# TUBERCULOSIS AND LEPROSY — FURTHER IMMUNOLOGICAL STUDIES

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## Introduction

The idea that infection with *Mycobacterium tuberculosis* may produce cross sensitivity to the allied organism *Mycobacterium leprae* has been the subject of numerous papers during the last fifteen years, particularly from South America and from France. In three recent papers[1, 2, 3] one of us (J.L.) discussed the literature of the subject and presented recent work. It was concluded that there was strong evidence that natural tuberculous infection, as revealed by a positive tuberculin test, and also BCG vaccination, could and usually did sensitize a person to the leprosy bacillus, as shown by a positive lepromin test; and that this sensitization might possibly be accompanied by relative immunity to leprosy.

The possibility of the reverse phenomenon was also considered, i.e. infection with either *M. leprae* or some allied organism inducing sensitivity to tuberculin, but evidence on the matter was lacking.

While these articles were in the press there appeared the reports of Edwards *et al.*[4, 5] suggesting that in certain countries there appeared to be a non-specific factor which could cause a positive tuberculin test. They found that in certain areas, particularly in India and in Egypt, there were two types of response to tuberculin, (a) a high grade sensitivity (fairly strong reaction to a weak dose of tuberculin, 5 or 10 T.U.) which indicates the

specific response to tuberculous infection, and (b) a low grade sensitivity (small reaction to a small dose of tuberculin which appears as a larger reaction to a strong dose such as 100 T.U.) which is considered to constitute a non-specific response.

Regarding the nature of the factor producing the non-specific response, Edwards *et al.* make the following statements. "The cause is still unknown." "It is more prevalent in rural than in urban areas." "The hypothesis was offered that it is due to infection with an organism antigenically related to *M. tuberculosis*."

It has been shown that *M. leprae* is antigenically related to *M. tuberculosis*. Moreover, in all the areas mentioned by Edwards *et al.* (the south-eastern United States, Egypt, India) leprosy is endemic. On the other hand in the south-eastern United States leprosy is rare, while the non-specific factor is reported to be prevalent there, and also leprosy is endemic in Mexico where the non-specific factor is not common. It seems most unlikely that in all the countries where the non-specific factor is found to operate it could be caused by infection with *M. leprae*. It is, however, possible that, in certain areas, leprous infection might be one factor tending to produce sensitivity to *M. tuberculosis*.

The objects of the work here reported were (1) to obtain more data on cross sensitivity between tuberculous infection and leprous infection; (2) by using the methods of Edwards *et al.* to obtain evidence whether, in Nigeria, a non-specific factor influenced the result of the tuberculin test, and if so (3) to get evidence whether, in Nigeria, this non-specific factor could be infection with the leprosy bacillus.

**General Background of the Work**

In the work reported previously [1,2] from the Uzuakoli area of Eastern Nigeria, most of the healthy persons studied were adolescents and adults, with high tuberculin-positive and lepromin-positive rates; correlation between the two tests, though definite, was incomplete. In the present investigation it was planned to study healthy children, with lower tuberculin-positive and lepromin-positive rates, which might facilitate more accurate correlation.

By collaboration with the local mission school authorities it was arranged to test all the children, both boys and girls, in two large day schools. The ages of the children were between 5 and 16 years.

The schools were situated near Uzuakoli, East Nigeria, an area where clinical tuberculosis of any kind appears uncommon, where there are practically no cows (because of trypanosomiasis), where

milk in any form is not a common article of diet, and where tuberculosis of bovine origin apparently does not occur.

On the other hand, leprosy is common in the area, the incidence in the past having been of the order of 5 per cent of the population; many of the cases, however, were mild and " closed." In addition, there is in the near vicinity a leprosy settlement with several hundred patients, mostly open cases, who have a certain amount of contact with surrounding markets and villages.

**Methods**

621 children between the ages of 5 and 16 were tested with PPD 5 Tuberculin Units and, if the reaction was less than 6 mm., they were tested again with 100 Tuberculin Units. At the same time, all the 621 children were given an intradermal injection of lepromin prepared and standardized biologically at the Leprosy Research Unit, Uzuakoli.

**Methods of Reading**

TUBERCULIN. Measurements were made of definite areas of oedema.

LEPROMIN. For the present purpose, only the late (Mitsuda) reaction is considered, for in the dark-skinned Africans the reading of the early reaction is often not easy, and the late reaction is found more reliable. The late reaction consists of the formation of a nodule at the site of the injection of lepromin, the nodule usually appearing within two weeks and being at its maximum size about 21 days after the injection. The readings here recorded were made on the 21st day.

Those with no nodule formation, or a tiny one only just palpable, were recorded as *Negative.*

Those with a small but easily palpable nodule, usually measuring 2-3 mm. in diameter, were recorded as *Weak Positive.*

Those with a larger and very easily palpable nodule were recorded as *Strongly Positive.*

**Results**

The results of the simultaneous tuberculin and lepromin tests are given in Tables I-III together with the $X^2$ values. Table I gives the results for the entire age group 5-16 years, Table II the results for the age group 5-8 years, and Table III the results for 9-16 years.

The anlyisis of these results was kindly undertaken by Dr. Ian Sutherland of the Medical Research Council's Statistical Research Unit, who states that each of the three values of $X^2$ is undoubtedly significant, confirming the reality of the association between the results of the two tests. As regards the results in the 9-16 years

sub-group, inspection of the individual values contributing to $X^2$ $[(O-E)^2 \div E]$ shows quite a smooth relationship between the two tests, i.e. the stronger the tuberculin reaction, the stronger is the lepromin reaction. There are no breaks which might suggest non-specificity of weak tuberculin reactions. However, in the 5-8 years sub-group it appears that the *strong* reactions, i.e. those greater than 10 mm. to 100 T.U. and greater than 5 mm. to 5 T.U., behave as a group and show no association with the lepromin reaction. This pattern, if real, is difficult to interpret; the numbers, however, are small and the effect may only be due to chance.

**Discussion**

I COMPARISON OF LEPROMIN AND TUBERCULIN REACTIONS

A significant correlation has been demonstrated between the lepromin and tuberculin reaction in the group investigated. This, however, could have resulted from the simultaneous exposure of the population to leprosy and tuberculosis. It is felt that further elucidation of this relationship could best be made by undertaking simultaneous tuberculin and lepromin studies

(a) in an area in which tuberculosis occurs but not leprosy,
(b) in an area in which leprosy occurs but not tuberculosis, and
(c) in an area in which neither tuberculosis nor leprosy is found.

The first is easy to find, but it is doubtful if the latter two exist.

II. EVIDENCE THAT THERE IS A NON-SPECIFIC FACTOR TENDING TO CAUSE A POSITIVE TUBERCULIN TEST

If such a factor operated in Nigeria, it might be expected to reveal itself in two ways: (a) by a tuberculin-positive rate too high to be explained by the known prevalence of tuberculous infection, and (b) by the high frequency of cases in which tuberculin sensitivity was of low or moderate degree and revealed only by large doses of tuberculin, as described by Edwards *et al.*

(a) *The tuberculin-positive rate in Eastern Nigeria*: The tuberculin-positive rates in our present studies in children and adolescents are influenced by the standards applied in reading the tuberculin test. If the rather rigid standard is adopted to a 6 mm. or more response to 5 T.U., and 11 mm. or more response to 100 T.U., the positive rate was 44.3 per cent. If less rigid standards are adopted, and 6 mm. or more reaction to 5 T.U. or 100 T.U. are considered significant, the positive rate rises to 68.3 per cent. How do these figures fit in with the known incidence of tuberculosis in the area?

A few cases of tuberculosis have been seen among the leprosy patients and in the general population, but a definite opinion has been formed that tuberculosis is not common in the area where this study was made. It seems unlikely that the present incidence of tuberculosis alone can explain the tuberculin-positive rates here recorded in children and adolescents. Moreover, in a previous study in this same area 80.2 per cent of adults were found to be definitely positive to 50 T.U.

(b) *Comparison of our findings using PPD tuberculin with those of Edwards et al.*: The results reported by Edwards *et al.* are given below, followed by our findings in Nigeria presented in a comparable form:—

| | Response to 5 T.U. (or 10 T.U.) | | | | | Response to 100 T.U. in those showing 0-5 mm. response to 5 T.U. | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age | No. | 0-5mm. | 6-10mm. | Over 10mm. | | | 0-5mm. | 6-10mm. | Over 10mm. | |
| Age | No. | 0-5mm. | 6-10mm. | Over 10mm. | | | 0-5mm. | 6-10mm. | Over 10mm. | |
| **INDIA** | | 5 T.U. | | | | | | | | |
| 5-10 | 1206 | 85% | 9% | 6% | | 674 | 40% | 22% | 38% | |
| | | | | 15% | | | | | 60% | |
| 11-15 | 924 | 77% | 12% | 11% | | 447 | 32% | 20% | 48% | |
| | | | | 23% | | | | | 68% | |
| 5-15 | 2130 | 81% | 11% | 8% | | 1121 | 37% | 21% | 42% | |
| | | | | 19% | | | | | 63% | |
| **EGYPT** | | 10 T.U. | | | | | | | | |
| 5-8 | 1119 | 64% | 17% | 19% | | 558 | 50% | 41% | 9% | |
| | | | | 36% | | | | | 50% | |
| 9-12 | 1403 | 47% | 22% | 31% | | 556 | 38% | 45% | 17% | |
| | | | | 53% | | | | | 62% | |
| 13-16 | 490 | 32% | 17% | 51% | | 123 | 29% | 47% | 24% | |
| | | | | 68% | | | | | 71% | |
| 5-16 | 3012 | 51% | 20% | 29% | | 1237 | 43% | 43% | 14% | |
| | | | | 49% | | | | | 57% | |
| **MEXICO** | | 10 T.U. | | | | | | | | |
| 5-8 | 499 | 75% | 2% | 23% | | 351 | 89% | 6% | 5% | |
| | | | | 25% | | | | | 11% | |
| 9-12 | 913 | 63% | 2% | 35% | | 536 | 84% | 11% | 5% | |
| | | | | 37% | | | | | 16% | |
| 13-15 | 315 | 46% | 1% | 53% | | 130 | 70% | 18% | 12% | |
| | | | | 54% | | | | | 30% | |
| 5-15 | 1727 | 63% | 2% | 35% | | 1017 | 84% | 10% | 6% | |
| | | | | 37% | | | | | 16% | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **DENMARK** | | | 10 T.U. | | | | | |
| 5-8 | 1636 | 97% | 1% | 2% | 1507 | 91% | 1% | 2% |
| | | | 3% | | | | 6% | |
| 9-12 | 5600 | 95% | 1% | 4% | 5098 | 95% | 4% | 1% |
| | | | 5% | | | | 5% | |
| 13-16 | 2606 | 90% | 2% | 8% | 2269 | 94% | 5% | 1% |
| | | | 10% | | | | 6% | |
| 5-16 | 9842 | 95% | 1% | 4% | 8874 | 94% | 4% | 2% |
| | | | 5% | | | | 6% | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **NIGERIA** | | | | | | | | |
| | | | **Response to 5 T.U. P.P.D.** | | | | **Response to 100 T.U. in those showing 0.5 mm. response to 5 T.U. or 10 T.U.** | |
| 5-8 | 287 | 84.1% | 7.3% | 8.3% | 242 | 59.9% | 27.2% | 12.9% |
| | | | 15.6% | | | | 40.1% | |
| 9-12 | 262 | 58% | 21.8% | 20.2% | 152 | 31.6% | 46.0% | 22.4% |
| | | | 42% | | | | 68.4% | |
| 13-16 | 72 | 37.5% | 30.5% | 32.0% | 27 | 14.8% | 48.2% | 37.0% |
| | | | 62.5% | | | | 85.2% | |
| 5-16 | 621 | 67.8% | 16.1% | 16.1% | 421 | 46.8% | 35.4% | 17.8% |
| | | | 32.2% | | | | 53.2% | |

A study of these figures shows that the findings in Nigeria are comparable to those recorded in India and Egypt, where the non-specific factor is considered to operate; our findings are widely different from those recorded in Mexico and Denmark where the non-specific factor is considered to operate little, if at all. The prominent feature is the high proportion of persons showing a feeble reaction to 5 T.U., but showing a much greater reaction to 100 T.U. Therefore, if the hypothesis of Edwards *et al.* is correct, it is possible that there is a non-specific factor present in the population studied in Nigeria.

III. THE POSSIBILITY OF LEPROSY INFECTION CONSTITUTING A NON-SPECIFIC FACTOR CAUSING A POSITIVE TUBERCULIN TEST

No conclusions can be drawn from the present investigation as to whether or not the leprosy bacillus is a factor in producing a positive tuberculin test.

**Summary**

(i) 621 children between the ages of 5 and 16 years in Eastern Nigeria were tested with 5 Tuberculin Units of P.P.D., and if the reaction was less than 6 mm. they were tested again with 100 Tuberculin Units. At the same time all the children were given an intradermal injection of lepromin, and the late reaction (Mitsuda) read.

(ii) A statistically significant correlation was demonstrated between the lepromin and tuberculin reaction in the group investigated. However, this could have resulted from the simultaneous exposure of the population to tuberculosis and leprosy.

(iii) The tuberculin-positive rates appeared to be higher than could be explained by the incidence of tuberculosis in the area.

(iv) The results of the tuberculin tests with the two different doses of P.P.D. were similar to those reported by Edwards *et al.* in parts of the world where they consider that a non-specific factor is responsible for reactions to 100 Tuberculin Units in those negative to 5 Tuberculin Units.

(v) No conclusion could be drawn as to whether or not the leprosy bacillus is a factor in producing a positive tuberculin test.

## TABLE I

*Tuberculin and Lepromin Reactions in Age Group 5-16 Years*

| Result of Lepromin Test | Result of Tuberculin Test: 6 mm. or more to 5 T.U. | | Reaction to 100 T.U. in those with 0-5 mm. to 5 T.U. | | | |
|---|---|---|---|---|---|---|
| | 11 mm. or more | 6-10 mm. | 11 mm. or more | 6-10 mm. | 0-5 mm. | Total |
| Strong + | 33 | 30 | 8 | 15 | 4 | 90 |
| Weak + | 43 | 43 | 35 | 42 | 28 | 191 |
| Negative | 24 | 27 | 32 | 92 | 165 | 340 |
| Total ... | 100 | 100 | 75 | 149 | 197 | = 621 |

$X^2$ = 162.83 with 8 degrees of freedom.

## TABLE II

*Tuberculin and Lepromin Reactions in Age Group 5-8 Years*

| Result of Lepromin Test | Result of Tuberculin Test: 6 mm. or more to 5 T.U. | | Reaction to 100 T.U. in those with 0-5 mm. to 5 T.U. | | | |
|---|---|---|---|---|---|---|
| | 11 mm. or more | 6-10 mm. | 11 mm. or more | 6-10 mm. | 0-5 mm. | Total |
| Strong + | 0 | 3 | 1 | 4 | 3 | 11 |
| Weak + | 10 | 10 | 16 | 9 | 15 | 60 |
| Negtive | 14 | 8 | 14 | 53 | 127 | 216 |
| Total ... | 24 | 21 | 31 | 66 | 145 | = 287 |

$X^2$ = 51.93 with 4 degrees of freedom
(combining the strong and the weak positive lepromin reactors)

## TABLE III

*Tuberculin and Lepromin Reactions in Age Group 9-16 Years*

| Result of Lepromin Test | Result of Tuberculin Test: 6 mm. or more to 5 T.U. — 11 mm. or more | 6 mm. or more to 5 T.U. — 6-10 mm. | Reaction to 100 T.U. in those with 0-5 mm. to 5 T.U. — 11 mm. or more | 6-10 mm. | 0-5 mm. | Total |
|---|---|---|---|---|---|---|
| Strong + | 33 | 27 | 7 | 11 | 1 | 79 |
| Weak + | 33 | 33 | 19 | 33 | 13 | 131 |
| Negative | 10 | 19 | 18 | 39 | 38 | 124 |
| Total ... | 76 | 79 | 44 | 83 | 52 | = 334 |

$X^2 = 70.70$ with 8 degrees of freedom.

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