

NATURE AND FAMILIAL CHARACTER OF THE LEPROMIN REACTIONS^{1, 2}

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Bacillary destruction, i.e., lysis, within macrophages is the essential condition for the development of hypersensitivity; the development of epithelioid cells is a consequence of that lysis (⁷). It has been demonstrated that in guinea-pigs the three species of mycobacteria *M. tuberculosis*, *M. leprae*, and *M. lepraemurium* have the capacity to provoke hypersensitivity demonstrable by tuberculin injections (⁹). It is believed that this fact indicates chemical similarity in their antigenic structure. Although lysogenic action upon *M. leprae* is exhibited by the macrophages of normal guinea-pigs, a macroscopically positive late lepromin reaction is observed in these animals only after hypersensitization (⁸). The lepromin used in these tests (⁸) contained about 0.74 mgm. of *M. leprae* per ml., and was prepared according to Hayashi's technic (³). Macrophages of rats do not display lysogenic properties against *M. lepraemurium*, but even in rats macroscopically positive lepromin reactions have been induced after BCG vaccination (¹⁰). In each experimental situation the macroscopic-positive state was a consequence of an increase of the tissue reaction, but no cytologic changes have been detected (^{8, 10}).

In contrast with animal species, human populations show a dimorphism in reacting to leprosy bacilli. Lysogenic capacity in man appears to have a hereditary background, first, because, as a general rule, it is impossible to change the lepromatous form of leprosy to the tuberculoid form, and secondly, because the macroscopically positive late lepromin reaction has been shown to be a familial trait. Children with negative lepromin reaction are more frequent among families in which both parents are negative in the lepromin reaction (⁵). On these grounds human beings can be classified as lysers and nonlysers of *M. leprae*. The behavior of macrophages among the lysers appears to be similar to that of guinea-pigs, while among the nonlysers the macrophages seem to react like the corresponding cells in rats (⁷). It seems likely, therefore, that experimental results observed in animals may also hold for man. By this analogy, on the basis of results in animals, sensitization would be induced in lysers by both *M. leprae* and *M. tuberculosis*, while in nonlysers sensitization would be effected by *M. tuberculosis*

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but not by *M. leprae*. Since hypersensitivity can be made evident by means of tuberculoproteins and leproproteins in each case, an association of the early lepromin reaction with the Mantoux reaction may be expected. Similarly macroscopic manifestation of the histologically positive late lepromin reaction would depend upon a previous sensitization by *M. tuberculosis* or *M. leprae*, enhancing the lysogenic capacity of the macrophages. If that hypothesis is valid, observation of an association between the late lepromin and Mantoux tests is to be expected.

In practice, however, high correlations are not to be anticipated. Discordant and discrepant cases are expected including (1) positive early lepromin reaction and negative Mantoux reaction, (2) negative early lepromin reaction and positive Mantoux reaction, (3) positive late lepromin reaction and negative Mantoux reaction, and (4) negative early lepromin reaction and positive late lepromin reaction. These may be explained as follows:

1. A strong stimulation by leprosy bacilli is required for demonstration of hypersensitivity to leproproteins by means of the tuberculin test (⁹). Tuberculoproteins, moreover, are less efficacious than bacillary suspensions in the detection of hypersensitivity (^{1, 2}). For this reason, subjects giving a positive late lepromin reaction and/or an early lepromin reaction may not respond to the Mantoux test.

2. Leproproteins occur in low and variable concentration in lepromin. Therefore subjects hypersensitized by *M. tuberculosis* and/or *M. leprae* (i.e., exhibiting a positive Mantoux reaction and/or a positive late lepromin reaction) may not show a positive early lepromin reaction on injection, especially if the lepromin is of low bacillary content.

If the lepromin used for testing has a low content of leprosy bacilli, the correlation of the early lepromin reaction and the Mantoux test should be higher among persons with a macroscopically positive late lepromin reaction. Cases of tuberculosis are found infrequently in rural areas, in contrast to cases of leprosy, which are numerous in rural populations in Brazil. It may therefore be supposed that persons living in such areas, who give macroscopically positive late lepromin reactions, are more frequently lysers who have been made hypersensitive by *M. leprae*. A strong stimulation by leprosy bacilli, however, is necessary for the demonstration by the tuberculin test of hypersensitivity to *M. leprae*. For this reason, persons exhibiting a late lepromin reaction, even with poor lepromin, may be expected to be strongly sensitized, and more prone to exhibit both the Mantoux reaction and an early lepromin reaction.

Since it has been demonstrated that the macroscopically positive late lepromin reaction is a familial trait (⁵), the same may be expected for the early lepromin and the Mantoux reactions.

In the present paper the associations of the lepromin and Mantoux

TABLE 1.—Association between the lepromin and Mantoux reactions.

Reactions	Negative negative	Negative positive	Positive negative	Positive positive	Total	χ^2 ; 1 d.f.
Late LR—early LR	374	39	168	62	643	34.22; $P < 0.001$
Late LR—Mantoux reaction	363	50	169	61	643	21.49; $P < 0.001$
Early LR—Mantoux reaction	467	75	65	36	643	28.34; $P < 0.001$

TABLE 2.—Association between the early lepromin reaction and Mantoux reaction among the subjects with macroscopically positive and negative late lepromin reaction.

Late lepromin reaction	Reactions analyzed	Negative negative	Negative positive	Positive negative	Positive positive	Total	χ^2 ; 1 d.f.
Positive	Early lepromin reaction —Mantoux reaction	140	31	29	30	230	24.09; $P < 0.001$
Negative	Early lepromin reaction —Mantoux reaction	328	43	35	7	413	0.91; $P > 0.70$

reactions, and their distribution among families, have been investigated, in order to furnish information on the nature of lepromin reactions in man.

MATERIALS AND METHODS

Subjects in a random sample of 100 families living in a Brazilian rural area (Cosmopolis, State of São Paulo) were inoculated on the volar surface of the right arm with 0.1 ml. of lepromin prepared according to the Mitsuda-Hayashi technic⁽³⁾. Mantoux tests were made on the volar surface of the left arm by injection of 1:1,000 tuberculin. All of the tests were made by one of the authors (R.Q.). A census was conducted in the studied area prior to the sampling in order to include only white, complete, unrelated families of larger size.

Since a large proportion of clinically weak positive lepromin reactions (+) may not be correlated histologically, reactions of this strength have been disregarded by leprologists. For the purposes of the present study, however, the weak and strong reactions have been pooled. The lepromin available for this study had a relatively low bacillary concentration (0.4 mgm. per ml.). On this basis the development of a conspicuous infiltrative element, 3 mm. or more in diameter, was considered as positive for a late lepromin reaction. The presence of an infiltrative erythematous halo, 10 mm. or more in diameter, was considered as positive for the early lepromin reaction. The Mantoux reaction was considered positive if an infiltrate exceeding 10 mm. in diameter was observed.

The early lepromin and Mantoux reactions were read 48 hours after injection. The late lepromin reaction was read 30-40 days after lepromin injection.

RESULTS

As expected, an association was demonstrated among the three reactions (Table 1). Data presented in Table 2 show a strong correlation of the early lepromin reaction and the Mantoux reaction only among subjects exhibiting a macroscopically positive late lepromin reaction. A correlation was not detected among subjects not giving a late lepromin reaction.

In Table 3 marriage types are classified in three categories with respect to the responses observed in each of the skin tests performed. These categories are: (1) positive vs. positive; (2) positive vs. negative; (3) negative vs. negative. In the absence of relationship between the responses in parents and children the frequency of positive reactions among the offspring should be similar for the three marriage categories considered. However, Table 3 shows a positive correlation for each lepromin test, but not for the Mantoux reaction. This situation suggests strongly an intrafamilial relationship for the lepromin reaction.

DISCUSSION AND CONCLUSIONS

The evidence here presented seems to support Hadler's hypothesis that in their basic mechanism of response toward leprosy bacilli, lepromin reactions in man vary in a way similar to that of guinea-pigs (lyzers) and rats (nonlyzers). The early lepromin reaction may be expected in all persons properly sensitized by the injection of leproproteins derived from the destruction of leprosy bacilli. Since lepro-

TABLE 3.—Distribution of the macroscopically late lepromin reaction, early lepromin reaction and Mantoux reaction among children born to 100 families classified according to marriage types.

Marriage types	Late lepromin reaction			Early lepromin reaction			Mantoux reaction		
	Number of families	Number of children	Negative children	Number of families	Number of children	Negative children	Number of families	Number of children	Negative children
			No.			%			No.
Positive x positive	28	123	64 52.0	8	32	19 59.4	12	49	44 89.8
Positive x negative	48	215	164 76.3	27	112	90 80.4	43	197	173 87.8
Negative x negative	24	105	89 84.8	65	299	276 92.6	45	197	182 92.4
Total	100	443	317 71.6	100	443	385 86.9	100	443	399 90.1
Independence— test χ^2 ; 2 d.f.			34.30 ; P < 0.001			33.02 ; P < 0.001			2.25 ; P > 0.30

proteins are present in low and variable concentration in lepromin, it is not to be expected that nonlysers would frequently exhibit an early lepromin reaction. As a matter of fact, it is well known that the frequency of a positive early lepromin reaction is very low in lepromatous patients. It is reasonable, therefore, to suppose that lepromatous patients exhibiting an early lepromin reaction have been hypersensitized by *M. tuberculosis* or some other unknown agent.

The hypothesis is attractive that the familial nature of the late lepromin reaction (Table 2) would reflect both histologic reactive capacity, probably determined on a genetic basis, and the influence of environmental factors, i.e., previous sensitization by one of at least two mycobacterial species, *M. tuberculosis* and *M. leprae*. Certain other facts support this hypothesis: BCG vaccination (¹¹) or repeated lepromin injections (⁶) will induce sensitization shown by a late lepromin reaction among subjects previously lepromin-negative. As in the case of the finding reported by Hadler and Ziti for rats (¹⁰), a positive late lepromin reaction without histologic correspondence has been described for man (⁴). In contrast, the familial nature of the early lepromin reaction (Table 2) tends to reflect environmental influences, since positive early lepromin reactions may be found among hypersensitized nonlysers.

The question may be raised, however, why a familial correlation was not observed in the case of the Mantoux reaction, since *M. leprae* can sensitize for the tuberculin test. A possible explanation is as follows:

Since tuberculosis cases are unknown in the rural area surveyed, positive Mantoux sensitivity may be expected, among subjects randomly sensitized, through urban contacts, as well as among subjects with more intense exposure to leprosy bacilli. Prolonged exposure to *M. leprae* would provide the strong stimulation required for the demonstration of hypersensitivity to *M. leprae* by the tuberculin test. Since in each case there is a correlation with age, positive responses to the Mantoux test would be correlated particularly with high age, a situation probably responsible for the independence of marriage type and the distribution of reactions in the offspring. It is noteworthy that among the 111 subjects reacting positively in the Mantoux test 60.4 per cent were of the parental generation offspring.

SUMMARY

The distribution of lepromin and Mantoux reactions was investigated in a randomized sample of 100 families living in a Brazilian rural area (Cosmopolis, State of São Paulo). A census was conducted in the studied area prior to the sampling in order to include only white, complete, unrelated families of larger size.

Analysis of the data collected supports the following hypotheses:

1. The early lepromin reaction may be considered as an allergic response to leproproteins contained in lepromin.
2. The macroscopically positive late lepromin reaction reflects both the capacity of the subject's macrophages for lysing leprosy bacilli, and the influence of sensitizing agents stimulating the lysogenic ability of the macrophages.
3. The lysogenic capacity of macrophages probably has a hereditary basis.

RESUMEN

Ha sido investigada la distribución al azar de las reacciones a la lepromina y Mantoux en 100 familias que viven en un area rural brasilera (Cosmopolis, Estado de San Pablo). Previamente se realizó un censo en el area en orden de incluir solamente familias blancas, completas, grandes y que no tuvieren relación.

El analisis de los datos coleccionados apoyan la siguiente hipótesis:

1. La reacción temprana de la lepromina puede ser considerada como una respuesta alérgica a las leproproteínas contenidas en la lepromina.
2. La reacción tardía positiva macroscópica refleja tanto la capacidad de los macrófagos del sujeto para lisar los bacilos leproso como la influencia sensibilizante de los agentes que estimulan la habilidad lisogénica de los macrófagos.
3. La capacidad lisogénica de los macrófagos probablemente tiene una base hereditaria.

RÉSUMÉ

La distribution des réactions à la lépromine et des réactions de Mantoux a été étudiée dans un échantillon de 100 familles vivant dans une région rurale by Brésil (Cosmopolis, Etat de Sao Paulo), choisie au hasard. Avant de procéder à l'échantillonnage, un recensement avait été mené dans la région étudiée, afin de n' inclure dans leur totalité que des familles larges, constituées par des individus de race blanche, et non apparentées entre elles.

L'analyse des données recueillies s'accorde avec les hypothèses suivantes:

1. La réaction précoce à la lépromine peut être considérée comme une réponse allergique aux leproproteines contenues dans la lépromine.
2. La réaction positive tardive à la lépromine qui se manifeste de façon macroscopique témoigne à la fois de la capacité des macrophages de l'individu à détruire les bacilles de la lèpre et de l'influence d'agents sensibilisants qui stimulent de pouvoir lysogénique des macrophages.
3. La capacité lysogénique des macrophages repose probablement sur une base héréditaire.

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