Lepromin Test in Noncontacts (Mainly 1-19 Years Old) Living in an Area of Low Leprosy Endemicity[1, 2]

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Healthy individuals without known exposure to *Mycobacterium leprae*, living in an area of low leprosy endemicity were lepromin tested, to study:

1. Late lepromin (Mitsuda) reaction
2. Mitsuda reaction according to age group
3. Mitsuda reaction related to sex
4. Mitsuda reaction in whites and nonwhites (Negroes, mulattoes)
5. Correlation between early (Fernández) and late (Mitsuda) lepromin reactions
6. Correlation between Mantoux and Fernández reactions
7. Correlation between Mantoux and Mitsuda reactions.

MATERIALS AND METHODS

Patients: Three hundred and twenty-seven persons living in orphanages, 1-19 years old; 18 individuals 40-59 years old, hospitalized in the Hospital of the Medical Faculty; and 45 persons 60 years old or more, living in an asylum for aged and destitute people were studied.

The subjects aged 1-19 years were the most suitable for study since those who were hospitalized had serious illness and those living in the asylum were not in the best physical condition and perhaps their diet was not always adequate.

The sample distribution by age, sex and race is indicated in Table 1.

Exposure to *M. leprae* was not known for any of these subjects though it is possible for a certain number of adults as they lived in an area where leprosy is endemic (prevalence rate around 1/1,000)

Method. Lepromin, having a bacillary content of 20 million bacilli/ml was kindly provided by the Instituto de Leprologia (Rio de Janeiro). The tests were performed in 1962, in the left arm, anterior surface. According to Dr. M. Tuma (personal communication) this lepromin fulfills routine purposes perfectly and is satisfactory for use in children, adults, healthy persons and patients with leprosy.[4]

The response was read at 48 and 72 hours and weekly from the 7th to 91st day. The largest response elicited was that considered significant in each case.

The criteria for recording the early and late reactions were those adopted at the VIIth International Congress of Leprology([14]).

The tuberculin test was performed in the right forearm, anterior surface, with purified tuberculin, 1 TU per 0.1 ml.[5] (RT 23 with 0.005% Tween 80) obtained from the Statens Seruminstitut, Copenhagen. Response was read after 48 hours. The method used in reading the Mantoux reaction was that recommended by the Fifth Pan-American Tuberculosis Congress

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[4] In a comparative study requested by WHO with "standard" lepromin (160 million bacilli/ml.) and diluted antigen containing 120, 80, 40 and 10 million bacilli/ml Tuma observed that if a nodule of 3 mm is accepted as the criterion of positivity (as it was in the present paper) a lepromin of 40 million bacilli/ml is considered completely satisfactory for the lepromin reaction. A comparative study between the lepromins containing 20 and 40 million bacilli/ml was also done, at WHO's request. Dr. Tuma considered that the latter lepromin can be replaced by the former (Dr. Tuma's reports to WHO) without detriment to the results, when an induration of 3 mm is considered as the lower limit of positivity ([13]).

[5] Equivalent to 1:10,000 Old Tuberculin.

TABLE 1. *Lepromin test in noncontacts. Sample distribution.*

Age group	Number and %	Male	Female	White (W)	Non-white (NW)
1–4	48 (12%)	14	34	29	19
5–9	112 (29%)	40	72	68	44
10–14	137 (35%)	100	37	87	50
15–19	30 (8%)	23	7	20	10
40–59	18 (5%)	8	10	15	3
60+	45 (11%)	30	15	36	9
Total	390 (100%)	215	175	255	135

where infiltration or induration of 5 mm or more in diameter were regarded as positive.

It should be noted that edema or infiltration of 5 mm or more but less than 10 mm may also be nonspecific in the presence of prior infection by acid-fast, nonpathogenic organisms antigenically related to *M. tuberculosis*. This is more often observed when higher doses of tuberculin are used.

Differences between proportions in age-groups, whites (W) and nonwhites (NW) and sex were tested only in the age groups in which the samples were adequate.

The lepromin reading schedules in noncontacts and the relevant conclusions were reported at the VIIIth International Congress of Leprology ([5]): ". . . should the data be confirmed, readings of the Mitsuda reaction in non-contacts on the 35th day should make for a higher percentage of positivity (about 85% for 1 +, 2 + and 3 +) with a better indication of the degree of intensity (1 +, 2 + and 3 +). In scientific investigations it is interesting to take another reading on the 49th day so as to reach 90% positivity or more. If it is desired to study the doubtful reactions, various weekly readings should be made from the 21st day to the 49th."

RESULTS & COMMENTS

Late lepromin (Mitsuda) reactivity related to age-groups. (Table 2) From age-groups 1-4 to 15-19 there is a significant increase in the proportion of lepromin positivity (1 +, 2 + and 3 +), from 48% to 97% respectively. This is in accordance with the observations that "reactivity to lepromin increases rapidly with age, from negativity in infancy to almost universal positivity after adolescence in endemic areas and is associated with relative resistance." ([28]).

The data confirm those of Del Favero ([8]) in Brazil, Martinez ([20]) in Spanish Guinea, and Guinto, *et al.* ([11]) in the Philippines. The slight difference compared with Del Favero's data, in Candeias, can be explained by the difference in reading criteria (positive reactions in Candeias measured at least 4 mm).

The added proportion of 2+ and 3+ reactions also increases with age; from 19% to 57% respectively for 1-4 to 15-19 years.

These observations show the pattern and trends of lepromin reactivity in noncontacts in the four age-groups studied. Since lepromin positivity ". . . is regarded as an expression of a certain amount of resistance to *M. leprae* directly proportionate to the degree of positivity," ([14]), the results indicate, as already known, that the majority of the population has a certain resistance to leprosy. Even if subjects are nonreactors to lepromin in infancy and in early ages, reactivity becomes rapidly evident ([26]) be-

TABLE 2. *Mitsuda reaction in noncontacts in relation to age.*

Age \ Mitsuda	− & ±	+	++ & +++	Total
1–4	25 (52%)	14 (29%)	9 (19%)	48
5–9	49 (43%)	41 (36%)	22 (21%)	112
10–14	17 (12%)	60 (44%)	60 (44%)	137
15–19	1 (3%)	12 (40%)	17 (57%)	30
40–59	6 (34%)	9 (50%)	3 (16%)	18
60+	17 (38%)	13 (29%)	15 (33%)	45

cause there exists the potential capacity for this response. Therefore the lower proportion of lepromin reactors in children than in adolescents and adults does not mean that they are more susceptible to leprosy.

In age group 15-19, 97% had a positive macroscopic late reaction. We do not know what proportion could also have a positive histologic reaction, since biopsies could not be performed. This leads to a question: what would be the proportion of the nonreactors and, therefore, of more susceptible individuals? Studies taking also into account histologic examination and epidemiologic observations should be carried out to determine this, especially in individuals 20-29 years old, in whom the lepromin reactivity reaches practically the highest proportion and where the nonreactors could be better studied and attempts could be made to convert their reaction.

The proportion of nonreactors and of more susceptible individuals should be low, if in fact the higher rate of lepromatous leprosy in the population does not exceed 15 per 1,000, as pointed out by Newell ([22]). On the other hand, the attack rate in continuously exposed children aged 3 to 6 years, living in Culion and repeatedly observed for different periods of time was 36.2% ([16]). In the Nauru epidemics, the the most serious in the world, 30% of the population (about 1,500 natives) showed signs of leprosy. In the most endemic countries the rates may exceptionally reach 50 per 1,000 and more.

If these data may be extrapolated to other areas of the world it is likely that a relatively large proportion (roughly one-third) of the population could acquire leprosy but only a very small proportion would develop the lepromatous form of the disease. In fact spontaneous disappearance of certain leprosy lesions is frequent. In Lara and Nolasco's ([17]) study, 77% of early childhood cases were free of lesions before adult life.

The proportion of lepromin reactors among individuals 40-59 and 60+ years old is lower, around 65%. Is this because they were ill and/or in poor physical condition? Epidemiologic observations have not shown that old people are more susceptible to leprosy.

With regard to illness, Rotberg and Fleury ([25]) reported that the Mitsuda reaction is positive in 85.7% of adult tuberculosis patients. When these were considered according to general status, satisfactory or poor, the proportion of nonreactors was respectively 7.5% and 35.2%. We have confirmed this observation in tuberculosis patients, in relation also to the tuberculin test. It is likely that in very debilitated individuals the proportion of nonreactors might be higher.

Mitsuda reaction related to sex. (Table 3). The differences between proportions of lepromin reactivity in males and females, in the age-group 1-4, 5-9 and 10-14 are not

TABLE 3. *Mitsuda reaction in noncontacts, related to age and sex.*

Age group	Mitsuda Sex	− & ±	+	++ & +++	Total
1–4	M	7 (50%)	3 (21%)	4 (29%)	14
	F	18 (53%)	11 (32%)	5 (15%)	34
5–9	M	22 (47%)	16 (34%)	9 (19%)	47
	F	27 (38%)	32 (44%)	13 (18%)	72
10–14	M	8 (9%)	46 (46%)	46 (46%)	100
	F	9 (24%)	14 (38%)	14 (38%)	37
15–19	M	0	7 (30%)	16 (70%)	23
	F	1	5	1	7
40+	M	17 (47%)	9 (25%)	10 (28%)	36
	F	6 (22%)	13 (48%)	8 (30%)	27

significant. The added proportion of 2+ and 3+ in males and females is similar.

These results confirm those of Rotberg ([24]) and Del Favero ([8]) in Brazil and Lara ([15]) and Guinto *et al.* ([11]) in the Philippines. The latter stated that no substantial difference between the sexes was found in any age-group and for all ages. In the light of these results it seems that males and females have a similar resistance against leprosy. If these data are confirmed by further studies and in different areas of the world, it could be deduced that the exposure, living conditions and other factors are responsible for the differences observed in the leprosy rates and lepromatous rates in males and females. More intensive action of these factors in lepromin-negative males could account for the development of more lepromatous cases among them.

Mitsuda reaction in whites and nonwhites (Negroes and mulattoes). (Table 4) When whites and nonwhites are compared in each group, the differences in proportion of lepromin reactivity are not significant.

These results are in agreement with some epidemiologic data reported in Brazil concerning prevalence rates and proportion of lepromatous and tuberculoid cases, which are similar in whites, Negroes and mulattoes ([6, 21, 23]).

Correlation between early (Fernández) and late (Mitsuda) lepromin reactions. (Table 5). Early lepromin reaction was only exceptionally positive: twice among 390 persons tested. In one of these the late lepromin reaction was negative.

In spite of the negativity of early lepromin reaction, the late reaction was positive in an increasing proportion from the 1-4 to the 14-19 year-old individuals. The association of early and late lepromin reactions (57%) in the 1-4 age-group is only apparent because at this age the proportion of late lepromin positivity is usually low. In fact this proportion increased, as expected, in the subsequent age groups, and among individuals 15-19 years old only 4% of cases of negative early lepromin reaction had also negative late reaction.

In the material studied and with present criteria, the early reaction was of no value in noncontacts. Perhaps new criteria for reading it should be considered.

TABLE 4. *Mitsuda reaction in noncontacts related to age and race.*

Age group	Mitsuda Race	− & ±	+	++ & +++	Total
1–4	W	15 (52%)	6 (21%)	8 (27%)	29
	NW	10 (53%)	8 (42%)	1 (5%)	19
5–9	W	31 (45%)	26 (38%)	11 (17%)	68
	NW	18 (41%)	15 (34%)	11 (25%)	44
10–14	W	11 (11%)	42 (48%)	34 (41%)	87
	NW	8 (16%)	18 (36%)	24 (48%)	50
15–19	W	1 (5%)	9 (45%)	10 (50%)	20
	NW	—	2	8	10
40+	W	22 (43%)	18 (35%)	11 (22%)	51
	NW	1	4	7	12

Correlation between the Mantoux and Fernández reactions (Table 6) It is evident that there was no association between the Mantoux and the Fernández reactions in the material studied. This confirms the data of Bechelli (4) and his conclusion that if a causal relationship between tuberculization and Fernández positivity were established, cross sensitization would occur within a very limited range and irregularly.

Correlation between the Mantoux and Mitsuda reactions. (Table 7) In the child community studied the percentage of tuberculin reactors was low, while the proportion of lepromin reactors was high. The proportion of lepromin reactors increased from the 1-4 to the 15-19 year old individuals independently of tuberculin positivity being 46% and 96% respectively. The same occurs when 2+ and 3+ lepromin positive reactors are considered; 19% to 61% respectively in the age-groups 1-4 and 15-19.

Among 56 tuberculin reactors 6 (11%) were lepromin negative. Apparently there was no association of tuberculin-positivity with a higher proportion of lepromin positivity, or with stronger reactors (2+ and 3+). However, the number of tuberculin reactors was too small for a firm conclusion to be drawn.

DISCUSSION

From the material studied it is likely that a very high proportion of individuals (96% in this study) may have lepromin reactivity independently of tuberculin sensitivity (as revealed by 1 TU with 5 mm and over of infiltration being considered as positive reaction) and may be expected to have a certain degree of resistance against leprosy.

The results are in agreement with other personal data and also with those reported by Swerts (27). He found that positive reaction to crude tuberculin (1:1,000) was low in the 5-10 year age-group (approximately 5%) and rose sharply between 16 and 20 years. The lepromin curves were very different, with decidedly higher percentages from the lowest age-groups upwards. According to the author, the findings indicate that in the population studied "impregnation" with *M. leprae* precedes that of *M. tuberculosis* and do not bear out the idea that the development of lepromin positivity is due to the Koch bacillus.

TABLE 5. *Fernández/Mitsuda reactions in noncontacts related to age.*

Age group	Mitsuda Fernandez	− & ±	+	++ & +++	Total
1–4	−	25 (57%)	13	6	44
	±	—	1	3	4
	+	—	—	—	—
5–9	−	47 (44%)	39 (37%)	21 (19%)	107
	±	2	2	1	5
	+	—	—	—	—
10–14	−	16 (12%)	59 (46%)	54 (42%)	129
	±	1	1	6	8
	+	—	—	—	—
15–19	—	1 (4%)	11 (36%)	16 (57%)	28
	±	—	—	2	2
	+	—	—	—	—
40–59	−	6	8	1	15
	±	—	1	2	3
	+	—	—	—	—
60+	−	15 (41%)	10 (28%)	11 (31%)	36
	±	1	3	3	7
	+	1	—	1	2

This was also observed by Doull *et al.* [9]. Following statistical analysis of their material they concluded: "Although there is a positive correlation between reactivity to tuberculin and that to lepromin, the excess of lepromin reactors among tuberculin-positive over the number expected if there were no association comprises a very small fraction of the total number reacting to lepromin. This is true both for small doses of tuberculin, reaction to which is regarded as specific for infection with *M. tuberculosis*, and for larger doses which may indicate prior infection with other species of mycobacteria. This suggests that lepromin reactivity among these children is caused, in most instances, by some factor other than infection with *M. tuberculosis* or correlated species." They also regarded the theory that the dose used in the lepromin test is the sensitizing factor responsible as unsatisfactory. In a further investigation, Guinto *et al.* [12] confirmed this finding.

This subject has been considered in great detail in our previous papers [2,3,4] where we referred to the contribution of others [7, 11, 18, 19]. Davey *et al.* [7] noted that the wide variation in the percentage of

TABLE 6. *Correlation Mantoux/Fernández reactions in noncontacts related to age groups.*

Age-group	Fernandez / Mantoux	−	+	Total
0–9	−	155	0	160
	+	5	0	
10–19	−	142	0	167
	+	25	0	
40–59	−	10	0	18
	+	8	0	
60+	−	26	2	45
	+	17	0	

lepromin-positivity between one studied area and another and the irregularity of the movement of these figures through succeeding age groups makes it hard to believe in the action of a common influence. They raised the question of how tuberculin could induce 97% lepromin conversions in one locality and only 42% in another. According to them, "The difference between one area and another are indeed related, not to the proportion of tuberculin-positivity but to the lepromin-positive rate. Where the percentage of lepromin-positivity is high, a high proportion of tuberculin-positives are also lepromin-positive; where the proportion is low, the proportion of positivity to the Mitsuda reaction is like-

TABLE 7. *Correlation Mantoux/Mitsuda reactions in noncontacts related to age groups.*

Age group	Mitsuda / Mantoux	− & ±	+	++ & +++	Total
1–4	−	26 (54%)	13 (27%)	9 (19%)	48
	+	—	—	—	—
	++	—	—	—	—
5–9	−	48 (45%)	41 (38%)	18 (17%)	107
	+	1	—	1	2
	++	—	—	3	3
10–14	−	16 (14%)	51 (43%)	51 (43%)	118
	+	1	5	2	8
	++	−	4	7	11
15–19	−	1 (4%)	8 (35%)	14 (61%)	23
	+	—	2	—	2
	++	—	2	3	5
40+	−	19 (50%)	10 (26%)	9 (24%)	38
	+	3	4	3	10
	++	1	8	6	15

wise low." They considered it impossible to reconcile these findings with the theory that tuberculosis is inducing lepromin positivity in any significant degree. Summarizing their findings, they maintained that sensitivity to tuberculin and lepromin tends to be associated in the same individuals in both rural and urban areas. In the latter, it is possible that tuberculosis infection is responsible for the association to a slight degree. However, in the rural areas, where tuberculosis is less widespread, it is impossible to discover any evidence that there is an appreciable influence on sensitivity to lepromin.

In our own studies ([2,3,4]) there were some groups in which there was association between tuberculin and lepromin reactivities beyond certain limits of Mitsuda reaction positivity. However, the excess of lepromin reactors constituted only a small fraction of the total number of these reactors. Furthermore ([2]) in rural areas the percentage of tuberculin reactors is relatively low while that of lepromin reactors is in proportion much higher. Also ([3]) among the tuberculin-positive individuals there is a large variation in the percentages of lepromin positivity and in the excess of lepromin reactors from one place to another, even in the same area. It was concluded that "The overall review of the data set forth in this paper points to the possibility of the existence of cross sensitization to *M. tuberculosis* but apparently only within a limited range."

SUMMARY AND CONCLUSIONS

Correlative studies of lepromin (Mitsuda type) and tuberculin tests in 390 nonleprosy contacts (327 aged 1-19 years and 63 over 40 years) led to the following conclusions.

Readings of the Mitsuda reaction in noncontacts on the 35th day should yield a higher percentage of positivity (about 85%) with a better indication of the degrees of intensity (1+, 2+ and 3+).

From age-groups 1-4 to 15-19 there is a significant increase in the proportion of lepromin positivity which may reach about 95%. Stronger reactions also increase with age. The lower proportion of lepromin reactors in children than in adolescents and adults does not mean that they are more susceptible to leprosy.

When males and females, whites and nonwhites, were compared in each age-group, the differences in proportion of lepromin reactivity were not significant.

The early lepromin reaction (Fernández) was only exceptionally positive. In spite of the negativity of early reaction, the late reaction (Mitsuda) was positive in an increasing proportion in the 14-19 year-old individuals as compared with 1-4 year olds.

In the child community studied the percentage of tuberculin reactors was low, while the proportion of lepromin reactors was high.

There was no association between the Mantoux and the Fernández reactions.

The proportion of lepromin reactors, low in 1-4 year-old individuals, greatly increased in the older age-groups, reaching a maximum in the 15-19 year old individuals independently of tuberculin positivity. It appears that a very high proportion of individuals (96% in the present group) may have lepromin reactivity independently of tuberculin sensitivity and may be expected to have a certain degree of resistance to leprosy.

RESUMEN Y CONCLUSIONES

Se hicieron estudios correlativos de las pruebas de lepromina (tipo Mitsuda) y de tuberculina en 390 no-contactos de lepra (327 cuyas edades fluctuaban entre 1 y 19 años y 63 mayores de 40 años), llegándose a las siguientes conclusiones.

La lectura de la reacción de Mitsuda en los no-contactos al día 35 debe dar un mayor porcentaje de positividad (alrededor de 85%), con una mejor indicación del grado de intensidad (1+, 2+ y 3+).

Para los grupos etarios de la a 4 años y de 15 a 19 años, hay un aumento significativo en la proporción de positividad a la lepromina, que puede alcanzar alrededor del 95%. Las reacciones más intensas también aumentan con la edad. La menor proporción de reactores a la lepromina en los niños que en los adolescentes y en los adultos no quiere decir que ellos sean más susceptibles a la lepra.

Cuando en cada grupo etario se compararon hombres y mujeres, blancos y no-blancos, las

diferencias en la proporción de reactividad a la lepromina no fueron significativas.

La reacción de lepromina temprana (Fernandez) fué positiva sólo excepcionalmente. A pesar de la negatividad de la reacción temprana, la reacción tardía (Mitsuda) fué positiva en una proporción creciente en los individuos del grupo entre 14 y 19 años, en comparación con los del grupo entre 1 y años.

En la comunidad infantil estudiada, el porcentaje de reactores a la tuberculina fué bajo, mientras que la proporción de reactores a la lepromina fué alto.

No hubo asociación entre los reacciones de Mantoux y Fernandez.

La proporción de reactores a la lepromina, baja en el grupo de individuos entre 1 y 4 años de edad, aumentó enormemente en los grupos de mayor edad, alcanzando un máximo en los individuos del grupo entre 15 y 19 años, independientemente de la positividad a la tuberculina. Parece ser que una proporción muy alta de individuos (96% en el presente grupo) puede presentar reactividad a la lepromina, independientemente de la sensibilidad que tengan hacia la tuberculina, ye se puede presumir que tengan cierto grado de resistencia a la lepra.

RÉSUMÉ

Chez 390 contacts de lépreux, dont 327 âgés de 1 à 19 ans et 63 ayant dépassé 40 ans, n'ayant pas reçu antérieurement de lépromine, on a procédé à des études de corrélations entre les épreuves à la lépromine (type de Mitsuda) et à la tuberculine. Ces études ont mené aux conclusions suivantes.

Une proportion plus élevée de réactions positives (environ 85 pour cent) devrait être obtenue lorsqu'on procède à la lecture de la réaction de Mitsuda chez les individus non contacts, au 35ème jour; cette méthode permettrait également de mieux distinguer les divers degrés d'intensité (1 +, 2 + et 3 +). Du groupe d'âge 1 à 4 ans au groupe d'âge 15 à 19 ans, on constate une augmentation significative de la proportion de positivité à la lépromine, qui peut atteindre 95 pour cent dans ce dernier groupe. Les réactions les plus fortes augmentent également avec l'âge. Le fait qu'une proportion plus faible de réacteurs à la lépromine soit constatée chez les enfants comparés aux adolescents et aux adultes, ne signifie pas que ceux-là soient plus susceptibles à la lèpre.

La comparaison, par groupes d'âge, de la proportion de réactions positives à la lépromine chez les hommes et chez les femmes, chez les blancs et chez les colorés, ne permet pas de mettre en évidence des différences significatives.

La réaction précoce à la lépromine (Fernandez) n'a été qu'exceptionnellement positive. Malgré le fait que la réaction précoce soit négative, la réaction tardive (Mitsuda) a été positive dans une proportion de plus en plus élevée des cas chez les individus âgés de 14 à 19 ans, comparée à ceux âgés de 1 à 4 ans.

Dans la communauté d'enfants qui a été étudiée, la proportion de réacteurs à la tuberculine était faible, alors que la proportion de réacteurs à la lépromine était élevée.

On n'a pas observé d'association entre les réactions de Mantoux et de Fernandez. La proportion de réacteurs à la lépromine, qui était faible dans le groupe d'âge de 1 à 4 ans, était progressivement plus élevée dans les groupes d'âge plus avancés, atteignant son maximum dans le groupe de 15 à 19 ans, et ceci indépendamment de la positivité à la tuberculine. Il apparait qu'une très forte proportion d'individus (96 pour cent dans le groupe étudié) peuvent présenter une réactivité à la lépromine, indépendamment de la sensibilité à tuberculine, témoignant par là d'un certain degré de résistance à la lèpre.

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