A NOTE ON THE TUBERCULIN REACTION IN LEPROSY

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An exhaustive review of publications pertaining to the cutaneous reactivity of leprosy patients to tuberculin preparations was made by Wade in 1950 ([8]). The material reviewed dated back to the first reported tests by Nicolle in 1907, and included the results obtained by the McKinley Committee ([6]) in 1937 with some ten "TPT" tuberculins made from human *M. tuberculosis* and other mycobacteria, and those of Badger and associates ([2]) in 1940 with PPD preparations made from various mycobacteria.

The early tests employed Old Tuberculin either by the von Pirquet or the Mantoux method. With a few exceptions they showed no difference in reactivity between the clinical types of leprosy, or between leprosy patients and normal population controls. Subsequently, when purified protein derivatives were used in the Mantoux test there was some evidence of lower frequency of tuberculin reactions in lepromatous as compared with nonlepromatous leprosy and with normal controls, although the findings were far from conclusive. In his conclusions Wade stressed the need for further investigations in this field, with different dosages of tuberculin and possibly with other antigens, in the hope of obtaining further information regarding the nature of the lepromin anergy of lepromatous patients.

Recent reports on this subject have been made by, among others, Hale and associates ([5]), Rutgers ([7]) and Fernandez ([4]). Hale *et al.* in Malaya observed that all leprosy patients, regardless of type, had a lower Mantoux rate to 10 TU PPD than the normal population, but that the difference was marked in children and not in adults. Using OT (1:1,000), Fernandez found a markedly lower frequency of tuberculin reactions (43%) in 44 lepromatous patients, apparently mostly adults, than in 39 with tuberculoid lesions (97.4%). Among adult Bantus, on the other hand, Rutgers failed to obtain substantial differences in reactivity to 5 TU of PPD in 62 lepromatous and 54 tuberculoid patients (82% and 76%, respectively), or in 88 household contacts (89%) and 145 other healthy controls (70%), the latter presumably noncontacts. It therefore seems evident that differences in reactivity to tuberculin between patients with lepromatous and tuberculoid leprosy or between leprosy patients and normal population controls have been definitely established and that further confirmation is desirable.

PRESENT REPORT

In 1955, and again in 1960, studies were made in the Philippines of the reactivity to tuberculin of patients with lepromatous and tuberculoid leprosy and of normal population controls. In each study all tests were made with the same stock of commercial (Parke-Davis) PPD in a uniform dose of 0.0001 mgm. per 0.1 cc., or 5 TU. All tests and readings were made by the authors; reactions were measured after 48 hours and indurations with an average diameter of 5 mm. or larger were regarded as positive. The results of the 1955 and 1960 studies are given in Tables 1 and 2, respectively.

FIRST STUDY, 1955

The lepromatous patients tested in 1955 were those of the third series of the clinical evaluation studies of the Leonard Wood Memorial ([3]). There were 195 at the Central Luzon Sanitarium, near Manila, and 199 at the Eversley Childs Sanitarium in Cebu. All of these patients were bacteriologically positive and lepromin negative. The tuberculoid patients were from Cebu City, Mactan Island and Talisay, and with few exceptions all were under treatment as outpatients at the Cebu Skin Clinic. Of the 130 tuberculoids, 17 were bacteriologically positive reactional cases. The rest were bacteriologically negative; 86 patients had small tuberculoid lesions of minimal or slight extent. The 631 healthy persons tested in the 1955 study belonged to the general population of Opon, Mactan Island, an area of relatively high leprosy prevalence (about 18 per thousand for all types of leprosy).

As seen in Table 1, for all the age groups tested the frequency of reactions to 5 TU of PPD was significantly lower for the lepromatous patients than for those with tuberculoid leprosy or for the healthy controls. The age-adjusted percentages of reactors were: 58.1 for the lepromatous patients, 82.2 for the tuberculoids, and 86.7 for the healthy population.

The lepromatous patients in the 1955 study came from two widely separated institutions and were natives, respectively, of Luzon and Cebu. No difference in tuberculin reactivity was found between pa-

TABLE 1.—*Tuberculin reactivity of persons with lepromatous and tuberculoid leprosy and of healthy controls to the same lot and dose of PPD.[a] First study, 1955.*

Age group (years)	Lepromatous patients		Tuberculoid patients		Healthy controls	
	Number tested	Positive (per cent)	Number tested	Positive (per cent)	Number tested	Positive (per cent)
10 - 14	48	31.3	13	46.2	16	50.0
15 - 19	62	45.1	15	66.7	114	69.3
<20	284	63.7	102	89.2	501	94.2
Total	394	58.1[b]	130	82.2[b]	631	86.7[b]

[a]Lot: Park-Davis PPD, Lot 025753-H-026558-V; dose, 0.0001 mgm., or 5 TU.

[b]Total percentages are adjusted to the age distribution of 1,658 persons tested in 1955 and 1960, as constituted into age groups of 10-14, 15-19 and 20 years and over.

No appreciable differences were observed in the frequency of tuberculin reactions in the various adult age groups (20-29, 30-39, etc.). No children under ten years of age were included in the tests.

tients from Luzon (195 patients, 57.2%) and those from Cebu (199 patients, 56.0%).

SECOND STUDY, 1960

The tests done in 1960 were probably more valid than those of the first study, for several reasons. Most of the leprosy patients and all of the healthy population controls came from predominantly rural areas of Cebu Province. Of the controls, 115 were immediate relatives and household associates of leprosy cases in five scattered towns and 118 were residents of the town of Talisay. With few exceptions, the latter group consisted of persons without household exposure to leprosy. None of the patients and healthy controls in the second study had been lepromin-tested previously, eliminating the possibility that prior testing with lepromin might cause some reactivity to tuberculin. The lepromatous patients included only those recently admitted to the Eversley Childs Sanitarium, Cebu, as it was felt that prolonged stay in an institution might also give rise to some tuberculin reactivity, possibly from tuberculous infection. We were able to test only a limited number of tuberculoid cases in this study.

TABLE 2.—*Tuberculin reactivity of persons with lepromatous and tuberculoid leprosy and of healthy controls to the same lot and dose of PPD.*[a] *Second study, 1960.*

Age group (years)	Lepromatous patients			Tuberculoid patients			Healthy controls		
	Number tested	Positive (per cent)		Number tested	Positive (per cent)		Number tested	Positive (per cent)	
		Total	2+ & 3+		Total	2+ & 3+		Total	2+ & 3+
10-14	11	27.3	9.1	5	20.0	20.0	28	46.4	25.0
15-19	40	37.5	30.0	8	37.5	12.5	47	72.3	44.6
<20	155	51.6	38.7	51	70.6	35.3	158	86.7	51.9
Total	206	47.4[b]	35.0[b]	64	61.2[b]	30.2[b]	232	81.3[b]	48.7[b]

[a]Lot: Park-Davis PPD, Lot 025753-H-026558-V; dose, 0.0001 mgm., or 5 TU.

[b]Total percentages are adjusted to the age distribution of 1,658 persons tested in the 1955 and 1960 studies, as constituted into age groups of 10-14, 15-19 and 20 years and over.

Of the 64 tuberculoid patients, 33 were bacteriologically positive and 31 were negative. Age-adjusted percentages of tuberculin reactors were 50.1% for the 33 positives and 78.6% for the 31 negatives. No differences were observed in the frequency of tuberculin reactions in the various adult age groups. No children under 10 years of age were included in the study.

All the 206 lepromatous patients were bacteriologically positive. Of the 64 patients with tuberculoid leprosy, 33 were in a reactional condition and were bacteriologically positive; 22 were bacteriologically negative at the time of the tests but had formerly been positive reactional tuberculoid cases. The remaining 9 tuberculoid patients were bacteriologically negative and relatively early cases with lesions of slight extent, like the majority group of the tuberculoid cases in the 1955 study. Of the 64 tuberculoid patients, 6 were in degree T-1, 20 were T-2 and 38 were T-3; 46 were patients at the Eversley Childs Sanitarium, and the rest were outpatients under treatment by the Cebu Traveling Skin Clinic and the Cebu Skin Clinic.

Lepromin tests were performed simultaneously with the tuberculin tests in all pa-

tients, as also in the 115 healthy controls who were siblings or household associates of leprosy cases, the same batch of lepromin being used throughout. The lepromatous patients were lepromin (Mitsuda) negative, with the exception of 5 who gave small reactions somewhat larger than 4 mm. diameter. Of the 33 bacteriologically positive patients with reactional tuberculoid lesions, 27 (81.8%) were Mitsuda positive; the 31 bacteriologically negative tuberculoid patients were 87.1 per cent Mitsuda positive. Only 2 of the 115 healthy controls failed to give positive Mitsuda reactions.

As shown in Table 2, the patients with active lepromatous leprosy in our second study (1960) again reacted with lower frequency to 5 TU of PPD than did the healthy controls from the same geographic area. The age-adjusted rates for tuberculin reactors were: 47.4 per cent of 206 lepromatous patients as against 81.3 per cent of 233 healthy controls. In addition, the lepromatous patients gave reactions of somewhat weaker intensity (35.0% of 2+ and 3+ degrees) than the normal controls (48.7% of the same degrees).

Among the 64 tuberculoid patients, the age-adjusted frequency of reactions to 5 TU of PPD was 61.2 per cent, a figure slightly higher than that for the lepromatous patients (47.4%) but appreciably lower than that for the healthy controls (81.3%). Our findings with regard to tuberculin reactivity of tuberculoid cases in this study thus differs from those obtained in 1955, in which 130 tuberculoid cases were found to react with a frequency (82.2%) close to that of the normal population (86.7%) and much higher than that of lepromatous patients (58.1%).

The difference between the 1955 and 1960 results regarding the tuberculin reactivity of tuberculoid patients may be due, in part at least, to the fact that in 1955 the tuberculoid patients were mostly bacteriologically negative, nonreactive cases with minimal lesions, whereas a large proportion of those tested in 1960 were bacteriologically positive or clinically advanced and many were in a reactional condition or had been in reaction. As stated in footnote to Table 2, of the 64 tuberculoid patients 33 were bacteriologically positive and 31 were negative when tested; the age-adjusted tuberculin frequencies were: 50.1 per cent of the positives and 78.6 per cent of the negatives, showing that in frequency of tuberculin reactions the former approximated the lepromatous patients (47.4%) while the latter came very close to the normal controls (81.3%).

Regarding the healthy controls of the 1960 study, the age-adjusted rates of the reactions to 5 TU of PPD were, for the 115 contacts, 86.1 per cent, and for the 118 "noncontact" Talisay residents, 75.6 per cent, a difference not significant in the statistical sense. For brevity, the contact and noncontact groups were combined in Table 2 into a single group of healthy controls, of whom 81.3 per cent reacted to tuberculin.

COMMENT

In the two separate studies here reported, the definitely lower frequency of reactions to tuberculin in persons with active lepromatous leprosy as compared with normal population controls has been established. The question arises whether this lower frequency results from the lepromatous condition, that is, from the same cause which is responsible for the lepromin negativity or anergy, or whether persons who were originally or essentially tuberculin negative are more susceptible than others to lepromatous leprosy. Suggestive is the observation that the tuberculoid cases in reaction, bacteriologically positive, gave a tuberculin rate approximating that of the lepromatous group, while that of the nonreactional tuberculoid cases resembled that of the healthy controls. It would be desirable in this respect to study the reactivity of lepromatous patients and of comparable normal controls to other mycobacterial antigens and also to antigens of other than mycobacterial nature. Such studies should help in interpreting the specificity of the complete depression of the Mitsuda reaction and the partial one of the tuberculin reaction in lepromatous leprosy.

SUMMARY

Two separate studies were made of the tuberculin reactivity of lepromatous and tuberculoid patients and of normal population controls, using in each instance the same stock and the same dose (0.0001 mgm. or 5 TU) of PPD. In the first study, the age-adjusted frequencies of positive tuberculin reactions were: for lepromatous patients 58.1 per cent, for tuberculoid patients 82.2 per cent, and for healthy controls 86.7 per cent. In the second study the corresponding figures were: 47.4 per cent for the lepromatous cases, 61.2 per cent for the tuberculoids, and 81.3 per cent for the healthy controls. In addition, only 35.0 per cent of the lepromatous patients gave strong reactions (2+ and 3+ intensity), as compared with 48.7 per cent of such reactions in the control population.

A definite lowering of frequency of tuberculin reactivity in patients with lepromatous leprosy has thus been established, although about 50 per cent were found to react to 5 TU of PPD. It appears from our findings that a reduction in frequency of tuberculin reactivity likewise occurs in tuberculoid patients during reactional phases in which they become bacteriologically positive.

RESUMEN

Se hicieron dos estudios separados de la reactividad a la tuberculina de los enfermos lepromatosos y tuberculoideos y de testigos de la población normal, usando en ambos casos el mismo lote y la misma dosis (0.0001 mgm. o 5 UT) de DPP (PPD). En el primer estudio, las frecuencias ajustadas a la edad de las reacciones positivas a la tuberculina fueron: para los lepromatosos, 58.1 por ciento; para los tuberculoideos, 82.2 por ciento; y

para los testigos sanos, 86.7 por ciento. En el segundo estudio, las cifras correspondientes fueron: 47.4 por ciento para los lepromatosos, 61.2 por ciento para los tuberculoideos y 81.3 por ciento para los testigos sanos. Además, solamente 35.0 por ciento de los lepromatosos acusaron potentes (intensidad de 2+ y 3+), comparado con 48.7 por ciento de esas reacciones en la población de testigo.

Se ha establecido así, pues, una reducción bien definida en la frecuencia de la reactividad a la tuberculina en los enfermos de lepra lepromatosa, aunque aproximadamente 50 por ciento se mostraron reactores a 5 UT de DPP. A juzgar por los hallazgos, parece que también hay una reducción en la frecuencia de la reactividad a la tuberculina en los tuberculoideos durante las fases reaccionales en las que se vuelven bacteriológicamente positivos.

RESUMÉ

Deux études ont été menées en vue d'étudier la réactivité à la tuberculine de malades lépromateux et tuberculoïdes et celle d'une population témoin, en utilisant dans chaque cas le même lot et la même dose de PPD (0.0001 mg, soit 5 TU). Dans la première étude, les fréquences, ajustées par âge, des réactions positives à la tuberculine ont été: 58.1% pour les malades lépromateux, 82.2% pour les tuberculoïdes, et 86.7% pour les témoins sains. Dans la seconde étude, les chiffres correspondants ont été: 47.4% pour les lépromateux, 61.2% pour les tuberculoïdes, et 81.3% pour les témoins sains. En outre, 35.0% des malades lépromateux ont donné des réactions fortes (d'intensité 2+ et 3+), contre 48.7% de réactions analogues dans la population témoin.

Un affaissement marqué de la réactivité à la tuberculine a donc été établi chez les malades lépromateux, encore que, comme il a été observé, 50% réagissent à 5 TU de PPD. Il apparaît de nos observations qu'une réduction de la fréquence de la réactivité à la tuberculine survient selon toute vraisemblance chez les malades tuberculoïdes durant les épisodes réactionnels au cours desquels ils deviennent bactériologiquement positifs.

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