# THE GENETICS OF RESISTANCE TO LEPROSY[1,2]

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The familial character of the macroscopically positive late lepromin reaction (LR) has been shown previously[1,2]. It was observed that in children failure of late response to lepromin is more frequent in families in which both parents are LR-negative. This intra-familial relationship seems to depend upon a genetic background, for it is known that environmental agents are not capable of changing the lysogenic capacity of macrophages for *M. leprae*. Thus, as a general rule, lepromatous patients are never changed into tuberculoid patients. This fact permits a tentative hypothesis to explain the familial nature of the late lepromin reaction on a genetic basis. Since most children born to LR-negative parents are also LR-negative, a recessive autosomal gene in homozygosis may be postulated as responsible for the inability of the macrophages to lyse *M. leprae*. There is great risk, however, in accepting a hypothesis based on such data, because the familial character reflects both histologic reaction and the influence of environmental factors. These difficulties may be circumvented by clinical investigation of the familial distribution of the late lepromin reaction among the relatives of leprosy patients (leprosy contacts). Such subjects in fact, are more intensely exposed to sensitizing agents, such as repeated lepromin inoculations, BCG vaccination, and primary infections by *M. leprae*, than are persons in the general population. It may be expected, therefore, that this situation would strengthen the correlation between the macroscopic and microscopic reactions provoked among leprosy contacts by injection of lepromin.

## MATERIALS AND METHODS

Three groups of parents were analyzed:

Group 1. Each parent exhibited a positive lepromin late reaction.

Group 2. One parent gave a positive late lepromin reaction while the other was LR-negative.

Group 3. Each parent was LR-negative.

Group 1 included 41 families in which one parent was affected by the tuberculoid form of leprosy (LR +++), while the other was a healthy person showing a late lepromin reaction (LR +++).

Group 2 included 35 families in which one parent was affected by lepromatous leprosy (LR −), while the other was healthy, showing a positive reaction (LR +++).

Group 3 included 24 families in which both parents were lepromatous.

In each of these families there were at least two children. All families were under the medical control of the Leprosy Dispensaries of Campinas and Santos, State of São Paulo, Brazil.

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A genetic hypothesis was formulated, based on the assumption of an autosomal fully dominant gene accounting for the ability of macrophages to lyse *M. leprae*. The method suggested by Fisher (4) was considered applicable to the data since in the population the rate of positive late lepromin reaction was high.

According to this method the total number of families all of whose offspring belong to the dominant phenotype, when both parents are known to be dominant, may be calculated as follows:

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

The total expected number of families all of whose offspring belong to the dominant type, when only one parent has the dominant phenotype, may be calculated according to the following formula:

$$\sum N_s[(p/p + 2q) + (1/2)^s (1 - p/p + 2q)]$$

In each formula N stands for the observed number of families of size s, and p for the frequency of the dominant gene, while $q = 1-p$ represents the frequency of the recessive gene.

The expected number of families with at least one late lepromin reaction among the children is determined by subtracting from the total number of families the number of families in which all of the children exhibit a positive late lepromin reaction.

The frequency of LR-negative cases, plus the cases of leprosy resulting from contagion among subjects married to leprotic partners, is about 25 per cent (unpublished data). This value can be taken as an estimate of the proportion of the recessive homozygotes in the general population. Under the assumption that mating is at random, $q^2$ would be equal to 0.25 and p and q estimated as 0.50.

Children with a weak late lepromin reaction (LR +) and children with strong reactions (LR ++ and LR +++) were pooled in the calculations, in the light of the following facts: (1) the frequency of weak reactions (LR +) among the children was very low; (2) the intensity of the late lepromin reaction is correlated with age groups, and (3) the age variation in the sample was high.

## RESULTS AND CONCLUSIONS

Data on the observed and expected number of families with at least one parent presenting a positive late lepromin reaction, in which all of the children exhibited a late lepromin reaction, are presented in Table 1. The table shows that the data permit the hypothesis of an autosomal gene pair responsible for the late lepromin reaction. The results support the hypothesis that the ability of macrophages in an individual to lyse *M. leprae* depends on the presence of a completely dominant gene.

Under the circumstances indicated it may be expected that children born to lepromatous parents would all be LR-negative. Actually, although a high frequency of negative reaction was found among these children (Table 2), the extent was not total, as would be expected on the basis of the hypothesis formulated. The discrepancy, however, represented by a figure of 30.9 per cent for a macroscopically positive late lepromin reaction among the offspring of lepromatous parents, can be explained by the following additional relevant factors:

1. BCG vaccination may induce the requisite sensitization for a macroscopically positive late lepromin reaction even among lepromatous subjects (3, 6), in spite of the fact that neither clinical nor

TABLE 1.—*Genetic analysis of late lepromin reaction assuming dominant inheritance, according to Fisher's method*[4].

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

TABLE 2.—*Distribution of the offspring born to lepromatous couples according to the macroscopically late LR and the leprosy contagion.*

| LR | Healthy | Leprosy patients | | | Total | |
|---|---|---|---|---|---|---|
| | | L | I | T | No. | % |
| − or ± | 20 | 28 | 4 | — | 52 | 64.2 |
| + | 4 | — | — | — | 4 | 4.9 |
| ++ | 12 | — | — | — | 12 | 14.8 |
| +++ | 10 | — | 1 | 2 | 13 | 16.1 |
| Total | 46 | 28 | 5 | 2 | 81 | 100.0 |

L = lepromatous I = indeterminate T = tuberculoid

bacteriologic changes may be evident (6). Macroscopically positive late lepromin reactions, without active participation of macrophages, have been fully demonstrated in rats (5).

2. Depending on the penetrance of the gene for the lysogenic ability of the macrophages, it may be expected that a fraction of phenotypes unable to lyse *M. leprae* would have the dominant genotype. Therefore marriages in which each partner was LR-negative might produce LR-positive children.

3. The frequency of illegitimate children appears to be higher among the offspring of leprosy patients than in the general population. This fact cannot be ignored in explaining the dominant phenotype among the offspring of lepromatous parents.

There are no empiric data in support of any of these several factors, which may be combined in their operation, or alternative. Work on the possibilities concerned is in progress.


## SUMMARY

The late lepromin reaction was investigated among children of persons with polar, i.e., lepromatous and tuberculoid, types of leprosy. The data secured correspond with the view that the lysogenic capacity of macrophages for leprosy bacilli is a dominant trait, provided that allowance is made for a discrepancy found among children born to parents each of whom is lepromatous. The exception to the postulated inheritance may be ascribed to the influences caused by BCG vaccination, incomplete penetrance of the gene for leprosy resistance, and illegitimacy among the offspring of leprosy patients.

## RESUMEN

Fué investigada la reacción tardia de la lepromina entre hijos de personas con tipos de lepra polar, i.e., lepromatosa y tuberculoide. Los datos obtenidos corresponden con el punto de vista de que la capacidad lisogénica de los macrófagos para los bacilos leprosos es el rasgo dominante, provisto de que se haga una concesión para la discrepancia encontrada entre los hijos de padres cada uno de ellos lepromatosos. La excepción a la postulada herencia puede ser adscripta a la influencia causada por la vacunación BCG, incompleta penetrance del gen para la resistencia leprosa e ilegitimidad entre la prole de pacientes lepromatosos.

## RESUME

La réaction tardive à la lépromine a été ètudiée chez des enfants de personnes atteintes d'un type polaire de lèpre, c'est à dire de lèpre lépromateuse ou de lèpre tuberculoide. Les données obtenues concordent avec l'hypothèse qui fait de la capacité lysogénique des macrophages pour les bacilles de la lèpre un caractère dominant, du moins si l'on néglige une discordance notée chez les enfants nés de parents qui sont tous deux atteints de lèpre lépromateuse. L'exception ainsi faite au postulat de la transmission héréditaire de cette caractéristique peut être attribuée à l'influence de la vaccination par le BCG, à la penetrance incomplète du gène responsable de la résistance à la lèpre, ou à des naissances illégitimes parmi les enfants des malades de la lèpre.


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