins

leprosy distribution	62 monozygotic pairs	40 dizygotic pairs
both affected	37	8
type concordant	32	6
both lepromatous	11	2
both tuberculoid	19	4
both borderline	2	—
type discordant	5	2
one affected	25	32
lepromatous	6	8
tuberculoid	18	20
borderline	1	4

Another approach to the problem has been the application of case-control studies comparing the prevalence of different genetic markers in diseased individuals with non-diseased control groups. Many markers have been examined in this context, among them the blood groups ABO, Rh, MN, Kidd, Kell, Cellano, Duffy, Lutheran, erythrocyte enzymes phosphoglucomutase 1 and 2, and phosphatase, adenylate kinase, adenosine deaminase, G6PD; serum proteins Hp, Gc, Gm, Pi, Inv, Tf, atypical pseudocholinesterase, ability to taste phenylthiourea, and histocompatibility antigens at the A, B, C and D loci (for references see Blackwell (1988)). Several of these studies have found apparent associations, but these have in general not been consistent between populations. This suggested that the few apparently significant associations might be attributable to multiple comparisons or to inappropriate control groups (e.g. the use of hospital staff, who may be particularly inappropriate as controls for a disease such as leprosy, with strong socio-economic and ethnic correlates). On the other hand, associations between

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

leprosy and certain HLA-DR haplotypes have now been observed consistently enough to suggest a real effect (see table 3). Most interesting is the HLA-DR2 allele, which has been found associated with both lepromatous and tuberculoid leprosy in several Asian populations (Japan, Korea, Thailand, India), and HLA-DR3, which has been found associated with tuberculoid leprosy (but significantly lacking in lepromatous leprosy) in populations from Venezuela and Surinam (Ottenhoff & De Vries 1987).

TABLE 3. RESULTS OF CASE CONTROL STUDIES COMPARING FREQUENCY OF HLA-D SPECIFICITIES BETWEEN LEPROSY CASES AND CONTROLS

(Numbers in parentheses are relative risks of those associations which were considered statistically significant ($p < 0.05$, uncorrected for multiple comparisons). TT, Polar tuberculoid leprosy; LL, polar lepromatous leprosy.)

population (reference)	patients tested	controls	specificities increased	specificities decreased
Mexican (Rea & Terasaki 1980)	19TT	174	DRw2	—
Japanese (Miyanaga *et al.* 1981)	54TT	167	DR1 DR2 (2.9) DRw8 DQw1 (13.1)	DR4 (0.46) DRw53 (0.51)
Japanese (Izumi *et al.* 1982)	295LL	110	DR2 (8.7) DQw1	DRw9 (0.2) DRw53 (0.3)
	74TT	110	DR2 (5.9)	—
Venezuelans (Ottenhoff *et al.* 1984)	32LL	32	DQw1 (2.7	—
Thai (Schauf *et al.* 1985)	35LL	32	DR5	—
	32TT	32	DR2 (7.4) DQw1 (6.7)	
Korean (Kim *et al.* 1987)	152LL+TT	155	DR1 (2.5) DR2 (2.6) DRw9 (2.6) DQw1 (2.6)	DR4 (0.5) DRw53 (0.4) DQw3 (0.4)
Venezuelans (Ottenhoff & De Vries 1987)	35BL/LL	212	—	DR3
	32TT	212	DR3 (3.3)	—

The most convincing evidence for genetic determinants in leprosy has also depended upon HLA-type data, but is based upon family segregation rather than case-control analyses. Here the argument requires HLA data on parents and children in families with at least two affected children, and compares the haplotype distribution observed in the affected children with that expected if the allocation of parental haplotypes were random (see figure 2). An elegant method for deriving an appropriate χ^2 statistic from data pooled from families of different sizes has been provided by Nijenhuis (De Vries *et al.* 1976). Table 4 summarizes data from several studies that have applied this approach. The overall results are consistent and convincing, favouring a non-random allocation of haplotypes from unaffected or lepromatous parents to tuberculoid children and from lepromatous parents to lepromatous children. Interestingly enough, there is no evidence of a non-random distribution of haplotypes in children without leprosy in such families. Such evidence suggests strongly that HLA antigens, or genes tightly linked to the HLA region, are involved not in determining whether or not an individual

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

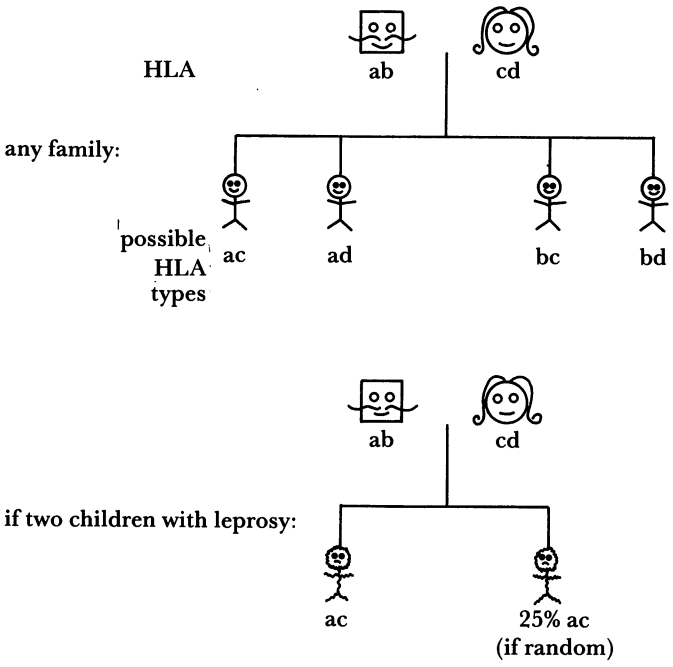

FIGURE 2. Experimental design of HLA segregation studies. Parental haplotypes labelled a/b (paternal) and c/d (maternal) respectively. If allocation random, probabilities of each combination ac, ad, bc, bd are equal, and probability that any two 'affected' (i.e. with leprosy) children share same haplotype combination should be 25%. Comparison of observed frequency with this expectation forms basis for statistical test results in table 4.

TABLE 4. COMBINED RESULTS FROM HLA SEGREGATION STUDIES AS SUMMARIZED BY VAN EDEN (1983), EXTRACTED FROM DE VRIES *ET AL.* (1976), FINE *ET AL.* (1979), DE VRIES *ET AL.* (1980), LAWRENCE *ET AL.* (1980), KEYU *ET AL.* (1985)

(TT, BL, LL refer to polar tuberculoid, borderline lepromatous and polar lepromatous leprosy, respectively.)

to children with	from parents with	random segregation	
TT leprosy	no leprosy or BL/LL leprosy	no	$p = 5 \times 10^{-6}$
TT leprosy	TT leprosy	yes	n.s.
BL/LL leprosy	no leprosy or BL/LL leprosy	no	$p = 8 \times 10^{-4}$
BL/LL leprosy	TT leprosy	yes	n.s.
no leprosy	no, TT or LL leprosy	yes	n.s.

n.s., Not significant.

manifests leprosy at all, but in determining the type of leprosy that is manifested, whether it be of the tuberculoid or lepromatous variety. In addition, the parental sources of the segregating haplotypes indicate that the HLA-linked gene determining a tuberculoid response behaves like a recessive, whereas that for lepromatous disease behaves like a dominant. Given the case-control associations shown in table 3, the evidence is strongly in favour of some gene encoded within or very near the HLA-DR locus as playing that role.

We now know that the HLA-D region codes for so-called class II antigens, which are expressed on the surface of certain monocytic cells and are involved in presentation of antigens

Downloaded from rstb.royalsocietypublishing.org

to other monocytic (T helper or T suppressor) cells involved in cell-mediated immune processes. Evidence that this mechanism may underlie the association of HLA-D antigens in leprosy has recently come from Ottenhoff & De Vries (1987), who have shown that *in vitro* proliferation of T cells cloned from HLA-DR3 heterozygote TT leprosy patients required antigen-presenting cells sharing the HLA-DR3 allele.

Implications of the genetic evidence

The evidence favouring involvement of some genes in leprosy, in particular HLA-D or HLA-D-linked genes, is now very strong. What it means in epidemiological terms is less clear. It is interesting that the motivations and insights guiding this genetic work have in recent years been based less on an effort to explain population patterns of leprosy than on efforts to explain the pathogenetic mechanisms underlying different forms of the disease. Given the important role of the immune response, in particular the cellular immune response, in leprosy, it is not surprising that attention has concentrated on the genetics of immunological mechanisms and hence on the HLA region, in particular HLA-D loci. In this sense, the positive results are satisfying. On the other hand, the trend of the work has been towards detailed studies of cell lines derived from very few patients, with no evidence that these individuals are representative of the populations from which they came. There is increasing evidence that the genetic basis of susceptibility to leprosy involves multiple genes, and that it may vary within as well as between populations.

The strongest evidence thus far for genetical determinants in leprosy is that derived from family segregation studies. It should be recognized that this method requires multiple case families, and investigators have gone out of their way to find sibships with more than two cases, to increase the power of their studies. The method thus selects in favour of families with the strongest genetic determination. The cases in such families may not be typical of all leprosy in a population: indeed, several authors have commented that an appreciable proportion of cases ascertained in leprosy programmes have no known contacts within the household or family (Fine 1982). That 'familial' cases might have a different genetic basis from 'sporadic' leprosy in the same population was suggested by Van Eden *et al.* (1981), who found that HLA-DR2 was associated with the former, but not the latter, in studies in Maharashtra State in India.

Further evidence for multiple genetic mechanisms may be inferred from the fact that the twins' data (table 2) implied genetic control of the disease-or-not decision, whereas the HLA-segregation data (table 4) pointed only to a mechanism determining clinical type, within the diseased population. Such a dichotomy is itself consistent with a large body of data on the genetics of susceptibility to certain infections in laboratory animals, for example *Leishmania* infections in mice, which suggests independent genetic control of 'innate resistance' (e.g. to infection) and of 'acquired resistance' (e.g. affecting the course of infection). The analogy is especially apt in so far as it is the latter function that is controlled by genes linked to the histocompatibility system in mice.

There have been more genetic studies of tuberculoid than of lepromatous disease, for the simple reason that it is more frequent in populations and in multi-case families. The evidence favouring the involvement of a recessive HLA-linked determinant in tuberculoid disease, as shown in family segregation studies, is overwhelming. The evidence stands in contrast to the Uganda data shown in table 1, which revealed no evidence for a genetic influence.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

Unfortunately, all the family-segregation studies done thus far have been in Asian and South American populations, and thus we cannot be sure whether this apparent inconsistency reflects a difference between populations or between study methods.

We again see inconsistencies when examining the evidence for genetic determinants of lepromatous disease. Family-segregation studies show strong evidence for involvement of an HLA-linked factor, and this appears to behave as a dominant. On the other hand, multiple cases of lepromatous leprosy in a sibship or family are extremely rare in most populations, which explains why there have been so very few segregation studies of lepromatous disease. Recent data from a total-population survey in Malawi has confirmed the rarity of multiple cases of lepromatous disease in families. Out of 348 parents of confirmed multibacillary (lepromatoid) patients examined only one was found to have multibacillary leprosy. And only one of 575 children of multibacillary parents was found with multibacillary disease (J. M. Ponnighaus & P. E. M. Fine, unpublished data). In each case the expected prevalence, assuming a single dominant factor of high penetrance, is greater than 50%; but the observed prevalence is less than 1%, and only slightly greater than the expected prevalence of leprosy in the whole population. Even allowing for age adjustment and for considerable error in parentage information, such data are hardly suggestive of strong genetic influence unless the penetrance is extremely small, much smaller than that implied by the study data of twins (table 2). On the other hand, we are again comparing population data from Africa with family segregation data from Asia (China) and South America (Venezuela). Evidence that the genetic mechanism may differ between populations is also seen in the fact that, although the segregation data suggest a strong HLA or HLA-linked determination of leprosy type, and *in vitro* studies suggest the HLA-DR alleles are the functional units (Ottenhoff & De Vries 1987), HLA-DR2 has been found associated with both tuberculoid and lepromatous leprosy in Japanese populations (Izumi *et al.* 1982), whereas HLA-DR3 has been found associated only with tuberculoid disease in Venezuela (Ottenhoff & De Vries 1987).

The puzzle is a complicated one, and it is easier to see the next research protocol than the ultimate applicability of such information in the field. Some authors have justified genetic research on leprosy on the grounds that it might permit the identification of high-risk individuals in endemic populations, and that these individuals could be given special prophylactic treatment. I find it hard to take such suggestions seriously. The low prevalence and incidence of leprosy, the complexity of the epidemiological pattern and the genetic data so far make it unlikely, at least to me, that there will ever be a screening test of sufficiently high predictive value to be of use. Moreover, even if one had an assay, the cost and logistics of its application would be prohibitive, given the economic situation and needs of the populations in which leprosy persists today. I suspect that leprosy would disappear of its own accord, as it did from Norway, if endemic populations were economically and technically able to do such a screening and treatment exercise. This says nothing of the ethical implications of applying such a test, which, given the stigma attached to leprosy, would be serious in many communities.

There is a more sanguine appraisal of the potential for genetic studies. We are on the verge of a revolution in epidemiological genetics, as much of the human genome will soon be mapped or decoded and probes will become available to scan the entire genome for loci associated with leprosy and other diseases. I think the leprosy genetics picture will be an increasingly complicated one, but it may provide some element of satisfaction in explaining away a portion of the lingering variance in our understanding of the distribution of the disease.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

Perhaps the most credible potential applications of current genetic work on leprosy relate to vaccines. Among the many ironies of leprosy is the fact that there is currently a massive vaccination campaign against it, by accident. 'By accident', because BCG vaccine, given in most countries of the world to protect against tuberculosis, protects to some degree against leprosy as well. The actual protection imparted appears to vary greatly (as it does against tuberculosis) between different populations, being as high as 80% in some African populations and as low as 20% in Burma (Fine 1985). It has been suggested that this observed variation might reflect genetic differences between the populations studied. On the other hand, there are no data that support this hypothesis, and recent studies on the effectiveness of BCG against tuberculosis in Asian populations argue against it. Though BCG works poorly in the Indian subcontinent, it appears to impart high protection to Indians living in Great Britain (Fine 1988).

Because of this variable efficacy, an effort is now underway to improve upon BCG as an anti-leprosy vaccine. The pragmatists have taken the first step, and controlled trials are currently in progress to evaluate the protection imparted by simple mixtures of BCG and killed leprosy bacilli. The rationale here is that the addition of specific antigens may improve upon whatever non-specific protection is imparted by BCG alone. Simultaneously, attempts are being made to identify the antigens of *M. leprae*, and in particular the specific epitopes that are involved in protective, as opposed to suppressive or otherwise unhelpful immune responses. Here genetics may provide a useful tool. If it should turn out that the association between certain HLA-DR alleles and leprosy is due to specific activation of an inappropriate – perhaps T suppressor – response, then there might be an argument to screen out the epitopes recognized by these antigens from any vaccine preparation. It sounds like a remote possibility, but the technology is on the horizon. Whether it will ever benefit mankind in its efforts against leprosy, only time will tell.

References

Belknap, H. R. & Hayes, W. G. 1961 A genetic analysis of families in which leprosy occurs. *Lepr. India* **29**, 375.

Beiguelman, B. 1972 An appraisal of genetic studies in leprosy. *Acta Genet. med. Gemell.* **21**, 21–52.

Blackwell, J. M. 1988 Bacterial infections. In *Genetics of resistance to bacterial and parasitic infections* (ed. D. Wakelin & J. M. Blackwell), chap. 3. Basingstoke, U.K.: Taylor and Francis.

Bryceson, A. D. M. & Pfaltzgraff, R. E. 1979 *Leprosy*, 2nd edition. Edinburgh: Churchill Livingstone.

Burgess, P. J., Fine, P. E. M., Ponnighaus, J. M. & Draper, C. C. 1988 Serological tests in leprosy. The sensitivity, specificity and predictive value of ELISA tests based on phenolic glycolipid antigens, and the implications for their use in epidemiological studies. *Epidem. Infect.* (In the press.)

Chakravartti, M. R. & Vogel, F. A. 1973 A twin study of leprosy. *Top. hum. Genet.* **1**, 1–123.

De Vries, R. R. P., Lai A., Fat, R. F. M., Nijenhuis, L. E. & Van Rood, J. J. 1976 HLA-linked genetic control of host response to *Mycobacterium leprae*. *Lancet* ii, 1328–1330.

De Vries, R. R. P., Mehra, N. K., Vaidya, M. C., Gupte, M. D., Meerakhan, P. & Van Rood, J. J. 1980 HLA linked control of susceptibility to tuberculoid leprosy. *Tissue Antigens* **16**, 294–304.

Doull, J. A., Guinto, R. J., Rodriguez, J. N. & Bancroft, H. 1942 The incidence of leprosy in Cordova and Talsay, Cebu, P. I. *Int. J. Lepr.* **10**, 107–131.

Fine, P. E. M. 1981 Immunogenetics of susceptibility to leprosy, tuberculosis and leishmaniasis. An epidemiological perspective. *Int. J. Lepr.* **49**, 437–454.

Fine, P. E. M. 1982 Leprosy: the epidemiology of a slow bacterium. *Epidem. Rev.* **4**, 161–188.

Fine, P. E. M. 1985 The role of BCG in the control of leprosy. *Ethiop. Med. J.* **23**, 179–191.

Fine, P. E. M. 1988 The BCG story: lessons from the past, implications for the future. *Rev. infect. Dis.* (In the press.)

Fine, P. E. M., Wolf, E., Pritchard J., Watson, B., Bradley D. J., Festenstein, H. & Chako, C. J. G. 1979 HLA-linked genes and leprosy: a family study in Karigiri, South India. *J. infect. Dis.* **40**, 152–161.

Hastings, R. C. (ed.) 1985 *Leprosy*. Edinburgh: Churchill Livingstone.

Irgens, L. M. 1980 Leprosy in Norway – an epidemiological study based on a national patient registry. *Lepr. Rev.* **51** (suppl.), 1–130.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

Izumi, S., Sugiyama, K., Matsumoto, Y. & Ohkawa, S. 1982 Analysis of the immunogenetic background of Japanese leprosy patients by the HLA systems. *Vox Sang.* **42**, 243–246.
Keyu, X., De Vries, R. R. P., Honming, F., Van Leewen, A., Renbiao, C. & Ganyun, Y. 1985 HLA linked control of predisposition to lepromatous leprosy. *Int. J. Lepr.* **53**, 56–63.
Kim, S. J., Choi, I. H., Dahlberg, S., Nisperos, B., Kim, D. J. & Hansen, J. A. 1987 HLA and leprosy in Koreans. *Tissue Antigens* **26**, 146–153.
Lawrence, D. N., Bodmer, J. G. & Bodmer, W. F. 1980 Distribution of HLA antigens in Ticuna Indians of Brazil: results of typing a leprosy-affected family. *Tissue Antigens* **16**, 152–160.
Lie, H. P. 1938 Norwegian lepers in the United States. The investigations of Holmboe, Boeck and Hansen. *Int. J. Lepr.* **6**, 351–356.
Martinez Dominiguez, V., Garbajosa, P. G., Gyi, M. M., Tamondong, C. T., Sundaresan, T., Bechelli, L. M., Lwin K., Sansarricq, H., Walter, J. & Noussitou, F. M. 1980 Epidemiological information on leprosy in the Singu area of upper Burma. *Bull Wld Hlth Org.* **58**, 81–89.
McWhirter, N. (ed.) 1981 *Guinness book of records*, 28th edn. Trowbridge, U.K.: Redwood Burn.
Miyanaga, K., Jiyi, T., Maeda, H., Nakajima, S. & Kobayashi, S. 1981 Tuberculoid leprosy and HLA in Japanese. *Tissue Antigens* **18**, 331–334.
Newell, K. W. 1966 An epidemiologist's view of leprosy. *Bull. Wld Hlth Org.* **34**, 827–857.
Ottenhoff, T. H. M., Gonzalez, N. M., De Vries, R. P. R., Convit, J. & Van Rood, J. J. 1984 Association of HLA specificity LB-E12 (MB1, DC1, MT1) with lepromatous leprosy in a Venezuelan population. *Tissue Antigens* **24**, 25–29.
Ottenhoff, T. H. M. & De Vries, R. P. R. 1987 HLA class II immune response and suppression genes in leprosy. *Int. J. Lepr.* **55**, 521–534.
Rea, T. H. & Terasaki, P. I. 1980 HLA-DR antigens in tuberculoid and lepromatous leprosy. *Lepr. Rev.* **51**, 117–123.
Schauf, V., Ryan, S., Scollard, D., Jonasson, O., Brown, A., Nelson, K., Smith, T. & Vithayasai, V. 1985 Leprosy associated with HLA-DR2 and DQw1 in the population if north Thailand. *Tissue Antigens* **26**, 243–247.
Sergeantson, S., Wilson., R. R. & Keats. B. J. B. 1979 The genetics of leprosy. *Ann. hum. Biol.* **6**, 375–393.
Simpson, J. Y. 1841 Antiquarian notices of leprosy and leper hospitals in Scotland and England. Part III. *Edinb. med. surg. J.* **57**, 394–429.
Spickett, S. G. 1962 Genetics and the epidemiology of leprosy: I. The incidence of leprosy. *Lepr. Rev.* **33**, 76–93.
Van Eden, W. 1983 HLA and leprosy: a model for the study of genetic control of immune response in man. Drukkerij J. H. Pasmans B. V. 's-Gravenhage.
Van Eden, W., Gonzalez, N. M., De Vries, R. R. P., Convit, J. & Van Rood, J. J. 1985 HLA-linked control of predisposition to lepromatous leprosy. *J. infect. Dis.* **151**, 9–14.
Van Eden, W., Mehra, N. K., Vaida, M. C., D'Amaro, J., Schreuder, G. M. T. & Van Rood, J. J. 1981 HLA and sporadic tuberculoid leprosy: a population study in Maharashtra, India. *Tissue Antigens* **18**, 189–193.
White, S. J., Stone, M. M. & Howland, C. 1978 Genetical factors in leprosy: a study of children in Uganda. *J. Hyg., Camb.* **80**, 205–216.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES