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INFLUENCE OF REPEATED LEPROMIN INJECTIONS ON THE MITSUDA SKIN REACTION[1, 2]

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It is known that both BCG vaccination and repeated lepromin injections can sensitize for the development of macroscopically positive late lepromin (Mitsuda) reactions among formerly Mitsuda-negative persons. Some discrepant results have been published ([2]). The purpose of this paper is to investigate other details related to this subject.

MATERIALS AND METHODS

A sample of 1251 healthy leprosy contacts not reacting macroscopically (— or ±) to lepromin was submitted to a second lepromin test. The sample was classified in two groups. One included 834 subjects vaccinated orally with BCG (6 doses of 0.10 gm.). A second lepromin injection was applied from 3 months to 4 years after the last dose of BCG. The other group consisted of the remainder of the sample as an unvaccinated control group in which lepromin inoculations were made at corresponding times. Each group was subdivided in five classes including subjects tested 0, 1, 2, 3 and 4 years after the first inoculation.

All the tests were performed by the senior author (R.Q.), and the following criteria were used for classifying the late lepromin reaction:

— Absence of an observable or palpable element
± presence of perceptible element with a diameter smaller than 3 mm.
\+ presence of a conspicuous element, with infiltration, 3-5 mm. in diameter
++ presence of a conspicuous element, with infiltration, larger than 5 mm. in diameter
+++ presence of an ulcerated nodule.

For simplifying analysis of the data, ++ and +++ reactions were pooled and considered positive, while the —, ± and + reactions were considered as negative.

RESULTS

The proportion of positive reactions on second test among subjects formerly lepromin-negative or ±, classified by age, is indicated in Table 1. It is evident that the proportion of positive reactions on second test is independent of aging.

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TABLE 1.—*Proportion of macroscopically positive late lepromin reactions (++ and +++) revealed by a second lepromin test among previously lepromin negative leprosy contacts, classified by age, oral vaccination with BCG, and time elapsed since the first test.*

Age group in years	0 Years				1 Year				2 Years				3–4 Years			
	Vaccinated		Control		Vaccinated		Control		Vaccinated		Control		Vaccinated		Control	
	No.	Pos.	No.	Pos.	No.	Pos.	No.	Pos.	No.	Pos.	No.	Pos.	No.	Pos.	No.	Pos.
3–10	49	23	15	5	92	15	38	15	33	14	8	2	14	7	6	1
11–20	39	10	15	7	80	26	49	13	26	12	18	7	26	12	16	8
21–30	41	14	15	4	73	15	31	10	15	8	12	4	25	10	16	10
31–40	25	8	10	7	66	15	28	6	18	8	13	6	18	10	19	10
41–50	28	13	12	4	43	14	23	5	15	7	12	7	11	5	8	4
>50	28	9	8	3	44	11	25	10	11	2	9	5	14	7	11	6
Total. No.	210	77	75	30	398	96	194	59	118	51	72	31	108	51	76	39
. %	—	36.7	—	40.0	—	24.1	—	30.4	—	43.2	—	43.1	—	47.2	—	51.3
χ^2 ; 5 d.f.	5.94 P>0.30		4.83 P>0.30		8.38 P>0.05		4.79 P>0.30		2.94 P>0.70		3.45 P>0.50		1.14 P>0.95		3.83 P>0.50	

Table 2 shows that the proportion of positive reactions in the vaccinated group does not differ significantly from that in the nonvaccinated group.

The data presented in Table 2 indicate also that the proportion of positive lepromin reactions depends upon the time elapsed from the first inoculation (χ^2=42.83; 4 d.f.; P<0.001). The intensity of positive reaction is lower when the second inoculation is made more than one year after the first lepromin injection (Fig. 1).

DISCUSSION AND CONCLUSIONS

Souza-Campos *et al.* (4) have shown that macroscopically positive late lepromin reactions are more frequent among BCG-vaccinated children, 6 to 43 months old, than among nonvaccinated children simply injected twice with lepromin. They pointed out also, however, that the intensity of the late lepromin reaction among the vaccinated children decreased with age. In attempting to explain this difference, they

TABLE 2.—*Proportion of macroscopically positive late lepromin reactions (++ and +++) among formerly lepromin-negative subjects classified by the time (in years) elapsed since the first inoculation.*

Classes (years)	Group	No. healthy leprosy contacts	Positive lepromin-reactions		Independence—test χ^2 ; 1 d.f.
			No.	%	
0	Vaccinated	210	77	36.7	0.26 ; P>0.50
	Control	75	30	40.0	
	Total	285	107	37.5	
1	Vaccinated	398	96	24.1	2.67 ; P>0.05
	Control	194	59	30.4	
	Total	592	155	26.2	
2	Vaccinated	118	51	43.2	0.035 ; P>0.98
	Control	72	31	43.0	
	Total	190	82	43.2	
3	Vaccninated	45	19	42.2	0.71 ; P>0.30
	Control	45	23	51.1	
	Total	90	42	46.7	
4	Vaccinated	63	32	50.8	0.01 ; P>0.90
	Control	31	16	51.6	
	Total	94	48	51.1	
Grand Total	Vaccinated	834	275		
	Control	417	159		
	Total	1251	434		

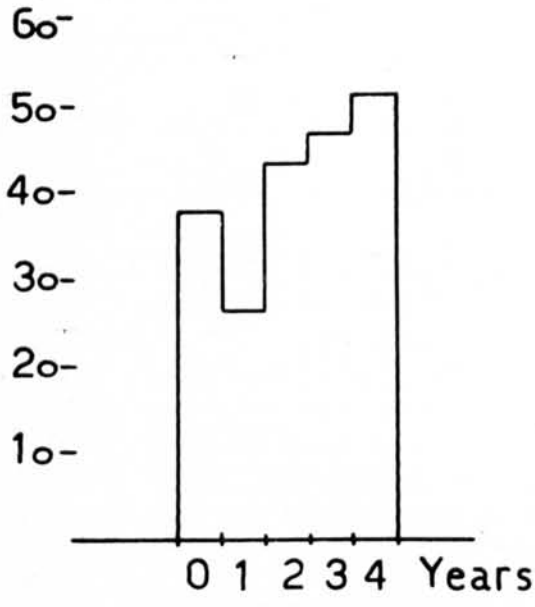

FIG. 1. Proportion of macroscopically positive late lepromin reactions (++ and +++) among 1,251 formerly lepromin-negative subjects classified by the time elapsed from the first inoculation.

suggested that absorption of the antigen from the intestinal tract probably diminished with advancing age. The sample here reported includes subjects in groups of higher age than those studied by Souza-Campos *et al.* (4), and their suggestion might explain the inefficacy of BCG in inducing macroscopically evident lepromin sensitization when administered orally. These results have practical implications, since this type of vaccination is commonly used as a routine procedure in Brazil for provoking positive lepromin reactions in all age groups.

As pointed out above, a positive late lepromin reaction is observed more frequently among subjects reinjected during the same year than among subjects reinjected after the lapse of one year from the first inoculation. This result leads to the conclusions that lepromin has a sensitizing effect in the development of a macroscopically positive late lepromin reaction, and that this sensitizing effect of lepromin may be expected to be of short duration.

If, as has been suggested, hypersensitization to *M. leprae* is a consequence of the ability of the macrophages to lyse leprosy bacilli (1), a macroscopically positive late lepromin reaction, caused by repeated lepromin injections, would be likely to occur among subjects previously manifesting a histologically positive reaction. Such a finding would support the view that the lysogenic ability of the macrophages for *M. leprae* is genetically determined (3). According to this view only subjects whose macrophages are able to lyse *M. leprae* may be expected to be hypersensitized by repeated lepromin injections. Therefore, the importance of lepromin reinjections for preventive purposes is doubtful.

It is apparent in Table 2 and Figure 1 that the frequency of posi-

tive reactions among subjects reinjected after two years increases again. This result suggests that environmental factors may produce an effect similar to the repeated lepromin injections. Among leprosy contacts the principal factor with this effect is probably primary infection by *M. leprae*.

SUMMARY

A sample of 1251 healthy leprosy contacts, not reacting macroscopically to lepromin, was injected a second time with lepromin. Of these, 834 were vaccinated orally with BCG after the first lepromin test. The remaining 417 were not vaccinated and were used as controls.

No difference was found between the groups in the proportion of macroscopically positive late lepromin reactions revealed by the second test. The results suggest that lepromin has a sensitizing effect of short duration.

RESUMEN

Un grupo de 1251 convivientes con enfermos de lepra fué injectado dos veces consecutivas con lepromin. Después del primer test, 834 fueron vacunados con BCG via oral. Los restantes 417 fueron como testigos.

Todos los convivientes estudiados en el presente experimento reagiran negativamente (LR — or ±) al primer lepromin test.

La proporción de LR positivas macroscópicas en el segundo test no fué significantemente diferente en los dos grupos estudiados.

Los resultados sugieren que el lepromin tiene un efecto sensibilizante de corta duración.

RÉSUMÉ

Un échantillon de 1,251 contacts sains de malades atteints de lèpre, et qui ne témoignaient pas de réaction macroscopiquement visible à l'injection de lépromine, ont été soumis à une seconde injection de lépromine. Parmi ces sujets, 834 furent vaccinés par le BCG par voie orale après la première épreuve à la lépromine. Les 417 autres contacts, qui n'avaient pas été vaccinés, servirent de témoins.

Aucune différence n'a été notée entre les deux groupes quant à la proportion de réactions tardives positives à la lépromine survenant à la suite de la deuxième injection et visibles macroscopiquement. Ces résultats suggèrent que la lépromine possède un bref effet de sensibilisation.

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