

SIGNIFICANCE OF THE RELATIONSHIP BETWEEN THE  
LEPROMIN AND TUBERCULIN REACTIONS IN LEPROSY  
CONTACTS

LEPROSY INFECTION; LEPROSY DISEASE; PRIMARY COMPLEX<sup>1</sup>

NELSON SOUZA CAMPOS, M.D., JOSÉ ROSEMBERG, M.D.  
AND JAMIL N. AUN, M.D.  
São Paulo, Brazil

Leprosy is regarded as a disease of low contagiousity. This concept is based on statistics that indicate low percentages of leprosy in contacts of patients. However, our observations show that in young children of leprosy parents the incidence is much higher than is shown by the statistics, although at that stage of life the benign tuberculoid type predominates.

If the frequency of tuberculoid cases is high, higher still is the proportion of the contacts who are resistant to the disease and lepromin positive because of a primary infection with leprosy, without evident manifestations of the disease. To this specific immunity must be added a state of cross resistance or immunity resulting from a primary infection with tuberculosis. These two factors—one of them specific, occurring especially in contacts of patients with infectious leprosy, and the other nonspecific or cross, more common because it is caused by a disease of greater contagiousity and greater prevalence—are in reality the reason for the low frequency of leprosy among the general population.

Studies of young children in preventoria provide information regarding the pathogenesis of the disease when consideration is given the results of the tuberculin and lepromin tests. These children, having been in contact with active sources of the disease for relatively long periods, are to be regarded as infected, and it is possible to determine, not only the real frequency of the disease, but also the numbers of individuals who are resistant, lepromin positive, and those who are susceptible, lepromin negative. Thus can be established the situations of *leprosy infection* and of *leprosy disease*, with and without resistance, as can be done in tuberculosis.

In tuberculosis, thanks to the tuberculin test, we can determine very closely the index of infection of a community. The tuberculin reaction being absolutely specific, a positive response always indicates—excluding BCG-vaccinated individuals—previous natural contact with the Koch bacillus and hence a “tuberculized” individual whose infection may or may not be demonstrable by x-ray examination. The tuberculin reaction is one of

<sup>1</sup> The manuscript of this article was supplied with an English translation of the discussion and conclusions; the rest of it was translated in the JOURNAL office. The terms “leprosy-infection” and “leprosy-disease,” hyphenated and in quotation marks to emphasize the concepts of infection without clinical manifestations and infection with lesions of the disease, appeared throughout the manuscript.—EDITOR.

hypersensitivity, which may or may not correspond to a state of immunity. Positivity may persist for life if contacts with the tubercle bacillus are repeated, or it may weaken and finally disappear if no new contacts are made. Tuberculin allergy being a state of hypersensitivity, it is generally more harmful than beneficial.

In tuberculosis, in spite of the progress made in the field of immunobiology, there is no test for resistance. By the positive tuberculin reaction, in the absence of clinical and radiologic signs, we can detect the tuberculized persons; and by the same test and clinical, laboratory, and especially by the x-ray evidence, we can tell those who have tuberculosis. Thus can be established with assurance a distinction between tuberculosis *infection* and tuberculosis *disease*.

Anatomopathologic and other findings reveal a considerable number of primary-infected persons who are healed, with the *complexo duro* (calcification), and who had not known they had had the disease. Thus we see that also in tuberculosis there are individuals who present a state of resistance to the infection, healing spontaneously, besides evolutive cases of variable severity.

Careful study of the young children of the Jacaré and Goiânia preventoria from the clinical and immunoallergic points of view as regards leprosy reveals an identical situation. There is no test for allergy in leprosy, but there is one which, if positive, reveals a state of resistance or immunity, and, if negative, a state of susceptibility. In tuberculosis we cannot predict the developments in a tuberculin-positive case, which may exhibit a state of resistance to the disease with a tendency to cure, or an unfavorable condition with a progressive tendency. In leprosy, on the contrary, a positive Mitsuda reaction always indicates a state of resistance, relative or absolute, whether it be among healthy persons or among patients. A negative response to lepromin in healthy people, may indicate, the absence of previous contagion or absence of resistance, while in leprosy contacts it indicates essentially a predisposition with tendency—when it does not remain a state of leprosy infection—to the clinical development of leprosy disease.

A positive Mitsuda reaction may occur in the presence or absence of tuberculin hypersensitivity. If it is positive in a case which certainly has had no contact with a leprosy patient, then we think of tuberculosis as the cause of the state of cross resistance or immunity. If, in the first place, the tuberculin reaction also is positive, it is more than evident that the tuberculosis infection is the cause of the immunity. If, on the other hand, the tuberculin reaction is negative, tuberculosis infection as the cause of a cross immunity cannot be ruled out entirely, since as has been said a certain number of persons with primary Koch-bacillus infections lose their tuberculin hypersensitivity with the passing of the years, while the immunity persists. Nevertheless—although this has not yet been demonstrated—the existence of other factors capable of producing cross im-

munity against leprosy should be borne in mind, at least as a working hypothesis.

It is an accepted concept that the tuberculosis infection and the tuberculosis disease confer a state of resistance to leprosy infection. This view has been perfectly demonstrated in a study of ambulatory tuberculosis cases. Tuberculosis-contact children who were healthy and tuberculin-sensitive, or who had evolutive tuberculosis, or who were in a state of clinical cure, but who had no family history of leprosy, showed over 90 per cent lepromin positivity—not counting those who had been vaccinated with BCG. Thus in leprosy there is, besides a state of specific resistance conferred by leprosy infection, a state of cross resistance or immunity due to tuberculosis infection.

Based on these concepts, as revealed by the clinical and immuno-allergic study of preventorium children of leprosy parents who had had long contact with parents suffering from the infectious form of the disease, and confirmed by the findings mentioned above, there is presented the following tabulation (Table 1) which we will proceed to explain and justify.

TABLE 1.

Tuberculin reaction	Lepromin reaction	Leprosy contagion	Tuberculosis contagion	Immunoallergic and clinical condition
—	—	—	—	Unaffected.
—	—	+	—	Leprosy infection. Predisposition or susceptibility.
—	+	+	—	Leprosy infection. Specific resistance or immunity.
+	—	+	+	Tuberculosis and leprosy infection. Susceptibility to leprosy; probably latent leprosy.
+	+	+	+	Tuberculosis and leprosy infection. Specific and cross resistance.
+	+	—	+	Tuberculosis infection. Cross resistance to leprosy.
+	—	—	+	Tuberculosis infection. Leprosy-receptive.

TUBERCULIN-NEGATIVE AND LEPROMIN-NEGATIVE; NO CONTACT WITH  
TUBERCULOSIS OR LEPROSY

Persons negative to both tuberculin and lepromin, with no known contact with either tuberculosis or leprosy, are unaffected persons. Their future depends on the capacity of the organism to react when it is faced



with its first contact with the bacillus of tuberculosis or of leprosy. The capacity to react is congenital, and may be revealed either positively, thereby creating a state of resistance (presence of the "N" factor of Rotberg,) or negatively, i.e., as a lack of the capacity of antibody formation, which constitutes a state of susceptibility to infection. Absolute anergy, and likewise absolute immunity, are exceptional. There are variations between the two extremes conditioned by various factors, intrinsic or extrinsic.

#### CONTACT WITH LEPROSY WITHOUT TUBERCULIN SENSITIVITY

1. *Lepromin-positive*.—A positive Mitsuda reaction in a contact with a patient with a lepromatous leprosy, without previous contact with the Koch bacillus and therefore tuberculin negative, indicates a state of specific resistance or immunity resulting from previous infection by the Hansen bacillus. The infection may not manifest itself clinically, existing only as the state of leprosy infection, or it may become manifest as the leprosy disease in its benign form, tuberculoid, or perhaps in the indeterminate form but always of benign course—stationary or changing to tuberculoid. This is one of the most frequent observations in the preventoria. Data on two groups of such children, without and with clinical manifestations, in the Jacaréi and Goiânia preventoria are given in Table 2.

TABLE 2.—*Lepromin-positive and tuberculin-negative preventoria children, by age and degree of the Mitsuda reaction; (a) the leprosy infection group without clinical manifestations, and (b) the leprosy disease group, with regressive or residual tuberculoid lesions.*

Age group (years)	Leprosy infection groups				Leprosy disease group			
	No. of cases	Mitsuda reaction			No. of cases	Mitsuda reaction		
		1+	2+	3+		1+	2+	3+
0—4	16	8	7	1	6	1	2	3
5—9	32	15	10	7	10	1	3	6
10—14	29	10	8	11	8	3	—	5
Over 14	3	1	1	1	4	—	—	4
	—	—	—	—	—	—	—	—
Total	80	34	26	20	28	5	5	18

2. *Lepromin-negative*.—A negative Mitsuda reaction in a lepromatous-case contact, with no tuberculosis contact, indicates a state of predisposition or susceptibility to leprosy. There is a lack of resistance, at least at the time, and very probably a state of leprosy infection in a period of latency with great likelihood of developing manifest disease of a pro-

gressive form, indeterminate or lepromatous. In a study of the incidence of leprosy among the children of the Santa Terezinha preventorium during the period 1927-1946, when 119 became leprosy, it was found that among the 84 given the Mitsuda test only 3 reacted positively, and they all had the tuberculoid form. The others, lepromin negative, were predominantly of the indeterminate form, with a few lepromatous. This susceptibility or predisposition to the disease of the lepromin-negative contacts led to standards of close observation of such children, and the recommendation that they be vaccinated with BCG. The children of the Jacaré preventorium also showed the same findings, on a smaller scale. Of the 81 who became leprosy between 1932 and 1955, 33 were lepromin tested and only 4 were positive; they were of the tuberculoid form, while the rest were lepromatous or indeterminate.

A recent study in the Jacaré and Goiânia preventoria revealed the fact that there were 73 children negative to both tests, of whom 52 (71%) were without apparent clinical lesions (i.e., leprosy infection cases predisposed to become clinically leprosy), while 21 (29%) had lesions of the indeterminate form (i.e., leprosy-disease cases). These cases are now receiving sulfone treatment, and are being given oral BCG in doses of 0.2 gm. weekly. The effect of BCG is being studied with respect to its capability of converting the lepromin reaction in patients with indeterminate leprosy.

#### CONTACT WITH TUBERCULOSIS WITHOUT CONTACT WITH LEPROSY

1. *Lepromin-positive*.—The production of conditions in the organism that determine positivization of the lepromin reaction is not confined solely to contact with contagious leprosy patients. It has been reported by several authors, among them Fernandez, Chaussinand, Floch, and ourselves, that natural primary infection with tuberculosis as revealed by the positive tuberculin reaction can also excite this reactional capability; and so can BCG vaccination. In a study made at the Instituto Clemente Ferreira, working with tuberculosis-contact children, allergic to tuberculin, who had no history of contact with leprosy patients, we obtained with the lepromin test in 29 individuals not vaccinated with BCG the results shown in the first part of Table 3. The second part of that table shows the results in 73 children who had been vaccinated with BCG.

In the 29 tuberculin-sensitive, unvaccinated children, all but a few under 15 years of age, no less than 89.7 per cent gave positive reactions, a majority of them above the 1+ grade. The same thing is seen in the vaccinated group but in greater degree; 98.6 per cent were positive, only 1 of the 73 being negative, and more than one-half were 3+. It seems that in this group there was a reinforcement of the conditions that lead to positivity of the lepromin reaction in such cases.

Thus it is seen that primary infection with tuberculosis, and also BCG vaccination, are capable of establishing in the organism conditions that

determine positivity to the lepromin test. The state of resistance to leprosy so revealed we may call cross resistance or immunity. Tuberculin sensitization is one of the most important factors which, because of the wide dissemination of tuberculosis and its contagiousity, is concerned in lepromin

TABLE 3.—Results of the lepromin test in tuberculosis-contact children, tuberculin sensitive but without known contact with leprosy (state of cross resistance or immunity); (a) not vaccinated, and (b) vaccinated with BCG.

Age group (years)	Unvaccinated group						BCG vaccinated group					
	No. of cases	Mitsuda reaction					No. of cases	Mitsuda reaction				
		—	±	1+	2+	3+		—	±	1+	2+	3+
0-4	10	—	1	—	4	5	11	—	—	1	2	8
5-9	6	—	1	1	4	—	27	—	—	7	6	14
10-14	9	1	—	5	—	3	17	1	—	3	2	11
Over 14	4	—	—	2	2	—	18	—	—	4	9	5
Total	29	1 2		8	10	8	73	1 —		15	19	38
Per cent		10.3		89.7				1.4		98.6		

positivity in the general population, and this explains the low index of the infectiousness of leprosy.

2. *Lepromin-negative*.—Lepromin negativity associated with negativity to tuberculin can mean either an unaffected organism in the absence of effective contact with both tuberculosis and leprosy, or an organism without resistance. In the latter case the negative reactivity may be due to loss of a previous tuberculin sensitivity. This group will be discussed in more detail in the next section, in which we consider the presence of both infections.

#### CONTACT WITH BOTH LEPROSY AND TUBERCULOSIS

1. *Lepromin-negative and tuberculin-negative*.—A case with leprosy contact which is nevertheless negative to lepromin, and is without prior tuberculin sensitization, may be considered a case of leprosy infection without resistance or immunity, liable later on to develop clinical manifestations.

2. *Lepromin-negative and tuberculin-positive*.—If the case just mentioned should later develop tuberculin hypersensitivity, it would be more than a receptive organism but probably a case of *latent leprosy*, whose clinical manifestations—when they should develop—would be of a form of poor prognosis. When tuberculous infection precedes leprosy contagion it induces, in the great majority of cases, a state of resistance to leprosy. But when the reverse order of events occurs, which happens frequently, the organism becomes more susceptible to tuberculous infection, as is



shown by the high index of tuberculin hypersensitivity in lepromatous leprosy cases.

In Table 4 are shown the figures for the preventorium children with leprosy contagion whose lepromin reactions were negative while the tuberculin reactions were positive. Those in the first group, without clinical manifestations, were in a state of predisposition or susceptibility to leprosy, probably in a state of latency, and liable to develop lesions of the indeterminate or lepromatous form. Those in the second group, in the same immunoallergic situation, had developed the disease.

TABLE 4.—*Tuberculin-positive and lepromin-negative children with leprosy contact, (a) without clinical manifestation of the disease but in a state of predisposition or susceptibility, probably in a state of latency, and (b) with clinical manifestations of the indeterminate and lepromatous forms.*

Age group (years)	Without lesions	With lesions	
		Indeterminate	Lepromatous
0—4	3	2	—
5—9	16	3	—
10—14	10	1	2 <sup>a</sup>
Over 14	2	—	—
Total	31	6	2

<sup>a</sup> Segregated.

The 31 cases of the first part of Table 4 need the most careful supervision, since in our opinion they are very likely to become leprosy. All of the cases involved in that table have been given BCG, and those with lesions are under sulfone treatment.

3. *Lepromin-positive and tuberculin-positive.*—Cases with both reactions positive reveal a state of resistance and both specific and cross immunity. They are of good prognosis, and they constitute a large majority of cases observed in the preventoria, whether without clinical manifestations of the disease or with lesions of tuberculoid leprosy. The former have leprosy infection with immunity, and it is probable that they have acquired a primary lymph-node complex, without clinical manifestations. The latter have the disease in the nodular or sarcoidal tuberculoid form. We see below, in Table 5, the large number of cases with tuberculoid leprosy in its nodular, sarcoid and circinate varieties, the nodular one predominating. The frequency of this variety of the tuberculoid form of leprosy among the children of lepromatous parents will be the subject of

a study in which we will attempt to explain its pathogenic significance. These lesions appear in a cicatricial stage, relative or absolute. No indeterminate case was observed in this situation.

TABLE 5.—Results of the lepromin test in tuberculin- and lepromin-positive cases with both tuberculosis and leprosy contact, and a state of specific or cross resistance, (a) without clinical manifestations of leprosy, and (b) with active, involuted or cicatricial tuberculoid lesions.

Age group (years)	Without lesions				With tuberculoid lesions			
	No. of cases	Mitsuda reaction			No. of cases	Mitsuda reaction		
		1+	2+	3+		1+	2+	3+
0—4	25	11	7	7	6	—	1	5
5—9	89	34	18	37	14	1	1	12
10—14	95	23	19	53	13	1	4	8
Over 14	30	3	10	17	11	—	1	10
Total	239	71	54	114	44	2	7	35

Noteworthy are the large proportions of strong Mitsuda reactions in these two groups of cases—47.7 per cent of the 239 without lesions, and 79.5 per cent of the 44 with lesions.

#### DISCUSSION

Through observation of the results of the lepromin and tuberculin tests performed on children who were contacts of leprosy and tuberculosis patients, we have arrived at the conclusion that there exists a state of specific resistance or immunity following leprosy infection, and a state of cross resistance due to tuberculosis infection, as has been reported by other authors. These two factors are responsible for the low prevalence of leprosy.

Nevertheless, careful study of leprosy contacts with exposure to cases with open forms of the disease reveals, besides a high percentage of infected individuals who are free from manifestations of the disease—lepromin-positive and therefore resistant bearers of a “leprosy infection”—also a high proportion of individuals with resistance who develop tuberculoid leprosy, of the nodular and sarcoidal forms that are peculiar to childhood and which always heal spontaneously.

Besides these resistant, lepromin-positive contacts, there is a smaller percentage of contacts in the state of leprosy infection who are lepromin negative and therefore without such resistance, and who consequently are



liable to a situation of evolutive "leprosy disease," with manifestations of the indeterminate or the lepromatous form. This evolutive tendency, of bad prognosis, is most marked when nonreactors to both tests later present a positive tuberculin reaction. This seems to signify that the state of leprosy infection was so marked that it was not modified in spite of a subsequently-established tuberculous impregnation.

Among children living in preventoria it is therefore possible, by the results of the lepromin test, to detect those in the state of leprosy infection without clinical manifestations who have resistance and those who are without it. Clinical observations, also, reveal on the one hand a high percentage of children with healed or healing tuberculoid lesions in whom the lepromin test reveals a high degree of resistance and immunity, and on the other hand relatively few lepromin-negative cases with indeterminate lesions, possibly evolutive cases.

A much-discussed question is that of the existence of a primary complex in leprosy. Although denied by some workers, this idea has been suggested or accepted by others, who speak of it either as the primary complex or the inoculation lesion. Are not the nodular lesions of childhood leprosy, and even the sarcoidal ones both in children and adults, the clinical manifestations of a primary complex? Do they not present clinical, immunologic, and evolutive characteristics that differ in all respects from the features of the tuberculoid type of leprosy? Their sites of preference, their regular tendency to spontaneous healing, and the facts that they never evolve to other clinical forms or types, never relapse, and seem to confer upon the organism a state of indisputable immunity, are these not problems to be resolved in the study of pathogenesis of leprosy?

The high percentage of contact children in the state of leprosy infection, lepromin-positive and therefore with resistance, and even those with tuberculoid lesions in various evolutive stages, in contacts with persons with the open forms of the disease is apparently contradictory. The classical view is that children are susceptible to leprosy, and this concept has determined the prophylactic measures employed for their protection. However, the situation is different if we consider on the one hand the child born of leprosy parents who lives with them, and on the other hand the child without leprosy background who first comes into contact with a leprosy patient at a more advanced age. In the former situation the child usually develops a state of leprosy infection, or of leprosy disease of benign form, always with resistance evidenced by lepromin positivity, rather than an evolutive form of the disease. In the latter situation the child is much more liable to develop an evolutive form of the disease, indeterminate or lepromatous.

The great majority of reported cases of lepromatous leprosy in early childhood were in the latter situation. This leads to the idea that contact children inherit a condition of general resistance, probably of nonspecific nature, that protects them against the first onslaughts of bacilli received

in the first years of life. The great rarity of leprosy in the two first years of life seems to justify this point of view. We do not believe that the period of latency, which is considered to be long in leprosy, can explain this rarity. Our own observations in preventoria are that more than 50 per cent of the cases of leprosy appear during the first year after removal from the source of infection, and that more than 90 per cent occur by the third year. Only the existence of a constitutional state of resistance can protect them in this period of life, when and where the closeness of contact with the source of infection is most intimate, intense and frequent. The infection to which they are exposed is defeated by this state of natural resistance, while the organism establishes a specific resistance as a consequence of this first infection. This resistance protects them either completely, in which case they do not present evidence of the infection but only remain Mitsuda positive, or relatively, in which case they evidence the infection in the resistance forms, nodular or sarcoidal tuberculoid. However, this state of natural resistance seems to be temporary, for if these children—once removed from contact—should after three years be again exposed to infection they would then be liable to develop evolutive forms of the disease, indeterminate and lepromatous.

#### CONCLUSIONS

The study of the correlation of the results of the tuberculin and lepromin tests, carried out in preventoria among children of persons with leprosy and who consequently had been exposed to infection, leads to the conclusion that there exists a state of specific resistance or immunity due to leprosy infection, and a state of cross resistance due to tuberculous infection.

The results of the tuberculin and lepromin tests among these leprosy contacts have established two different situations. (1) A state of "leprosy infection" and one of "leprosy disease." The individuals are lepromin positive and have specific resistance, or cross resistance, or both. They may be apparently healthy, or they may present lesions of the tuberculoid type of the disease. (2) A state in which resistance is lacking, and the individuals are lepromin negative. They may be apparently healthy, or they may have lesions of the indeterminate or lepromatous forms of the disease. This study, and careful examination of these children, demonstrate that the incidence of leprosy among close contacts is much higher than is indicated by the epidemiological data.

The results of the correlation of the tuberculin and lepromin reactions leads to an orientation of the criteria of surveillance of contact children in preventoria. Most attention should be given, first, to the lepromin-negative and tuberculin-positive children, and, next, to those who are negative to both lepromin and tuberculin.

The high frequency of positive lepromin reactions in cases without evident manifestations of leprosy, as well as the high incidence of tubercu-

loid cases—nodular and sarcoidal—among the close contacts of patients with open forms of the disease, suggest (1) the existence of a lymph-node complex without clinical manifestations, and (2) that those manifestations, by their own characteristics, correspond to the initial or inoculation lesion.

#### CONCLUSIONES

El estudio de la correlación de los resultados de las pruebas de la tuberculina y la lepromina, llevadas a cabo en preventorios en niños de padres leprosos y que, por consiguiente, habían estado expuestos a la infección, lleva a la conclusión de que existe un estado de resistencia o inmunidad específica debido a la infección leprosa y un estado de resistencia cruzada debido a la infección tuberculosa.

Los resultados de las pruebas con tuberculina y lepromina en estos contactos de leprosos establecieron dos situaciones distintas: (1) Un estado de "infección leprosa" y uno de "enfermedad leprosa." Los individuos son lepromino-positivos y poseen resistencia específica o resistencia cruzada o ambas. Pueden estar aparentemente sanos o presentar lesiones de la forma tuberculoidea de la enfermedad. (2) Un estado en que falta la resistencia y los sujetos son lepromino-negativos. Pueden estar aparentemente sanos o mostrar lesiones de las formas indeterminada o lepromatosa de la dolencia. Este estudio y el examen cuidadoso de estos niños demuestran que la incidencia de la lepra entre los contactos íntimos de los leprosos es mucho más alta que lo indicado por los datos epidemiológicos.

Los resultados de la correlación de las pruebas de la tuberculina y la lepromina conduce a una orientación de las pautas de vigilancia en los preventorios de los niños que han estado en contacto con leprosos. Primero, debe prestarse la mayor atención a los niños lepromino-negativos y tuberculino-positivos, y después a los que son negativos tanto a la lepromina como a la tuberculina.

La alta frecuencia de reacciones positivas a la lepromina en casos sin manifestaciones evidentes de lepra, así como la alta frecuencia de casos tuberculoideos—nodulares y sarcoidales—entre los contactos íntimos de enfermos que tienen formas abiertas de la dolencia, sugieren: (1) la existencia de un complejo linfoganglionar sin manifestaciones clínicas y (2) que esas manifestaciones, por sus propias características, corresponden a la lesión inicial o de inoculación.