THE RELATIONSHIP AND SIGNIFICANCE OF THE MANTOUX AND LEPROMIN REACTIONS IN LEPROSY

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A great many investigations have been carried out in attempts to elucidate, first, the reactivity of leprosy patients to tuberculin, a subject well reviewed by Wade (7), and then of late years the relationship between the lepromin and tuberculin reactions. The concept that persons immune to tuberculosis may also be immune to leprosy has recently received support from some workers. Attention has been sharply focused on this possibility by the introduction of BCG vaccination as a prophylactic measure in tuberculosis. Fernandez (3) reported conversion of lepromin-negative healthy persons to positive reactors by the inoculation of killed tubercle-bacillus suspensions, or—and especially—by BCG vaccination. Many leprologists regard the positive lepromin reaction as an indication of a certain degree of immunity against leprosy, and BCG is being used as a potential prophylactic in this disease. The initial findings of de Souza Campos (6) on the use of BCG vaccination among leprosy contacts are encouraging.

The work reported here was undertaken to elucidate possible interrelationships between leprosy and tuberculosis.

EXPERIMENTAL

Leprosy patients of two institutions, the Sungei Buloh Settlement, Selangor, and the Trafalgar Home, Singapore, were chosen for this investigation. In the former place 434 were tested, and in the latter place 351, a total of 785. Their lesions were classified as tuberculoid, lepromatous or atypical according to the criteria already described by Hale and associates (4).

As controls for the Mantoux reaction, 51 healthy Singapore school children were tested, using 10 tuberculin units (TU), and also 50 active tuberculosis patients, with only 1 TU.

As another part of the study 177 healthy children in Singapore between the ages of 1 and 15 years, all Mantoux and lepromin negative, were inoculated with BCG vaccine (0.1 cc. intradermally over the deltoid muscle), and 6 months later they were retested with both tuberculin (10 TU) and lepromin. For comparison, 137 Mantoux negative-reacting leprous children of the same age range were similarly inoculated with BCG, and—this time after three months—were retested as with the others.

The Mantoux test was performed using old tuberculin (Burroughs Wellcome), and the results were read 48 hours after the inoculation. An area of inducation and erythema extending 5 mm. or more was considered to be a positive reaction.

For the lepromin test the reagent used was the purified antigen described by Dharmendra (²), 0.1 cc. being inoculated intradermally. The Fernandez reaction was also read after 48 hours. We felt that this reaction was of the same allergic type as the tuberculin response, and therefore adopted the same criteria of positivity as those used for that reaction.

RESULTS

Relationship of the two reactions.—Among the 51 healthy Singapore school children, 38 (74.5%) were Mantoux positive and 15 (29.4%) were lepromin positive. All of the children that gave positive lepromin reactions were examined carefully, but no evidence of leprosy was found. This reaction, therefore, was probably positive because of their sensitivity to tuberculin. Lowe and McNulty (5) obtained similar results in Nigeria. Leprosy is endemic in both Nigeria and Singapore, but Chaussinand (1) obtained similar results with the school children of Paris, where leprosy is extremely rare and where it was highly unlikely there had been exposure to that infection.

The tuberculosis patients were tested with the idea that, if the positive lepromin reactions found in the children were due to an allergy to some group-specific antigen of the mycobacteria resulting from exposure to the tubercle bacillus, then in active tuberculosis, where allergic responses are greater, a higher lepromin rate could be expected than in the normal population. Of the 50 patients tested, 44 (88%) were found to be Mantoux positive, and 27 (54%) reacted to lepromin.

The results of the two tests in the 177 children vaccinated with BCG are recorded in Table 1. Of 143 children who became Mantoux positive,

Result	Number	Per cent ^b	
Mantoux positive Lepromin positive	95	53.7	
Mantoux positive Lepromin negative	48	27.1	
Mantoux negative Lepromin positive	10	5.6	
Mantoux negative Lepromin negative	24	13.6	

 TABLE 1.—The effect of BCG vaccination of 177 children, 0-11 years of age, originally negative to tuberculin and lepromin.^a

a Antigens: Old tuberculin, 10 TU; Dharmendra so-called purified lepromin.

b Mantoux positive, 80.8%; lepromin positive, 59.3%.

95 (66%) also became positive to lepromin. This must have resulted from the allergy to BCG, as it was most unlikely that so many should have been exposed to leprosy in a period of six months. Of the 34 who did not become reactive to tuberculin, 10 (29%) reacted to lepromin.

This ability of BCG vaccine to render lepromin-negative children positive was also reported by Chaussinand and Lowe and McNulty. The TABLE 2.—Positive Mantoux rates in leprosy patients at the Sungei Buloh Settlement and the Trafalgar Home, Singapore, compared with general population of Singapore and Perak.

				Teprosy	patients					Ceneral	population		
Are		-	Sungei Bulol		T	rafalgar Hon	ne		Singapore			Perak	
(vears)	Type		Posit	tive		Posit	tive		Posi	tive		Pos	tive
		No. tested	No.	%	No.	No.	20	No. tested	No.	2%	No.	No.	20
	Lepromatous	20	+	20)	9 -	2	T						
6-10	Atypical	6	2	23	11	3	- 28	618	374	60	937	340	36
	Tuberculoid	10	3	T	1	1	T						
	Lepromatous	87	15	17)	22	1	32)						
11-15	Atypical .	28	6	32 22	43	21	49 42	2643	2036	1	5291	2767	52
	Tuberculoid	п	4	36	6	3	ī						
1	Lepromatous	85	35	41)	6	3	Ī						
16-20	Atypical	18	6	50.42	19	12	1	664	575	28	1054	684	99
	Tuberculoid	8	1	T	1	1	T						
	Lepromatous	74	9	8	142	104	73					-	
20+	Atypical	76	20	26 24	85	68	80 75						
	Tuberculoid	13	9	T		3	ī						
	Lepromatous	266	60	23)	179	116	65)						
Total	Atypical	131	40	30 26	158	104	66.64	3925	2985	26	7282	3791	15
	Tuberculoid	37	14	38]	14	5	36						
TOTAL		434	114		351	225							

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a Percentages are given only where numbers are sufficient.

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significance of this finding, that persons allergic to the tubercle bacillus are often allergic to lepromin as well, will be discussed later.

Mantoux test in leprosy patients.—The results of the Mantoux test on patients in the two leprosaria are shown in Table 2, in comparison with the rates of the normal population in Singapore and the State of Perak. The data on these places were selected because Singapore, much like the State of Selangor, has the highest positive rate in Malaya, while Perak possesses one of the lower rates.

Tuberculin positivity among the leprosy patients as a whole is shown to be very much lower than that of the general population, and the difference is more marked with the lepromatous and tuberculoid cases (totals, 39.6% and 37.3%) than among the atypical cases (total 50%). The patients at Sungei Buloh come from all over Malaya, but the majority are from Selangor where the settlement is situated. Nevertheless, the rate among the patients is even lower than in Perak, selected for its low rate. The rate in the highest-age group of Singapore patients tends to approach that of the normal population of that island.

This low rate among the leprosy patients may be due to the fact that most are "anergic." The uniformly negative lepromin reactions of the lepromatous cases would support this point, and the group relationship of the mycobacteria could account for the anergy to the tubercle bacillus.

Among the leprosy patients tested there were 48 with tuberculosis. Using one TU, only 21 (43.7%) were positive, and with 10 TU, 31 (64.7%). Comparison with figures of patients with tuberculosis alone shows that even when active tuberculosis complicates leprosy, the patients show reduced Mantoux rates.

Type of leprosy	No.				
and original lepromin results	of cases	Mantoux+ Lepromin+	Mantoux+ Lepromin—	Mantoux- Lepromin+	Mantoux- Lepromin-
Lepromatous Lepromin—	106	9	58	1	38
Atypical Lepromin—	17	6	6	-	5
Atypical Lepromin+	14	1	_	1	12
Total	137	16	64	2	55
Lepromatous of Atypical cas	cases : ses :	Mantoux conver Lepromin conver Conversion of b Mantoux conver	rsion 67/106 rsion 10/106 oth 9/106 sion 13/31 rsion 6/31	= 63.2% = 9.4% = 8.4% = 41.9% = 19.3%	

6/31 = 19.3%

Lepromin conversion Conversion of both

TABLE 3.-Effect of BCG vaccination on 137 Mantoux-negative children with leprosy.

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The results in the 137 negatively-reacting children with leprosy who were inoculated with BCG and retested three months later are presented in Table 3. From the results obtained it is quite obvious that the majority of these children with leprosy were not anergic, as 58 per cent of all the cases showed Mantoux conversion. These results agree with those of Lowe and McNulty, who found that the majority of the lepromatous cases can be made allergic to the tubercle bacillus, and that in a smaller proportion the lepromin reaction also becomes positive. The 42 per cent showing no response may represent the fraction truly anergic, due either to heavy infection with the leprosy bacillus or to hereditary or constitutional factors which render them incapable of allergic responses. In nearly all these persons the BCG vaccine produced no reaction at the site of inoculation.

TABLE 4.—The	Mantoux and	d lepromin	reactions i	n 69	cases	before	and	after	18	months
	residence an	d treatmen	nt in the Su	ngei	Buloh	Settler	nent			

Original fine	andings After 18 months residence				
Reaction group	No. of cases	Mantoux+ Lepromin+	Mantoux+ Lepromin—	Mantoux— Lepromin+	Mantoux
Lepromatous	cases (38))	-		
Mantoux+ (Lepromin—)*	4	1	1	0	2
Mantoux— (Lepromin—) ª	34	2	10	3	19
Atypical cas	es (31)	Second Street	a in the		
Mantoux+ Lepromin+	7	0	4	0	3
Mantoux+ Lepromin—	3	0	2	2 0	
Mantoux— Lepromin+	13	3	3 1		6
Mantoux— Lepromin—	8	0	1 0		7
Total	69	6	21	4	38

a Lepromatous cases are lepromin negative by definition.

Newly admitted patients.—In order to follow what was happening to the Mantoux reaction in leprosy, all the patients admitted to the Sungei Buloh Settlement during one month were followed up throughout their stay, and lepromin and tuberculin tests were repeated periodically. The findings in the 69 cases—38 lepromatous and 31 atypical—over a period of 18 months, given in Table 4, show that in both kinds of cases the Mantoux rate tended to increase during this period in the Settlement.

Among the lepromatous cases the over-all Mantoux rate increased from 10 per cent to 37 per cent (12 patients originally negative becoming positive), and among the atypical cases it increased from 32 per cent to 42 per cent (7 patients originally negative becoming positive).

On the other hand, six patients who were Mantoux positive on admission became negative, a result that was checked repeatedly, and it was noticed that these were the cases with heavy leprous infection. It is therefore apparent that leprosy patients in Malaya may either gain allergy to tuberculosis or lose an existing allergy.

The results in Table 4 also show that a patient (atypical, all lepromatous being negative) may be lepromin positive on admission but can lose his positivity during the course of the disease and treatment. This happened in 16 out of 20 cases in this 18-months period. On the other hand, 6 of the original 38 lepromin negatives became positive and consequently, by our criteria of classification, changed from lepromatous to atypical.

DISCUSSION

The allergy of tuberculous infection or that following BCG vaccination often results in allergic response to the leprosy bacillus, as judged by the lepromin test as performed in this study. This, in all probability, is only a response to some group-specific antigen common to both bacilli. A person who is allergic to the tubercle bacillus can be shown to be allergic to any mycobacterium, even to a saprophytic bacillus such as M. phlei (the timothy grass bacillus). If an allergic response is to be elicited in a Mantouxpositive person using the latter bacillus, then a large quantity must be inoculated as it cannot be produced by small inocula. Lepromin, including the so-called refined antigen of Dharmendra, consists of a suspension of bacillary bodies, and as used in 0.1 cc. quantities constitutes a large inoculum. We have noticed that any dilution of the Dharmendra antigen decreases the number of positive reactions elicited among the general population. On the other hand, tuberculin is a very different, soluble product and is used at so great a dilution that the response to it is probably much more specific.

It is assumed by most leprologists that a positive lepromin reaction indicates some immunity to leprosy. It is difficult, however, to assess the significance of the positive lepromin reaction seen in a Mantoux-positive individual in the absense of leprosy infection. Presumably it is the allergic or local tissue reaction that results from the introduction of the bacillus that enables the body to deal with the invader. This latter—probably nonspecific—type of response can be elicited by large numbers of leprosy bacilli, but smaller numbers may fail to do so. Nevertheless, this small number could well be an infective dose, meaning that infecting bacilli may disseminate and multiply long before the local concentration is sufficient to evoke an allergic response. The hypothesis that BCG vaccination is a prophylactic against leprosy because it renders lepromin-negative persons reactive, is therefore based on very tenuous grounds.

It was noted in this study that the small percentage of lepromin-negative leprosy cases that became positive after BCG vaccination failed to show any clinical change in their condition. The positive response to lepromin that results from active leprosy of the tuberculoid type, and is seen in some atypical cases, is probably specific and may be elicited with a much purer form of leprosy-bacillus antigen than is at present available. The introduction of some substance from the leprosy bacillus as refined and as active as tuberculin would enable us to eliminate these group-specific reactions.

The relatively low Mantoux rates found in the leprosy cases as a whole may be due to three possible causes. First, there may be a general loss of allergic reactivity; second, these persons, for hereditary or other constitutional factors, may be incapable of an allergic response to infection by either the tubercle or the leprosy bacillus; or, third, it may be that leprosy attacks essentially the Mantoux-negative individuals, and that we are therefore dealing with a selected population. Although some leprosy patients with gross infection did lose their Mantoux response, a greater proportion became Mantoux positive after eighteen months residence in the Sungei Buloh Settlement. Because 58 per cent of leprous children showed Mantoux conversion after BCG vaccination, the first two hypotheses, although operative in some instances, do not supply the complete solution. That leprosy infects specifically the Mantoux-negative person would appear to account for the major part of this effect among the inhabitants of Malaya.

Leprosy is well recognized among the people, more especially the Chinese and there is a tendency to segregate sufferers. This segregation could probably also result in screening from tuberculosis infection, so it is only when they come in greater contact with others, as when they enter the settlements, that they meet tuberculosis infection—which certainly exists in a settlement-and the Mantoux rate rises. In countries where voluntary segregation is not practiced to such an extent we would not expect to find this marked difference in the Mantoux rates between people with leprosy and the general population. In Singapore the tuberculosis rate is high, and although leprous children there show low Mantoux rates, as the age increases the rate approaches that of the rest of the community, probably because in this island the chance of tuberculosis contact is great. Thus it appears that tuberculosis probably does afford some protection against leprosy, a view expressed by Chaussinand who states that where tuberculosis is on the increase the prevalence of leprosy declines. On the other hand, however, leprosy gives no protection against tuberculous infec-

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tion, as is evidenced by the rise of the Mantoux rate in leprosy patients, either from contact or by means of BCG vaccination. Furthermore, quite a number of leprosy patients contract and die of virulent tuberculosis.

On this hypothesis, BCG is obviously worth using as a prophylactic against leprosy in young children, for if they can develop some form of tuberculosis infection they will probably exhibit greater immunity to leprosy, and this immunity may not be completely connected with allergy. Any protection given by BCG probably results from the local tuberculosis infection set up, and not from the lepromin positivity which may be consequent upon the vaccination. The initial report of de Souza Campos is encouraging, but there is an obvious need to conduct further carefully controlled experiments with BCG so that its efficiency as a leprosy prophylactic can be accurately assessed.

To summarize, we think that with the initial leprosy lesions probably all infected persons are lepromin positive. Conditions may be such that the body can control the infection, in which case lepromin positivity will persist. If, on the other hand, the infection is not controlled and the bacilli multiply greatly throughout the skin, the patient becomes anergic to them. This control of infection may be associated with skin pigmentation, humidity, or some unknown factor or factors. Whatever the outcome with regard to the lepromin test, the great majority of patients can and do respond to tubercle-bacillus infection with the development of the characteristic allergic response to tuberculin. The results indicate that persons who become Mantoux positive from contact with the tubercle bacillus have some resistance to leprosy, and for this reason BCG is worthy of further trial as a prophylactic in leprosy.

SUMMARY

1. Tuberculin (Mantoux) and lepromin (Dharmendra) tests have been carried out among leprosy patients and normal and tuberculous controls in Malaya and Singapore.

2. Leprosy patients were found to have a much lower positive Mantoux rate than the normal population, although this difference was more marked in children than in adults. In Singapore, the figure among adults with leprosy approached that of the normal population.

3. Children with leprosy were found to respond to BCG vaccination, giving a Mantoux conversion rate very little lower than that found in normal children.

4. It is suggested that leprosy infects a selected population, consisting of Mantoux negatives. That is, tuberculosis infection may give some protection against leprosy. On the other hand, evidence is produced which demonstrates that tuberculosis is readily superimposed on existing leprosy.

5. The conversion to a Mantoux positive state appears to be the essential feature, not the positive lepromin response, that may result from such vaccination. This latter response, it is suggested, is nonspecific.

RESÚMEN

1. Lleváronse a cabo reacciones a la tuberculina (Mantoux) y la lepromina (Dharmendra) entre leprosos y testigos normales y tuberculosos en Malaya y Singapore.

2. Los leprosos resultaron tener un índice positivo de Mantoux mucho más bajo que la población normal, aunque esta diferencia fué más notable en los niños que en los adultos. En Singapore, la cifra entre los adultos que padecían de lepra se aproximó a la de la población normal.

3. Los niños leprosos, según se descubrió, respondían a la vacunación con BCG, arrojando un índice de viraje de la Mantoux muy poco más bajo que el observado en los niños normales.

4. Sugiérese que la lepra infecta a una población escogida, que consta de sujetos negativos a la Mantoux; es decir, que la infección tuberculosa puede otorgar alguna protección contra la lepra. Por otro lado, se ofrecen datos demostrativos de que la tuberculosis se sobrepone fácilmente a una lepra preexistente.

5. El viraje a un estado de positividad Mantoux parece ser la característica esencial, no la respuesta positiva a la lepromina, que puede dimanar de la vacunación BCG. Esta última respuesta, se apunta, es anespecífica.

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