

# INTERNATIONAL JOURNAL OF LEPROSY

OFFICIAL ORGAN OF THE INTERNATIONAL LEPROSY ASSOCIATION

PUBLISHED WITH THE AID OF THE  
LEONARD WOOD MEMORIAL

Publication Office: School of Medicine, Tulane University,  
1430 Tulane Avenue, New Orleans 12, Louisiana  
Entered at the Post Office at New Orleans as second-class matter.

VOLUME 24, NUMBER 4

OCTOBER-DECEMBER, 1956

## EDITORIALS

*Editorials are written by members of the Editorial Board, and opinions expressed are those of the writers.*

### THE LEPROMIN REACTION AND NONSPECIFIC REACTIVITY TO TUBERCULIN

Of the several reported studies of the relationships of the reactions to lepromin and tuberculin there are three, two of them derived from the works of Lowe in Nigeria, and the third from that of Guinto and associates in the Philippines, which were either deliberately designed to provide comparisons with respect to sensitivity to small and large doses of tuberculin or that permit such comparisons, with the possibility in mind that high-dose tuberculin reactions may be nonspecific in nature. Recognizing that the thesis of nonspecificity developed by Palmer and associates<sup>1, 2</sup> is not as yet widely recognized, it may nevertheless be of interest to accept it provisionally and examine the results of those studies and certain others from that point of view.

Shortly after the first of the Nigerian reports was published,<sup>3, 4</sup> Lowe said<sup>5</sup> that he believed that the reports on the nonspecific factor<sup>2</sup> were in line with his own findings, and that a further study was being made, jointly with a tuberculosis specialist, using two doses of a PPD-type product (a "purified tuberculin" from the Institut Pasteur in Paris) for a

<sup>1</sup> PALMER, C. E. Tuberculin sensitivity and contact with tuberculosis; further evidence of nonspecific sensitivity. *American Rev. Tuberc.* **68** (1953) 678-694 (abstract in this issue).

<sup>2</sup> EDWARDS, L. B., PALMER, C. E. AND MAGNUS, K. BCG Vaccination. WHO Monograph Series No. 12, 1953, pp. 39-50.

<sup>3</sup> LOWE, J. AND McNULTY, F. Tuberculosis and leprosy; immunological studies. *Leprosy Rev.* **24** (1953) 61-90.

<sup>4</sup> LOWE, J. AND McNULTY, F. Tuberculosis and leprosy; immunological studies in healthy persons. *British Med. J.* **2** (1953) 579-584.

<sup>5</sup> LOWE, J. Personal communication (letters dated February 1 and March 30, 1954).

correlation of the results with those of the lepromin test. Sometime after Lowe's death, inquiries were addressed to both London and Nigeria about the results of that work. Subsequently a report of the findings was prepared by McFadzean,<sup>6</sup> and the data of the original study were re-examined by Davey with findings reported in this issue.<sup>7</sup>

The Lowe-McFadzean report is a brief one of tests of 621 school-children aged 5-16 years. The first test was made with 5 TU of the PPD product, and individuals with less than 6 mm. response were re-tested with 100 TU. There are detailed tabulations and analysis of which brings out points of interest.

The total figures (eliminating decimals) are as follows: Of the entire group, 281 were positive to lepromin, or only 45 per cent.<sup>8</sup> The tuberculin tests detected a total of 424 reactors, or 68 per cent of the lot—200 (32%) with the first test, and another 224 (36%) with the second test. The results with the 100 TU test are shown to place Nigeria along with other countries (Egypt and India) where there are high frequencies of the non-specific tuberculin reactivity. It was pointed out that it is unlikely that the prevalence of tuberculosis in the community, which is low, is sufficient to explain the high total tuberculin-positive rate, and that there is no evidence of a relation to infection by leprosy.

Calculations showed on the whole a statistically significant correlation between the lepromin and tuberculin reactions. The lepromin reactors among those positive to 5 TU were 75 per cent, but among those entirely negative to tuberculin they were only 16 per cent; the group reacting only to 100 TU was half-way between, with 45 per cent lepromin positives. The data tabulated below show a similar trend with respect to the *strength* of the positive lepromin reactions. They also show large differences of the rates of the two age groups.<sup>9</sup>

1. Total Group, Aged 5-16 Years (621)

(a) Positive to 5 TU (200/621, 32%):		
Strongly positive to lepromin (63).....	32%	} 75%
Weakly positive to lepromin (86).....	43%	
Negative to lepromin (51).....	25%	

<sup>6</sup> LOWE, J. AND MCFADZEAN, J. A. Tuberculosis and leprosy—further immunological studies. *Leprosy Rev.* **27** (1956) 140-147 (abstract in this issue).

<sup>7</sup> LOWE, J. AND DAVEY, T. F. Tuberculin and lepromin reactions in Nigeria; an analysis of the data of Lowe and McNulty. *Internat. J. Leprosy* **24** (1956) 419.

<sup>8</sup> Palpable reaction nodules 2-3 mm. in diameter were read as weakly positive. Considering the lepromin used, and the fact that in other tropical regions much higher percentages are obtained with regular Hayashi-Mitsuda lepromin, these readings may be accepted as valid positives. Which is not to say that all the nonreactors would have been negative with the more usual antigen.

<sup>9</sup> In the tabulations in this note the percentages of the high-dose reactors indicate the frequency among the first-test negatives. The proportions of the whole groups which they represent will be evident by simple arithmetic difference.

(b) Positive to 100 TU (224/421, 54%):		
Strongly positive to lepromin (23).....	10%	} 45%
Weakly positive to lepromin (77).....	34%	
Negative to lepromin (124).....	55%	
(c) Negative to both (197/621, 32%):		
Strongly positive to lepromin (4).....	2%	} 16%
Weakly positive to lepromin (28).....	14%	
Negative to lepromin (165).....	84%	

2. Group Aged 9-16 Years (334)

(a) Positive to 5 TU (155/334, 46%):		
Strongly positive to lepromin (60).....	39%	} 81%
Weakly positive to lepromin (66).....	43%	
Negative to lepromin (29).....	19%	
(b) Positive to 100 TU (127/179, 71%):		
Strongly positive to lepromin (18).....	14%	} 55%
Weakly positive to lepromin (52).....	41%	
Negative to lepromin (57).....	45%	
(c) Negative to both (52/344, 16%):		
Strongly positive to lepromin (1).....	2%	} 27%
Weakly positive to lepromin (13).....	25%	
Negative to lepromin (38).....	73%	

3. Group Aged 5-8 Years (287)

(a) Positive to 5 TU (45/287, 16%):		
Strongly positive to lepromin (3).....	7%	} 51%
Weakly positive to lepromin (20).....	44%	
Negative to lepromin (22).....	49%	
(b) Positive to 100 TU (97/242, 40%):		
Strongly positive to lepromin (5).....	5%	} 31%
Weakly positive to lepromin (25).....	26%	
Negative to lepromin (67).....	69%	
(c) Negative to both (145/287, 51%):		
Strongly positive to lepromin (3).....	2%	} 12%
Weakly positive to lepromin (15).....	10%	
Negative to lepromin (127).....	88%	

Correlation of the two kinds of reactions is no longer newsworthy. It is of interest, however, how relatively poor was the correlation among

individuals reacting only to the high dose of tuberculin. Entertaining the nonspecificity idea it might be said that whatever was the unknown antigenic factor responsible for the high-dose tuberculin positives, it is of relatively low effectiveness with respect to lepromin reactivity; but at the same time it is clear that a very large proportion of the minority who had not acquired even the low-grade sensitivity to tuberculin were incapable of reacting to a single dose of lepromin.

Turning now to the earlier study, Lowe and McNulty used the von Pirquet test to screen out the hypersensitives and then tested the negatives with 50 TU of the purified tuberculin. Lumping the results together, they reported that 80 per cent of 278 healthy adults were found positive, and 58 per cent of 81 children aged 1-15 years. (It was the fact that these rates were very high for the locality, where there is little clinical tuberculosis, that led Lowe to initiate the further study.) The lepromin rates were 81 per cent for the adults, but only 38 per cent for the children. The antigen used would seem to approach the effectiveness of the Hayashi-Mitsuda lepromin for adults but not for children.

In his re-examination of the original records, Davey<sup>7</sup> separated the data for the two tuberculin tests. Setting up the results essentially as before, the following distribution results.

1. *Adult group (278)*

(a) Positive, von Pirquet (79/278, 28%):	
Positive to lepromin (76).....	96%
(b) Positive to 50 TU (144/199, 72%):	
Positive to lepromin (121).....	84%
(c) Negative to both tests (55/278, 20%):	
Positive to lepromin (27).....	49%

2. *Child group (81)*

(a) Positive, von Pirquet (10/81, 12%):	
Positive to lepromin (9).....	90%
(b) Positive to 50 TU (37/71, 52%):	
Positive to lepromin (22).....	59%
(c) Negative to both tests (34/81, 42%):	
Positive to lepromin (0).....	0%

Here are seen relatively low percentages for the first test, and relatively high percentages for the second test although the dose was only 50 TU. This could perhaps be explained on the ground that the von Pirquet test is not equivalent even to 5 TU of PPD by the Mantoux test, and the lesser number of positives elicited by it would leave more to react to a large dose.

A point of interest with respect to the tuberculin negatives is that whereas one-half of the adults were recorded as giving positive lepromin reactions, none of the children was positive. Apparently a highly non-reactive lot! However, it should be noted that Lowe had not included

among the positives those with the 1+ grade of reaction, which were included in the later work.

This report points out that among the adults a very large number of positive lepromin reactions were associated with only mild degrees of tuberculin sensitivity, and many with none at all, and that the results with the children show strong presumptive evidence of the existence of nonspecific reactions to tuberculin.

A comparable study was made by Guinto, Doull and Mabalay,<sup>10</sup> although it was not specifically an inquiry concerning nonspecificity. The subjects were 544 schoolchildren 7-9 years of age in Cebu, Philippines. The first tuberculin test was with 1 TU of PPD (Parke, Davis), and the 468 who did not react to it were retested with 250 TU. The lepromin was of the Hayashi-Mitsuda type. In gross, a total of 72 per cent reacted to tuberculin, and 65 per cent to lepromin. An analysis of the data gives the following figures.

Positive to 1 TU (76/544, 14%):	
Positive to lepromin (64).....	84%
Positive to 250 TU (315/468, 67%):	
Positive to lepromin (239).....	76%
Negative to 250 TU (153/544, 28%):	
Positive to lepromin (52).....	34%

Here, with very small first dose of tuberculin used, the number of positives was low, about the same as with the von Pirquet test in Nigerian children, while the very large second dose elicited unusually many reactors, materially more than in the comparable Nigerian group that received 100 TU. The number is not, however, proportionately large, which suggests that with increases of the dose beyond a certain level (100 TU?) the law of diminishing returns comes strongly into effect. The proportions of both groups of tuberculin positives who also reacted to lepromin were high, but the authors pointed out that the indication of relationship of the two reactions was especially clear in the high-dose test. In this instance, despite their early age, rather more of the persistent tuberculin negatives were, lepromin positive than even in the older age group of Lowe and McFadzean, but that may be explained by the differences between the antigens used.

In considering the reasons for the large-dose reactions it is said that there is no assurance that they are necessarily due to tubercle-bacillus infection (as there probably is in the case of the small-dose reactions); that "some reactions to the second strength may have resulted from infection with mycobacteria other than the tubercle bacillus." However, the probability that so many children could have had latent leprosy infec-

<sup>10</sup> GUINTO, R. S., DOULL, J. A. AND MABALAY, E. B. Tuberculization and reactivity to lepromin. Association between lepromin and tuberculin reactions in school children in Cordova and Opon, Cebu, Philippines. *Internat. J. Leprosy* **23** (1955) 32-47.

tions was regarded as very remote, and no other mycobacterial infection is known in that region, so "until some better explanation is forthcoming" it might be assumed that most of the reactions to PPD were caused by the tuberculin bacillus.

The data here reviewed show that persons who react to small doses of tuberculin (the "specific" sensitivity) are in largest proportion also reactive to lepromin, that those who react only to large doses of tuberculin (the "nonspecific" sensitivity) are less likely to be lepromin positive, and that those who are quite negative to tuberculin give the smallest proportions of lepromin responses. It appears that the last group are least capable of response to such allergens encountered in life or administered in test doses, and it would be quite understandable if they should be found especially liable to infection with the pathogenic mycobacteria.

Since lepromin positivity has a more or less high degree of association with tuberculin sensitivity of both high and low grades, and since many if not most of the high-dose tuberculin reactions may be ascribable to nonspecific factors, the question follows whether lepromin positivity associated with the nonspecific condition may be related to resistance to leprosy infection as "natural" or "spontaneous" positivity in general is supposed to be. This question involves no retraction whatever of the thesis held by us personally for the past twenty years, that the Mitsuda test is one of capability to react to the dose of lepromin injected because of immunological changes induced by the injection of the lepromin, which is an allergen. However, one important thing has been added in more recent years, namely, evidence that an individual may be *conditioned* to react—i. e., that the basic capability of reacting may be enhanced—by nonspecific means, so that individuals who otherwise might not show a positive effect after a single injection may do so, and others may react more strongly.

It is a well-established fact that lepromin reactivity can be induced nonspecifically by BCG vaccination. The belief is widely held that this induced reactivity will be protective, as "spontaneous" lepromin positivity is supposed to be; and observations have been reported which indicate that that may be so.<sup>11, 12, 13</sup> If nonspecific tuberculin reactivity can be induced by other factors (and it is highly unlikely that 68% of the children aged 5-8 years in Nigeria and 72% of those 7-9 years old in Cebu could have been infected with either the tubercle or the leprosy

<sup>11</sup> DE SOUZA, CAMPOS, N. BCG in the prophylaxis of leprosy; a preliminary report. *Internat. J. Leprosy* **21** (1953) 307-312.

<sup>12</sup> DE SOUZA CAMPOS, N. Primeiros resultados do BCG na profilaxia de lepra. *Mem. VI Congr. Internac. Leprol.*, Madrid, 1953; Madrid, 1954, pp. 518-520.

<sup>13</sup> CONVIT, J. Studies of leprosy in the German ethnic group of Colonia Tovar, Venezuela. V. The morbidity rates in BCG-vaccinated and unvaccinated groups during five years. *Internat. J. Leprosy* **24** (1956) 269-274.

bacillus), and if as is evidently the case there is a considerable degree of association of lepromin positivity with such nonspecific tuberculin sensitivity to high doses, then that condition may very well contribute to resistance to leprosy infection.

There is suggestive collateral evidence in the findings of a special committee of the British Medical Research Council.<sup>14</sup> Studying some 56,700 schoolchildren in England with low and high doses of tuberculin (3 and 100 TU, OT) they found 28 per cent to react positively with the former and 16 per cent of the negatives (12% of the total) to do so with the latter. After 30 months follow-up they found the annual incidence of tuberculosis per thousand among the high-dose reactors (who were not vaccinated) to be only 0.74, against 1.94 among the unvaccinated group of persistent negatives. (Among those negatives who were vaccinated with BCG or with a vole-bacillus vaccine, the rates were 0.37 and 0.44, respectively.) That 0.74 rate was very different from the figure for the low-dose positives (i. e., those presumably sensitized by infection with the tubercle bacillus), for among them the case rate was also high, 1.75. The only concession to the idea of nonspecific reactivity—which was mentioned—was to suggest (parenthetically) the possibility that “the nontuberculous allergy” may be “associated with some protection against tuberculosis.” “The interpretation of weak reactions to tuberculin,” they remark, “requires further investigation.”

In this general connection there is interest in the note by Lampe, which appears in the correspondence section of this issue, on a hypothesis once entertained by Paneth that leprosy infection might be very prevalent in an endemic area. Working in the Karo Districts of Indonesia he had obtained 30 per cent positive Mantoux reactions in children under 15 years of age, and in 74 per cent of adults. Seeking some other reason than tuberculosis infection for these findings, he suggested that—supposing latent leprosy would give tuberculin positivity—wide dissemination of that infection might be the explanation. He abandoned the idea, however, when he found that persons with actual leprosy gave fewer tuberculin reactions than nonleprosy cases.

One other study will be noted, although tuberculin testing was not involved. Dharmendra and Chatterjee<sup>15</sup> determined the leprosy rates among 680 people in the Bankura district of India who had been tested with lepromin (Hayashi-Mitsuda type) 15 and 20 years before. Of 63 negatives (excluding 93 of them who had become positive during repeated

---

<sup>14</sup>[MEDICAL RESEARCH COUNCIL] B. C. G. and vole bacillus vaccines in the prevention of tuberculosis in adolescent. First (progress) report to the Medical Research Council by their Tuberculosis Vaccines Clinical Trials Committee. *British Med. J.* **1** (1956) 413-427 (abstract in this issue).

<sup>15</sup>DHARMENDRA AND CHATTERJEE, K. R. Prognostic value of the lepromin test in contacts of leprosy cases. *Leprosy in India* **27** (1955) 149-158; *reprinted in Internat. J. Leprosy* **24** (1956) 315-318 (with an addendum in this issue, Correspondence).

lepromin testing) 27 per cent had developed leprosy, and most of them (14 of the 17) were lepromatous. Of the 524 "spontaneous" positives only 3.2 per cent (17) had developed leprosy, and none of them was lepromatous.

(Of interest, too, is the fact that of the 93 converters mentioned only 5, or 5.4%, were with the disease, one of them lepromatous, whereas 10 of the 16 who did not convert had developed leprosy, 8 of them lepromatous. This is a rate of 63% for these persistently negative cases, which despite the unreliability of a rate derived from so small a group must be regarded as significant. In any event, it is very different from the results among the 47 run-of-the-mill negatives who were not reinjected, some of whom would undoubtedly have converted had they been repeatedly tested, since 85% of those who were reinjected did so. In that group of 47 only 7 cases developed, or 15%—6 of them lepromatous. One may speculate as to whether or not there may have been benefit for many from the single injections received, even though they showed no local response at the time.)

Now, among the 524 original positives some proportion must have been infected with the tubercle bacillus, or at least would have reacted to a small dose of tuberculin; and some very likely had latent leprosy infections, for Bankura was a hotbed of that disease. However, since India is one of the countries with high rates of large-dose tuberculin reactivity, there was in all probability a material proportion of individuals of that kind among the lepromin positives. Yet that group showed a relatively high degree of protection against overt leprosy infection. It is intriguing to speculate about the extent to which a nonspecific immunological condition, due neither to leprosy nor tuberculous infection, may have contributed to the resistance exhibited.

This is of course sheer speculation concerning a phenomenon not yet fully established or explained, but the possibility seems sufficiently interesting to justify the suggestion that immunological studies along this line, lepromin reactivity correlated with two-dose tuberculin testing, might be undertaken in various regions for future information. This would be but an extension of the study of the relationships of the two diseases, or more specifically of the reactions pertaining to them, which has aroused the interest of so many workers. There are, of course, obvious difficulties—including the necessity of waiting many years for the answer.

—H. W. WADE