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Leprosy and Genetics *

A Review of Past Research with Remarks concerning Future Investigations

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The few geneticists who are interested in leprosy have been working in this field only since 1962, and have made little progress in solving the problems presented by susceptibility to this disease.

This paper reviews the research that has been conducted, with particular reference to the search for associations between leprosy and certain genetic markers. In each area, the advantages and limitations of different techniques are described, and attention is drawn to sources of bias that may invalidate many of the results that have been published. Of particular interest is the discussion of a new technique for evaluating resistance to leprosy. The proposed technique is based upon the in vitro *transformation of blood monocytes into macrophages, and the observation of their behaviour against* Mycobacterium leprae.

The belief that a hereditary factor may be involved in susceptibility to leprosy is not new. It is supported by the well-known facts that (1) the disease fails to manifest itself in the majority of exposed subjects, even when they have been submitted to prolonged and intimate contact; (2) the risk of leprosy being contracted by relatives of index-cases increases according to their degree of consanguinity; and (3) environmental agents are not capable of changing one polar form of the disease into another—i.e., they cannot change typical lepromatous patients into typical tuberculoid individuals, and *vice versa*.

In recent years, various approaches to the problem have been used by geneticists. Associations between leprosy and genetic markers such as ABO and Rh blood groups, glucose-6-phosphate dehydrogenase deficiency, haptoglobins, transferrins, Au(1) antigen, and taste sensitivity to phenylthiourea have been explored in the search for pleiotropic effects. Pedigree analyses of families including leprosy patients have been conducted in order to test monogenic inheritance. Several characteristics related to fecundity have been analysed in order to evaluate the sterility rate among couples having leprosy. Other lines of investigation have included the study of the familial distribution of the late lepromin reaction and the histological study of leprosy resistance.

This paper reviews some of the research that has been conducted and makes some suggestions concerning future investigations. Topics related to (1) genetics and different forms of leprosy, (2) genetics and the pattern of leprosy in populations, and (3) the sex-ratio among leprosy patients have been intentionally omitted, not because of their lack of importance but because they are largely speculative—particularly when studied on the basis of epidemiological data that may be contradictory and biased. A discussion of these problems will be found in Spickett (1964).

LEPROSY AND GENETIC MARKERS

Leprosy and taste sensitivity to phenylthiourea

If a series of solutions (numbered 1-14) of phenylthiourea (PTC) is prepared with concentrations of $2.6/2^n$ g of PTC per litre of water (where n is the number of the solution), and human populations are tested with these solutions, a threshold phenomenon is observed. In all populations studied it has been demonstrated that the taste-threshold distribution for PTC is bimodal. The antimodal value discriminates the " tasters " (those who can taste PTC even in low concentrations) from the " non-tasters " (those who are unable to do so). Many of the non-

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tasters taste PTC only in high concentrations, while others are unable to taste its bitterness even in the stock solution.

Soon after Fox (1932) discovered that human populations are dimorphic with respect to their ability to taste phenylthiourea, this compound became widely used in anthropological genetics investigations. Upon the basis of the frequency of the occurrence of non-tasters, three major racial groups may be recognized (the approximate frequency is given in brackets): Caucasoids (30%), Mongoloids (8%), and Negroids (3%).

Genetic analysis has shown that this dimorphism is controlled by a major autosomal gene pair (T,t). Individuals with homozygous dominant (TT) and heterozygous (Tt) genotypes will have the " taster " phenotype, while those having the homozygous recessive (tt) genotype will have the " non-taster " phenotype.

Human populations exhibit the same dimorphism to compounds that have the N—C=S chemical grouping, many of which are antithyroid goitrogenic drugs (Richter & Clisby, 1942) and which are found abundantly in several edible vegetables (Greer & Deeny, 1959).

The possibility of a correlation between leprosy and taste sensitivity to PTC has been explored in several papers. In an early work, Beiguelman (1962b) reported the results of an investigation of the frequency of PTC non-tasters in subjects having lepromatous and tuberculoid forms of leprosy. No significant association was found between taste sensitivity and age, sex, or form of leprosy. However, the rate of non-tasters among 1559 Caucasoid leprosy cases was 19.5%, significantly lower than that found in the literature for healthy Caucasoid persons of Mediterranean origin (who show the lowest frequency of non-tasters among white populations). These results suggested a correlation between leprosy and ability to taste PTC and prompted further investigation. Beiguelman (1964b) tested a sample of 900 Caucasoid leprous patients by the technique of Harris & Kalmus (1949), and compared them with a control sample of 1000 healthy Caucasoids tested in the same way. The frequency of non-tasters among the leprous patients was 19.7%; among the healthy individuals it was 24.7% ($\chi^2 = 6.922$; 1 d.f.; $P < 0.01$). If the data obtained in this and the earlier investigation are pooled, the difference becomes more striking (leprous cases studied, 2459; non-tasters, 19.6%; $\chi^2 = 11.299$; 1 d.f.; $P < 0.001$).

Since the commonly used antileprotic drugs have an antithyroid goitrogenic effect, it might be supposed that they would modify the taste-thresholds of patients under treatment. However, this situation does not seem to arise, because cyclic changes of the thyroid equilibrium are not able to modify the taste-thresholds for PTC (Beiguelman, 1964c).

It was supposed that if the leprous non-tasters were more susceptible to antithyroid drugs than leprous tasters, they would respond better to treatment with antileprotic drugs having an antithyroid effect. This supposition was based upon the following factors:

(1) Thyroid metabolism seems to be related to the ability to taste PTC, non-tasters being more prone to develop adenomatous goitre or athyreotic cretinism (Harris et al., 1949; Kitchin et al., 1959; Shepard & Gartler, 1960; Fraser, 1961).

(2) A significantly lower frequency of non-tasters is found among leprosy patients (Beiguelman, 1962b, 1964b) and among patients affected with both tuberculosis and leprosy (Beiguelman, 1964a).

(3) The drugs commonly used in leprosy therapy, such as sulfones and thioureas, have an antithyroid effect (William & Bakke, 1962).

(4) Iodine administration increases the pathological effects of leprotic reactions.

However, a sample of 315 leprosy patients studied by Beiguelman & Marques (1964) showed no correlation between ability to taste PTC and clinical and bacteriological status. The patients were classified in the following groups:

(1) subjects showing clinical and bacillary regression during an adequate period (less than 4 years), without relapses;

(2) subjects showing prolonged clinical and bacillary regression, with a few relapses of short duration; and

(3) subjects showing frequent relapses of long duration and subjects not showing any regression.

The results of this study, therefore, do not support the supposition of an association between taste sensitivity to PTC and the response to antileprotic drugs that have an antithyroid effect.

ABO and Rh blood groups and leprosy

The search for possible associations between blood groups and susceptibility to leprosy began long before Mourant (1954) suggested the hypothesis that the antigens of infecting micro-organisms might

be involved in the determination of blood-group polymorphism (Puente, 1927/1928; Hayashi, 1929; Paldrock, 1929; Herivaux, 1931; Pinetti, 1931; Hasegawa, 1937; Valle, 1937; Cerri, 1938; Marti, 1947; Cesarino-Netto, 1952). However, the findings obtained in this field before 1952 cannot be accepted since they are open to criticism on several grounds—e.g., the classification of leprosy patients on a clinical-topographic basis, the inadequate statistical treatment of data, and the smallness of some samples.

The question was reopened after Aird et al. (1953) found a relationship between ABO blood groups and stomach cancer. The results of studies demonstrating associations between the following were published subsequently: O group and peptic ulcer (Aird et al., 1954; Buckwalter et al., 1956a, 1956b; Clarke et al., 1956); A group and gastric carcinoma (Koster et al., 1955; Buckwalter, Turner et al., 1957; Buckwalter, Wohlwend et al., 1957; Beasley, 1960); non-secretion of ABH antigens and duodenal ulcer (Clarke et al., 1957, 1959; Clarke, 1959; McConnell, 1959). Moreover, Lessa (1954) had pointed out that the frequency of the Rh negative group is higher in leprosy patients than in the general population. As a result of these findings, human geneticists investigated the possibility of an association between some red cell blood groups and leprosy (Beiguelman, 1962a, 1963, 1964d, Salzano & Ferlauto, 1962; Salzano et al., 1965; Hsuen et al., 1963; Yankah, 1965; Verma & Dongre, 1965; Povey & Horton, 1966). Contrary to Lessa's findings, the results obtained by these investigators did not support the hypothesis of an association between leprosy and Rh groups (Beiguelman, 1962a, 1963; Salzano & Ferlauto, 1962; Yankah, 1965). However, with respect to the ABO blood groups, conflicting although reconcilable conclusions were drawn. All except one group of authors found no evidence of a correlation between leprosy and the ABO system when samples of leprosy patients were considered as a whole, without distinction of the different clinical forms of the disease (i.e., when all leprosy cases were compared with non-leprosy cases). However, Hsuen et al. (1963) found a significantly higher frequency of the O group among leprosy patients than in the non-affected population.

Beiguelman (1963, 1964d) found a significant, although slight, excess of the O group among tuberculoid as compared with lepromatous patients. The data of Yankah (1965) indicate a similar but much greater difference. On the other hand, Salzano et al. (1965), Verma & Dongre (1965), and Povey & Horton (1966) found no difference between the polar types of leprosy with respect to ABO-group distribution.

The differing results obtained by these investigators may be attributable to sampling or to technical errors. For instance, if samples of leprosy cases are compared with samples of the general population used as controls, it is important to know (1) whether the proportions of positive and negative late lepromin tests are the same in both groups, (2) whether the samples consist of the same racial groups and have the same age-group and sex distributions, or (3) whether leprosy is excluded by clinical examination or merely by gross examination. Moreover, if the control samples are taken from blood-bank donors it may be asked whether the blood-group frequencies are not biased because of an excess of O donors. Finally, the results of such investigations may be affected if blood groups are determined with blood obtained by finger-puncture rather than by the more accurate procedure of investigating the antigens in washed erythrocytes with chosen anti-A, anti-B, and anti-AB sera, and the agglutinins of the serum with pooled A, B, and O red cells. Recognizing these difficulties, Beiguelman (1964d) reinvestigated the problem in order to confirm or disprove his 1963 findings. In this new study, to avoid the sources of bias discussed above, the following procedures were followed:

(1) Only lepromatous and tuberculoid unrelated patients were investigated.

(2) The classification of these two types of leprosy was confirmed histologically and by the lepromin test.

(3) Blood groups were determined by investigating antigens and agglutinins (direct and inverse proofs).

(4) Both the lepromatous and tuberculoid samples had the same proportions of ethnic groups and sexes and the same average age.

(5) The samples were reciprocal controls and therefore allowed a better comparison of people with proved positive and negative lepromin reactions. In this situation, the use of a sample of the general population for control was avoided.

Apart from the results of Hsuen et al. (1963), which are open to criticism on the grounds of an inadequate control sample, it may be concluded that no evidence exists to support the view that leprosy (including its different clinical forms) is associated with ABO or Rh blood groups. The same is true for the polar

types of leprosy when non-Negroid populations are analysed (including the data of Beiguelman, 1964d). Since the greater frequency of group O among tuberculoid than among lepromatous patients is observed only in Negroids (Beiguelman, 1964d; Yankah, 1965), the higher O frequency could merely reflect geographical variation in the blood-group distributions in African populations.

Leprosy and G6PD deficiency

The common genetic variants that cause glucose-6-phosphate dehydrogenase (G6PD) deficiency in human erythrocytes result from X-chromosome mutants. In this situation, males with an enzyme-deficient gene will always disclose the trait, while only homozygous females will have low G6PD levels (comparable with those found in deficient males).

The deficiency is harmless in itself, but haemolysis will occur in individuals with this trait when they are exposed to the fava bean or its flowers, or when they ingest certain drugs, particularly antimalarials that are chemically related to the 8-aminoquinolines (Beutler, 1959). Among several drugs tested, the sulfones have been described as being capable of causing haemolysis in G6PD-deficient subjects (Szeinberg et al., 1959; Desforges et al., 1959; Gilles et al., 1960; Gilles & Taylor, 1961).

Pettit & Chin (1964) and Beiguelman et al. (1966) investigated the possibility that G6PD-deficient lepromatous subjects might be more prone to exhibit haemolytic anaemia under treatment with sulfones. The data obtained by both groups do not support this possibility because the G6PD-deficient patients had no clinical history of icterus, haemoglobinuria, or decreased haematocrit. However, Beiguelman et al.[1] observed that, in 46% of G6PD-deficient patients, 25% or more of the red cells contained 4 or more Heinz bodies. In order to explain this apparent paradox, they suggested that lepromatous patients might have high haptoglobin levels. In this situation, the manifestation of haemoglobinuria, even during intense haemolysis, would not be expected. This hypothesis is supported by the following facts:

(1) Haptoglobin levels increase in several inflammatory diseases (Owen et al., 1959) and decrease to undetectable levels in several haemolytic diseases (Allison & Rees, 1957).

(2) The frequency of apparent ahaptoglobinaemia among leprosy patients is unsually high (Povey & Horton, 1966).

The frequency of G6PD deficiency in Caucasoid and Negroid lepromatous samples was compared by Beiguelman et al. (1966) with that in normal white and Negroid samples, the latter studied by Lewgoy & Salzano (1965). Since no significant difference was found, there seems to be no association between leprosy and G6PD deficiency.

Haptoglobins and leprosy

The haptoglobins are serum proteins that, among other functions, determine the level of haemoglobin in the serum. Disregarding the several rare types of haptoglobin, it may be considered that human populations are composed of individuals with three different haptoglobin types, which can be distinguished by the starch gel electrophoresis method. These types are designated 1-1, 2-1, and 2-2. An allelic autosomal gene pair (Hp^1 and Hp^2) may be considered as responsible for the three types.

The polymorphism of haptoglobins exists in all human populations, but the nature of the selective forces that maintain it is unknown. For this reason, the possible existence of a differential distribution of haptoglobin types among the different forms of leprosy has been explored by Schwantes et al. (1963) and by Povey & Horton (1966). No difference in the frequency of the Hp^1 gene was observed in the different clinical forms of leprosy. Moreover, Schwantes et al. showed that, among Caucasoid leprosy cases, the frequency of the Hp^1 gene is similar to that found among normal Caucasoids in the general population of Pôrto Alegre, Brazil (Tondo et al., 1962).

Transferrins and leprosy

The transferrins are serum proteins that, among other functions, combine with and transport iron. When the serum of most Caucasoids is tested by starch gel electrophoresis, a single major iron-binding protein band is found. The protein responsible for this band is named transferrin C. Very rarely, a fast-moving band, caused by transferrin B, is found. In Negroids a slower-moving iron-binding protein band, caused by transferrin D, may be found. The occurrence of these proteins has been attributed to three autosomal allelic genes.

Since the selective forces that maintain the polymorphism of the transferrins are unknown, the distribution of their types among leprous patients

[1] Beiguelman, B. et al. (1967) G6PD deficiency among lepers and healthy people in Brazil. *Acta genet. (Basel)* (in press).

was investigated by Povey & Horton (1966). These investigators reported that in all the sera of patients affected by different forms of leprosy, the transferrins were of type C-C, except for one possible type C-D. There is, therefore, no evidence of a correlation between transferrin types and leprosy.

Leprosy and Australian antigen

Blumberg (1964) found, in a transfused patient affected with haemophilia, an antibody that reacted with a protein present in the serum of an Australian aborigine but was absent from the serum of most normal people living in the USA. This protein was named Australian antigen, Au(1), by Blumberg et al. (1965). The Au(1) antigen is rare in the USA (0.1%) but has a higher frequency in Asian and Pacific populations (5%-7%) and in Mediterranean populations (1%-2%) (Blumberg & Melartin, 1966).

The Au(1) antigen was found to be associated with leukaemia, Down's syndrome, and other diseases involving the reticuloendothelial system (Blumberg & Alter, 1965; Blumberg et al., 1965). Moreover, it was found that lepromatous patients show a significantly greater frequency of Au(1) than do tuberculoid cases and controls (Blumberg & Melartin, 1966). It is also noteworthy that Au(1) is more frequent among males and is correlated to age-groups. Blumberg and his colleagues are at present studying the correlation observed between Au(1) antigen and lepromatous leprosy and the suggestion that Au(1) is inherited as a simple autosomal recessive gene.

PEDIGREE ANALYSES

In reviewing the literature on the epidemiology of leprosy, Spickett (1962a) made several observations on the transmission of leprosy within families. Although this author agreed that there might be other explanations, he assumed that the distribution of leprosy in some of the families studied might be consistent with Mendelian inheritance. Although the data he analysed do not fit single-factor expectancies, Spickett supposed that the simplest hypothesis could be that susceptibility to leprosy is controlled by a single irregularly dominant gene. Using the very large pedigrees of Acadian French families in New Brunswick, published by Aycock & McKinley (1938), Spickett calculated the penetrance of this supposed dominant gene to be 83.3%. He considered that the most satisfactory value would be obtained from the study of sibs none of whose parents had leprosy, and assumed that when leprosy occurs in a sibship one of the parents must have carried the gene and that the mating was probably of the heterozygous × normal type. Using the same method for data from Iceland, Dungal & Spickett (cited in Spickett, 1964) found a penetrance of 48.651%.

To explain the existence of different forms of leprosy in genetic terms, Spickett (1962b) considered it possible, but not proved, that the occurrence of different clinical types of leprosy is governed multifactorially.

FECUNDITY AND THE LEPROMATOUS FORM OF LEPROSY

The fecundity of leprosy patients has for long attracted attention because the birth-rate among them is considered to be lower than that in the general population (McCoy, 1913). In fact, orchiepididymitis is very common among lepromatous males. It has even been suggested that the extinction of leprosy in France in the 17th century was a consequence of the law obliging leprous persons and their descendants *(cagots)* to marry only among themselves (Barbezieux, 1913). The problem was reinvestigated by Beiguelman et al. (1965) because the available data were concerned with the birth rate in sanatoria or the number of living children per couple, no reference being made to the form of leprosy involved.

Data on the following factors were obtained from lepromatous women married to healthy men and those married to lepromatous men: duration of cohabitation, age of women at the beginning of cohabitation, proportion of couples who used contraceptive methods, number of pregnancies per woman, number of live-children per couple, abortion rate, stillbirth rate, provoked abortion rate, dead children per viable pregnancy, and sex-ratio of live and dead children.

Analysis of these data led to the conclusion that many lepromatous males are rendered sterile by the disease and are consequently less fecund than healthy males (as mentioned previously, orchiepididymitis is frequent among lepromatous males). However, in the fertile fraction, the fecundity was found to be similar to that of healthy males.

In women, fertility seems to be unaffected. The abortion rate observed in lepromatous females was similar to that found in healthy populations. As is known, the abortion rate in a healthy population is highly constant, with a modal value around 16% (Stevenson et al., 1959; Saldanha, 1962). This figure does not depend on social, economic, or cultural conditions.

FAMILIAL DISTRIBUTION OF THE LATE LEPROMIN REACTION (MITSUDA REACTION)

The lepromin reaction

Lepromin is a suspension of triturated lepromatous tissues rich in *Mycobacterium leprae* in an isotonic solution of sodium chloride sterilized by heating. When 0.1 ml of lepromin is injected intradermally, the subject may show a late reaction (Mitsuda reaction) which is observed clinically after 28-40 days, and/or an early reaction (Fernandez reaction) which is read macroscopically after 24-48 hours. When recorded clinically, the early and late lepromin reactions may be classified in five groups, according to their intensity (Table 1).

However, when the late lepromin reaction is analysed histologically, two classes may be distinguished:

(1) Positive reaction: a granulomatous infiltrate composed predominantly of epithelioid cells, assuming a tuberculoid structure, with AAR bacilli absent or rarely found.

(2) Negative reaction: an infiltrate exhibiting histiocytes deprived of epithelioid-cell characteristics, full of AAR bacilli (lepra-cells).

Bechelli et al. (1959) considered also a third class, in which histological changes " favour the hypothesis of positive reactions ". In this class they included incompletely granulomatous infiltrates in which epithelioid cells are not predominant, but are scattered and sparsely grouped, and have a tendency to develop nodular structures. Few giant cells may be observed in such biopsies, and AAR bacilli are either absent or found only rarely.

While the early lepromin reaction may be considered as an allergic response to leproproteins present in lepromin, the late lepromin reaction is considered to have a meaningful prognostic value, since it is believed that resistance to leprosy can be diagnosed on the grounds of the tissue reaction to lepromin. Such resistance is considered, at least, to be sufficient to confer protection against the lepromatous type of leprosy. As a general rule, lepromatous patients do not respond to lepromin, while individuals having the tuberculoid form of the disease give a positive reaction.

The histologically positive reaction derives from the ability of macrophages to lyse *M. leprae*, after phagocytosis, and their consequent transformation into epithelioid cells. The clinically positive response is considered to be a consequence of both the ability to lyse the bacilli and the influence of sensitizing agents that stimulate the lysogenicity of the macrophages (Hadler, 1953, 1956). It would seem, therefore, that the intensity of the macroscopic reaction to lepromin is directly associated with the grade of sensitivity. This situation would explain the reduction of the five clinical classes to two histological groups when the late lepromin reaction is analysed microscopically. It also would explain why

TABLE 1

EARLY AND LATE LEPROMIN REACTIONS CLASSIFIED ACCORDING TO INTENSITY OF CLINICAL RESPONSE [a]

Class	Early lepromin reaction	Late lepromin reaction
—	Presence of an erythematous halo smaller than 5 mm in diameter, or absence of an observable erythematous area	Absence of an observable or palpable element
±	Presence of an erythematous halo 5-10 mm in diameter	Presence of a perceptible element with a diameter smaller than 3 mm
+	Presence of an infiltrated erythematous halo 10-15 mm in diameter	Presence of a conspicuous infiltrated element with a diameter of 3-5 mm
++	Presence of an infiltrated erythematous halo 15-20 mm in diameter	Presence of a conspicuous infiltrated element with a diameter larger than 5 mm
+++	Presence of an infiltrated erythematous halo with a diameter larger than 20 mm	Presence of an ulcerated nodule

[a] After Bechelli & Rotberg (1956).

a few clinically lepromin-negative subjects are able to show a positive late lepromin reaction after being reinoculated with lepromin or vaccinated with BCG (Souza-Campos et al., 1962; Beiguelman, Quàgliato & Camargo, 1965).

Familial analysis

The distribution of the macroscopic late lepromin reaction in families free of leprosy was analysed by Beiguelman (1962c) in 220 Caucasoid couples and their 762 children. Practically all of them were unmixed descendants of Northern Italian immigrants living in the rural area of Rio das Pedras (State of São Paulo, Brazil). A close correlation was observed between the distribution of the lepromin responses in the offspring and that in the parental generation. Children of lepromin-negative parents were found to be more prone to exhibit failure of macroscopic late reactions. These results were confirmed by Beiguelman & Quagliato (1965) in tests of a random sample of 100 families free of leprosy living in another Brazilian rural area (Cosmópolis, State of São Paulo). A census was conducted in this region prior to the sampling in order to include only white, complete, unrelated families of larger size.

A genetic hypothesis for explaining the familial distribution

The results mentioned above led to a tentative genetic hypothesis to explain the familial pattern of the late lepromin reaction: a homozygous recessive gene was assumed to be responsible for the inability of macrophages to lyse *M. leprae*. This hypothesis was tested by clinical analysis of the familial distribution of the lepromin reaction (Beiguelman, 1965).

Macroscopic examination is not the most accurate procedure for studying the lepromin reaction, since the clinical response to lepromin is believed to be affected by both histological and environmental factors. However, it is believed that the sources of error were minimized by investigating the familial distribution of the Mitsuda reaction in the offspring of leprosy patients. Such leprosy contacts are more exposed to sensitizing agents (e.g., primary infections of *M. leprae*, repeated lepromin injections, and BCG vaccination) than individuals of the general population. Therefore, the correlation between the clinical and histological reactions among such contacts is likely to be higher.

The data were analysed genetically by a method suggested by Fisher (cited in Taylor & Prior, 1939). In this method, when both parents show the dominant phenotype, equation (1) below is used to calculate the total expected number of families whose offspring all have the dominant phenotype; equation (2) is used when only one of the parents shows the dominant phenotype:

$$\sum N_s \left\{ \left[1 - \left(\frac{2q}{p+2q} \right)^2 \right] + \left(\frac{3}{4} \right)^s \left(\frac{2q}{p+2q} \right)^2 \right\} \quad (1)$$

$$\sum N_s \left[\left(\frac{p}{p+2q} \right) + \left(\frac{1}{2} \right)^s \left(1 - \frac{p}{p+2q} \right) \right] \quad (2)$$

where N = observed number of families of size s; p = frequency of the dominant gene; $q = 1-p$ = frequency of the recessive gene.

The results of the analysis of the distribution of the late lepromin reaction, assuming dominant inheritance for resistance to leprosy, are given in Table 2. The expected number of families with at

TABLE 2

GENETIC ANALYSIS OF THE LATE LEPROMIN REACTION ASSUMING DOMINANT INHERITANCE [a]

Marriage	Class of family	No. of families		χ^2	d.f.
		Observed	Expected		
Positive × positive (41)	All children with positive reactions	27	29.663	0.865	1
	At least one child with negative reaction	14	11.337		
Negative × positive (65)	All children with positive reaction	23	27.050	1.038	1
	At least one child with negative reaction	42	37.950		
			Total	1.903	2
				P>0.30	

[a] Beiguelman (1965).

least one late lepromin reaction in the offspring was determined by subtracting from the total number of families the expected number of those in which all the children would show a positive reaction.

Since it was observed that, among subjects married to leprous partners, the frequency of lepromin-negative individuals was about 25% (this frequency includes healthy persons plus leprosy cases resulting from contagion), this value was taken as an estimate of the proportion of the supposed recessive homozygotes in the general population. Therefore, $q^2 = 0.25$ and $p = q = 0.50$.

The data in Table 2 support the hypothesis that an autosomal gene pair is responsible for the late lepromin reaction; it might, therefore, be expected that all the offspring of lepromatous parents would be lepromin-negative. However, the data observed do not confirm such an expectation. Of 81 children born to 24 lepromatous couples, 25 30.9%) showed a strong (++ or +++) macroscopic reaction to lepromin. It was supposed that this discrepancy could be ascribed to the influence of co-operative rather than alternative factors: incomplete penetrance of the genes, the high frequency of illegitimate children born to leprosy patients, and the influence of BCG vaccination.

HISTOLOGICAL STUDY OF INDIVIDUAL RESISTANCE TO LEPROSY

Leprologists agree that histological examination of biopsy material would be the best way to avoid the numerous sources of error involved in clinical readings of the lepromin reaction. However, it is difficult to use this method as a routine procedure. This situation prompted the development of a more accurate technique for testing the lysogenic ability of macrophages for *M. leprae* (Beiguelman & Barbieri, 1965; Beiguelman, 1966).

It is well known that, when maintained *in vitro*, blood monocytes develop into macrophages that resemble the wandering histiocytes of the tissues. The proposed method is based on the microscopic examination of such macrophages maintained in a tissue culture medium, after the addition of dead leprosy bacilli. The macrophages of both lepromatous and tuberculoid patients actively phagocytize the dead leprosy bacilli from the first day of incubation. After the phagocytic phase, a striking difference between the two types of culture is apparent. The macrophages of tuberculoid patients completely lyse the ingested bacilli, becoming practically free of lipids. However, the macrophages of lepromatous patients are unable to do this, and become transformed into typical lepra-cells whose cytoplasm contains numerous bacilli and droplets of lipids that are easily stainable by Sudan black.

The *in vitro* dimorphism of macrophages of leprosy patients for *M. leprae* was observed 20 years ago by Hanks (1947a, 1947b, 1947c) in cultures of the tissues of tuberculoid and lepromatous lesions. He reported that fibroblasts from tuberculoid lesions can destroy *M. leprae* while those from lepromatous lesions cannot, but degenerate and permit the bacilli to become free without signs of lysis. However, according to Hadler (1953) the cells thought by Hanks to be fibroblasts, which have great phagocytic and athrocytic activity and do not produce intercellular substance, are in reality fusiform macrophages.

With respect to the phagocytosis of *M. leprae* by macrophages that have originated from the blood monocytes of lepromatous patients, the first observation seems to be that of Benewolenskaja (1932).

The lack of lysogenic ability in the macrophages of lepromatous patients is specific to *M. leprae*. In all cultures that have been observed, macrophages from lepromatous subjects have been able to lyse *M. lepraemurium* as well as *M. tuberculosis*. Moreover, when damaged *M. leprae* are added to cultures of macrophages from lepromatous patients, lysis can easily be observed.

RESPONSE TO CHEMOTHERAPY AND GENETIC VARIABILITY OF *M. LEPRAE*

It is well known that chemotherapy often gives rise to drug-resistant strains of bacteria, especially in the more chronic infections. It is also known that some leprosy cases under treatment with a particular antileprotic drug become stationary after an initial phase of improvement, or relapse after inactivity has been achieved. This suggested the possibility that populations of *M. leprae* might become resistant to the action of antileprotic drugs. However, it was open to discussion because for more than 20 years the sulfones were used in the treatment of millions of cases. Moreover, since it is not yet possible to culture *M. leprae* in order to test drug resistance, such suggestions have been made only on theoretical grounds.

Doubt on this matter has recently been removed. By using the mouse footpad infection technique, Pettit & Rees (1964) were able to show beyond doubt that strains of *M. leprae* can become resistant to dia-

phenylsulfone (DDS). Seven patients who showed active disease and a high bacteriologic index, despite being under sulfone therapy for 13-15 years, were selected by these authors for investigation. Of these patients, who were treated with diaphenylsulfone for 6 months,

> " 4 improved both clinically and bacteriologically. In the other 3 patients the bacilli showed no changes, suggesting that they were not being killed by DDS; and 2 of these patients did not improve clinically. As bacterial morphology is probably the most sensitive means of determining therapeutic activity, there can be no doubt that these patients failed to respond to DDS. Using the new technique for producing leprosy in the mouse footpad, we were able to show that only the bacteria from these 3 patients were resistant to very high doses of DDS in the mouse. In our opinion the correlation of these laboratory findings with the clinical evidence of resistance fully establishes, for the first time, that DDS-resistant strains of *Myco. leprae* do exist in man. It can only be assumed that the other 4 patients, who had appeared to be resistant but nevertheless responded to DDS during the test period, had avoided treatment in the past—perhaps because they wanted to stay in the protective environment of the settlement " (Pettit & Rees, 1964).

Several genetic interpretations for drug resistance in leprosy may be proposed. It is of interest to set down those so intelligently discussed by Spickett (1964) when considering the results of a clinical trial in which patients treated with B663 (phenazine) suffered relapse with a raised bacteriologic index after a period of improvement:

> " 1. Mutations arose simultaneously in the pathogen populations of all the relapsed patients and these mutations were similar in giving resistance to B663. The probability that this could have occurred is vanishingly small.
>
> 2. A single mutation occurred in one population and bacilli of this strain were transmitted to other patients. There is not sufficient information in the report to tell whether or not such transmission could have taken place. Even if it could have, this explanation seems somewhat unlikely since it would be expected that the patient with the original mutant strain would have shown relapse before the others and this was not so.
>
> 3. The patients could have had contact with an individual carrying such a mutant strain. Again there is no evidence to tell whether or not this was possible, but if it was possible it could explain the results.
>
> 4. A new variety of bacilli resistant to B663 was produced as a result of a recombinational event in all the patients simultaneously. (It is frequently assumed that the only means of producing new genetic variance in bacteria is mutation; however, bacteria exhibit sexuality and show genetic recombination.) This might seem unlikely, but Thoday & Boam (1961) have shown that responses to selection may be remarkably regular, so this hypothesis is quite possible.
>
> 5. A new variety of bacilli was produced as the result of a recombinational event in the pathogen population of one of the patients and these bacilli were transmitted to the other patients. This hypothesis is open to the same objection as (2).
>
> 6. There was an environmental change that affected the resistance of all the patients to treatment. If such a drastic change in environment did occur it is difficult to see why the other patients were not affected " (Spickett, 1964).

According to Spickett the most likely hypothesis is that a strain of bacilli resistant to B663 occurred as a result of a recombinational event independently in all the relapsed patients who had been under treatment with B663 alone.

Although one may not be able to accept Spickett's conclusion, speculation about it might raise interesting questions to be solved when the culture of *M. leprae* becomes possible.

DISCUSSION

PTC, ABO, Rh, G6PD, haptoglobins, transferrins, Au(1), polymorphisms

As can be seen from the foregoing review, most of the geneticists interested in leprosy have written papers concerned with human polymorphisms—i.e., with inherited variations that may be related to disease susceptibility. Therefore, it can be said that leprosy has been used, in a blind fashion, for investigating whether this communicable disease is one of several forces that maintain different polymorphic systems discovered by hazard. Since only a few genetic markers are available in practice, the *a priori* probability of positive results in such a type of investigation is very low.

Do the higher frequency of blood group O among tuberculoid cases and the excess of PTC-tasters among leprosy patients, found by some investigators, reflect real associations, or are these results only a consequence of geographical variations in the distribution of genes? Whatever the answer, it makes no difference for practical purposes, for even if such correlations could be fully demonstrated, it is obvious that they would not be useful in the diagnosis or prediction of individual susceptibility or resistance to leprosy.

The only correlation whose existence seems to be unquestioned is the higher proportion of individuals with Au(1) antigen among lepromatous cases than among tuberculoid and normal people (Blumberg & Melartin, 1966). However, even this correlation is of little practical use in leprology. Moreover, no proof exists that the occurrence of Au(1) antigen is really an autosomal recessive trait. The fact that its presence is associated with diseases involving the reticuloendothelial system and/or white blood cells may reflect only a pathological condition and not a genotype manifestation correlated with a greater susceptibility to disease.

Pedigree analyses

The technique of pedigree analysis for the investigation of genetic mechanisms is more suitable for rare constitutional diseases. For the common traits it is useless because it will not, by itself, distinguish between a highly frequent recessive character and a dominant trait conditioned by a gene that is not fully penetrant. The technique is liable to lead to erroneous conclusions, even when one is dealing with rare constitutional diseases, because it involves the selection of single pedigrees or groups of genealogies from the literature. Moreover, when many generations are involved, it may be doubted whether the clinical information is correct for all members of the pedigree.

In view of these drawbacks, it seems hardly necessary to point out the fact that pedigree analysis is of little value in the search for genetic factors that may be involved in susceptibility to leprosy. Moreover, leprosy has a long incubation period, and the frequency of the disease is high in some populations. However, ignoring the unsuitability of the method for this purpose, some observations may be made about the results obtained by its use. It has been pointed out that the data collected do not fit the single-factor expectancies for susceptibility to leprosy. It is, therefore, risky to assume that susceptibility to leprosy is controlled by a dominant gene, in order to accept the two further hypotheses that this gene is not fully penetrant and that the forms of leprosy are controlled by a polygenic system.

Genetic studies related to the lepromin reaction

Data obtained with the lepromin test in family studies have also offered a monogenic explanation of susceptibility to leprosy. Contrary to the hypothesis formulated by Spickett (1962a), Beiguelman (1965) postulated that the gene for leprosy susceptibility is recessive, but the interpretation of his data may also be open to criticism.

The frequency of lepromin-positive subjects in the offspring of lepromatous couples was higher than would be expected in theory, necessitating the secondary hypothesis that this discrepancy was caused by incomplete penetrance of the genes, by the high frequency of illegitimacy among such offspring, and by the influence of BCG vaccination.

The observed and expected proportions (Table 2) were compatible with the hypothesis that susceptibility to leprosy is transmitted by a recessive gene on the basis of a further postulate—namely, that the frequency of homozygotes for the supposed recessive gene in the general population could be estimated from the frequency of clinically lepromin-negative responses among the partners of lepromatous patients.

However, the crucial point of criticism seems to be that, although the hypothesis that the lepromin reaction is genetically controlled is in some ways attractive, there is no guarantee of the hereditability of this trait. The demonstration that this reaction has a familial pattern (Beiguelman, 1962c; Beiguelman & Quagliato, 1965) may support, but is not a proof of, the theory that a genetic mechanism is responsible for the observed distribution.

Before the familial nature of the lepromin reaction was demonstrated, the hypothesis of its genetic causation was said to be supported by the following observations:

(1) Although newborn children show a negative lepromin reaction, most of them show the ability to give a positive reaction when further examined, although the time required to show such a reaction is variable. This ability seems in some cases to be acquired without any known environmental stimulus; in other cases it may depend upon previous sensitization by *M. tuberculosis* and/or *M. leprae*. Among adults the frequency of positive reactions is very high; from data on several populations that have been surveyed, it has been estimated to be about 80%.

(2) Experiments in which healthy lepromin-negative leprosy contacts were given periodic lepromin injections and BCG vaccination showed a few subjects who did not give positive responses in spite of being submitted to such sensitizing agents.

(3) Lepromatous patients are invariably lepromin-negative, while those suffering from the tuberculoid form of leprosy are invariably lepromin-positive; these characteristics cannot be changed by treatment.

(4) Histological study of the lesions and of the lepromin reaction in rats and guinea-pigs has shown that these animals can be used as models for the lepromatous and tuberculoid forms of leprosy. Experiments conducted in these species show that the ability (guinea-pigs) or inability (rats) of their macrophages to lyse *M. leprae* cannot be changed, at least not permanently.

(5) Macrophages obtained from lepromatous patients and maintained *in vitro* are unable to lyse *M. leprae* after phagocytosis, whereas those obtained from tuberculoid lesions are able to do so.

The first three observations listed above led Rotberg to suppose, in 1937, that the majority of human beings possess a hypothetical " natural factor ", probably inborn, and that a smaller group of human beings do not possess this factor. For simplicity he named this factor the " *N* factor ". People deprived of this factor would be members of an " anergic margin " and would permanently fail to give a positive lepromin reaction. On the other hand, those with this hypothetical factor would be lepromin-negative only temporarily, and would become lepromin-positive after sensitization by *M. leprae*, *M. tuberculosis*, BCG, or other sensitizing agents (Rotberg 1957a, 1957b).

As can be seen from points (2) and (3) above, the hypothesis that a positive lepromin reaction depends upon an inherited factor was based principally upon data obtained from leprosy contacts or from affected subjects. These data, however, may also support nongenetic interpretations, as recognized by Rotberg more recently: " It is also permissible to suppose that this defense-ability may depend upon some other unknown non-inherited factor that appears after birth " (Rotberg, 1957a). The same criticism can also be applied to observation (5), while no information exists for healthy individuals not related to leprosy patients.

In this connexion, the following questions arise:

(*a*) Accepting the existence of an " anergic margin" among the relatives of leprous persons does not mean that the same holds true for healthy people from the general population. In other words, although it is quite possible, it has not been proved that people unrelated to leprous patients would be permanently lepromin-negative in spite of being submitted to sensitizing factors such as BCG vaccination.

(*b*) Admitting the " anergic margin " to be a universal phenomenon would not mean that, in low-aged groups, factors such as BCG vaccination could not extinguish this margin by changing the pattern of response to lepromin. This possibility was suggested in an experiment conducted by Souza-Campos et al. (1962).

(*c*) If the possibility noted in (*b*) could be proved correct, it would not imply the absence of inherited factors controlling the lepromin reaction. For example, although left-handedness is considered to be caused by a hereditary factor, it is well known that a left-handed individual can be taught to become right-handed; furthermore, such a change is easier in early infancy. Similarly, although the ability to taste phenylthiourea and related compounds is beyond doubt an inherited trait, it is possible to change the individual taste-threshold by learning (Beiguelman, 1964c).

Consequently, it does not seem worth while to discuss the bias found in many of the data published for evaluating the so-called " anergic margin " in different populations (observation (2) above).

The only data that offer better support for the hypothesis that the lepromin reaction may be attributed to a genetic polymorphism of human populations are those obtained from observations in animals, chiefly the well-conducted experiments of Hadler (1953, 1956) and Hadler & Ziti (1953, 1955). Hadler used the rat and the guinea-pig as models for human populations, the rat representing the lepromin negatives and the guinea-pig the lepromin positives at a histological level. The results obtained support the view that the ability of macrophages to lyse *M. leprae* and their consequent changing into epithelioid cells can be clinically manifested only after sensitization. By studying the lepromin reaction in guinea-pigs, it was concluded that this sensitization may be provoked by *M. leprae*, *M. lepraemurium*, or *M. tuberculosis*. These agents are unable to induce a histologically positive lepromin reaction in rats, although it was demonstrated in these animals that positive clinical reactions without histological correspondence may occur as a consequence of hypersensitization.

These results were interpreted as a proof that hypersensitization by mycobacteria is reached only after the lysis of the bacilli by the macrophages. Therefore, guinea-pigs could be sensitized by all mycobacteria that were studied, while rats could be sensitized only by *M. tuberculosis*, since the other two species of mycobacteria are not lysed by their macrophages.

Since in human beings only indirect observations exist in support of Hadler's conclusions, it must be

added that unfortunately the mechanism of the late lepromin reaction in man is not fully understood. Consequently, some questions remain as matters for debate. For instance, when an individual who previously failed to respond to lepromin injections is changed into a lepromin-positive in further tests, it is not known whether the change is a consequence of (*a*) sensitization that allowed the lysogenic ability of the macrophages, present at birth, to be manifested macroscopically, or (*b*) a new ability to lyse *M. leprae* that was previously absent from the macrophages. Furthermore, it is not known whether or not there is a corresponding histological change. In any case it is not known whether the change is permanent or temporary.

With reference to possibilities (*a*) and (*b*), experiments conducted in rats and guinea-pigs support the view that environmental stimuli can only strengthen the ability of macrophages to lyse *M. leprae* in those who are constitutionally endowed for such lysis. However, no data in support of this view have been obtained from the study of human beings, apart from the observations that lepromatous cases cannot be converted into tuberculoid cases, and *vice versa*, and that some leprosy contacts are never changed into lepromin positives. It has been demonstrated in guinea-pigs and rats that drugs such as cortisone and a combination of chlorpromazine and promethazine can temporarily depress the ability of macrophages to lyse *M. leprae*, and that deoxycorticosterone stimulates this ability (Hadler et al., 1965). Therefore it may be asked if sensitizing agents might not be able to produce such stimulation, at least in a fraction of the population. Lysogenic ability could be a threshold phenomenon, and it might be possible to change the thresholds by " teaching " macrophages to lyse *M. leprae*.

With reference to the fact that it is not known if there is a histological change corresponding to an observed change in lepromin reaction, it would be necessary, in order to discuss this matter, to know the probability of finding histologically positive reactions in each class of lepromin response that is clinically analysed. The frequency and types of histological reactions in large samples have been investigated only in leprosy patients and, to a lesser degree, in healthy relatives of affected subjects (see, for example, Bechelli et al., 1959). Obviously, the frequency of histologically positive reactions in the different classes of macroscopic reactions cannot be used to estimate the frequency in the general population; for example, if a sample of lepromin-negative subjects is composed predominantly of lepromatous patients, a high correlation should be found between the clinical and histological readings. The same is true for the extremely positive reactions in a sample composed chiefly of tuberculoid patients.

Whether or not an observed change in lepromin reaction is permanent or temporary depends upon the constancy of the late lepromin reaction as clinically analysed. Data obtained from healthy leprous contacts are biased since if such subjects show a strong reaction (++ and +++) they are not submitted to further examination. Although not proved, it is believed that at least the +++ positive reactions have a histological correspondence. For this reason, individuals showing such reactions are, at least in Brazil, recalled for new tests only where there have been administrative mistakes. Normally, individuals with ++ and +++ reactions are systematically eliminated from retesting, and they cannot, therefore, provide information about the distribution of the differences between two consecutive reactions. Beiguelman & Quagliato (1964) have pointed out the wrong conclusions that can be drawn from such biased samples.

In vitro *studies of macrophages in relation to* M. leprae

As discussed previously, the fact that the *in vivo* ability or inability of macrophages is maintained *in vitro* cannot be considered as a proof that this trait is inherited. However, the data obtained in such work may be considered as important for the following reasons:

(1) It has been demonstrated that, in lepromatous patients, the absence of lysogenic ability of their macrophages is specific for *M. leprae*, since their macrophages are able to lyse *M. tuberculosis* and *M. lepraemurium*.

(2) The lysogenic inability of the macrophages of lepromatous individuals depends upon the integrity of the bacterial wall, since lysis can easily be observed when damaged *M. leprae* are added to cultures of such macrophages.

(3) The *in vitro* test devised by Beiguelman (1966) may be considered to be a refinement of the Mitsuda reaction that may facilitate the histological investigation of questions such as the following:

(*a*) whether or not the dimorphism found among lepromatous and tuberculoid patients also exists among healthy people;

(*b*) the pattern of reactions among clinically characterized leprosy variants;

(*c*) the possible existence of lysogenic thresholds, based on the speed of lysis of *M. leprae* by macrophages from healthy people; and

(*d*) the enzymatic differences between macrophages that can lyse and those that cannot lyse *M. leprae*. Although the results of studies of lesions are open to question, Hadler (1965) found that guinea-pig and rabbit macrophages (which are able to lyse *M. leprae* and *M. lepraemurium*) show high phosphatase (alkaline and acid) and lipase activity, while rat macrophages (which have no lysogenicity for those bacilli) have low phosphatase and lipase activity. This is a most important problem that merits further study, since it is possible that the enzyme system required to lyse leprosy bacilli may depend upon the lysosomes. Experience with cortisone—which, as is known, is a powerful agent inhibiting lysosomal function—also supports this view.

Response to chemotherapy and genetic variability of M. leprae

As noted previously, genetic interpretations of drug resistance in leprosy are possible only on speculative grounds, simply because it is not yet possible to culture *M. leprae*. The mouse footpad inoculation technique, while making it possible to detect drug-resistant strains of *M. leprae*, does not give the information necessary for genetic interpretations.

For practical purposes, the evidence of drug resistance in leprosy bacilli is not sufficient to justify the routine use of two or more drugs in combination, as has been suggested. According to Pettit & Rees (1964) the frequency of diaphenylsulfone resistance is very low. They estimate that probably 3 cases of diaphenylsulfone resistance have arisen among about 5000 patients with lepromatous leprosy; thus, their conclusion that drug resistance, at least to diaphenylsulfone, is not numerically important may be accepted.

CONCLUSIONS

It has been seen that geneticists have made few contributions to the solution of the problems presented by leprosy. It is regrettable that some clinical leprologists, perhaps impressed by the jargon and methods used by geneticists, may have expected too much from genetic work. However, it should be remembered that the few geneticists who are interested in leprosy have been working in this field only since 1962. This does not mean, of course, that if more of them had done so, they would have solved the major problems of leprosy. This is a realistic rather than a pessimistic point of view.

In any case, genetic studies related to leprosy have drawn attention to an old question—why, since the discoveries of Mitsuda and Hayashi, has there been no significant progress in the understanding of the late lepromin reaction in man? In spite of all the well-known deficiencies of lepromin, the only trait known to be completely associated with leprosy is the Mitsuda reaction—which clinical and epidemiological observations have shown to have undoubted prognostic value. Moreover, it is very likely that this reaction may depend upon a genetic factor.

Apart from its practical significance, the Mitsuda reaction has limited theoretical importance, since it is a complex reaction that cannot easily be related to an individual genotype. Consequently, it may be argued that it would be of doubtful validity to begin genetic work on the basis of a reaction whose mechanism is not clearly understood. Therefore, while awaiting systematic investigation of the mechanism of the Mitsuda reaction by teams composed of immunologists, biochemists, cytochemists, clinical leprologists, pathologists, and epidemiologists, either of the following courses could be pursued:

(1) Discouragement of research on the lepromin reaction and emphasis on the search for associations of leprosy with all possible polymorphic traits, and on speculation concerning genetic factors involved in *M. leprae* and its influence on the pathogenesis of leprosy, the effect of such factors on epidemiological studies, etc. Obviously, this does not seem to be the better course.

(2) The undertaking of a programme that might contribute to understanding of the mechanism of the lepromin reaction and that might accumulate information that would be useful in the future. However, such a programme would be neither short-term not economical. It can be summarized as follows:

(*a*) Investigation of types of response to lepromin at clinical, histological, and *in vitro* levels, in monozygotic and dizygotic twins as well as in sib pairs. This type of study will not give information about a specific mode of inheritance but could give information on the possible existence of an inherited factor for the Mitsuda reaction and evaluate the importance of such a factor in the manifestation of the response to lepromin.

(*b*) Investigation of the probable dimorphism in the reaction to leprosy bacilli among healthy individuals who are not related to leprosy patients, using the technique of differentiation of blood monocytes into macrophages. If the supposed dimorphism were found to exist, the proportion of lysers and non-lysers of *M. leprae* in different age-groups should be investigated, as should the possibility of heterogeneity between the sexes.

(*c*) Investigation of possible lysogenic thresholds and of their distribution. For example, if the distribution were bimodal it would be ascribed, before familial analysis were conducted, to monogenic inheritance of the trait. Depending upon the results of these studies, attention would be given to the factors that are able to modify such thresholds and to whether or not different forms of leprosy are dependent on this phenomenon.

(*d*) Studies of complete families involving leprosy cases, including clinical and histological examination of the type of the disease, clinical evolution of the disease, and study of the lepromin reaction of each family member at clinical, histological, and *in vitro* levels in order to look for patterns of family occurrence. Since it is suspected that illegitimacy is very high in the offspring of leprosy patients, it would be advisable to determine the blood group of each family member.

RÉSUMÉ

Examinant les résultats d'études sur l'association éventuelle de la lèpre et de certains marqueurs génétiques, l'auteur analyse une série de données sur la sensibilité gustative à la phénylthiourée, les groupes sanguins ABO et Rh, la carence en glucose-6-phosphate déshydrogénase, les haptoglobines, les transferrines et l'antigène « australien » (Au(1)). Cette analyse montre que, malgré l'existence possible d'une faible corrélation entre certains de ces marqueurs (sensibilité gustative à la phénylthiourée, groupe O et antigène Au(1)) et la lèpre, la connaissance de ce genre de faits n'est pas utile en pratique, car elle n'aide pas le léprologue à attribuer à tel ou tel facteur la résistance ou la sensibilité individuelle des sujets à la lèpre.

L'emploi d'analyses rétrospectives des arbres généalogiques dans les études sur la lèpre est condamné. On souligne en premier lieu qu'elles peuvent être sélectives et comporter des données cliniques incomplètes, et qu'en outre elles ne conviennent pas aux recherches génétiques sur la lèpre car il s'agit d'une maladie infectieuse qui a une longue période d'incubation, une grande fréquence dans certaines populations et se manifeste sous plusieurs formes cliniques. On ne peut donc accepter l'hypothèse, fondée sur ce type d'études, que la lèpre est conditionnée par un gène dominant à pénétrance incomplète.

En ce qui concerne les enquêtes sur la fécondité et la lèpre, on relève que, si le taux de stérilité parmi les lépromateux de sexe masculin est très élevé, cette maladie n'affecte pas la fécondité chez les femmes lépromateuses. Comme la stérilité chez les hommes survient généralement à la suite d'orchi-épididymites, on ne trouve aucune différence entre la fécondité de la fraction fertile et celle des individus normaux.

Il convient de noter l'impossibilité de faire des études génétiques et épidémiologiques sur la base d'une variabilité génétique de *Mycobacterium leprae* car on n'a pas réussi jusqu'à maintenant à le cultiver. Pour la même raison, les explications du mécanisme de la résistance de *Myco. leprae* aux médicaments ne peuvent être que des spéculations. L'analyse des études sur la distribution de la réaction tardive à la lépromine (réaction de Mitsuda) dans des familles permet de conclure que la distribution des réponses à la lépromine peut être considérée comme un caractère familial étant donné qu'il y a une forte corrélation entre les réactions chez les descendants et dans la génération des parents. Les enfants nés de parents négatifs à la lépromine sont plus enclins à ne pas présenter la réaction de Mitsuda.

L'auteur discute la valeur de l'analyse des données familiales sur la réaction de Mitsuda comme moyen de vérifier l'hypothèse d'une transmission monogénique, et critique l'hypothèse de l'existence d'un gène récessif de sensibilité à la lèpre. Après avoir souligné l'importance de la réaction de Mitsuda et donc la nécessité de mieux la connaître, il propose un programme de recherche grâce auquel les généticiens pourraient contribuer à une meilleure compréhension de la réaction, et montre l'utilité de l'application d'une nouvelle technique pour évaluer la résistance à la lèpre. Cette technique est fondée sur la transformation *in vitro* des monocytes sanguins en macrophages et sur l'observation de leur comportement vis-à-vis de *Myco. leprae*.

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