

## LEPROMIN SENSITIVITY

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### 1. Introduction

Lepromin conversion following BCG vaccination is now a well accepted fact although opinions differ about the extent to which the initial lepromin injection is responsible for the change. Wade (1956) has suggested that the test dose contributes by conditioning the individual to react; it would indeed be strange if the injection of leprosy bacilli had no effect whilst lepromin sensitivity had often to be ascribed to unrecognised contact with unrecognised organisms, that were probably less virulent.

Ignacio, Palafox and José (1955) produced lepromin positivity in children after repeated lepromin injections, work which has since been confirmed by Bechelli (1959). In an important controlled experiment, in which children were vaccinated with BCG, Doull, Guinto and Mabalay (1957) showed that 11.5% of the lepromin positives that followed the vaccination were due to 'natural causes' (i.e., causes unknown), 7.2% to the initial dose of lepromin and 33.4% to the actual vaccination. These studies have helped to evaluate some of the important causes of group sensitivity. The proportions, however, that became lepromin positive as a result of the lepromin test, or 'natural causes', should not obscure the still larger proportion that owed their conversion to BCG vaccination, nor the value of the mechanism 'lepromin test plus BCG vaccination plus lepromin test' which produced more conversions than any of the components alone.

### 2. The Multipuncture Depot Lepromin Test

In every investigation a test dose of 0.1 ml. of 1 in 20 lepromin, a tissue suspension of leprosy bacilli, has been injected intradermally. In the work now recorded we used the multipuncture depot lepromin test we previously described (Kinnear Brown and Stone). This correlates well with the classical Mitsuda over which it has advantages. It economises antigen, produces no discomfort, and need be applied only once to ascertain the effect of BCG vaccination. It is therefore especially useful for detecting poor reactors among contacts of patients or among the general population, and it can be used in any strength from 1 in 20 to 1 in 100 where it is desired to know who ought to be protected. Where the multipuncture injection was employed as an indicator, only those children who were subsequently BCG vaccinated showed lepromin conversion, suggesting that the small test dose had itself no appreciable effect on lepromin sensitivity.

3. The Influence of Tuberculin, Lepromin, and BCG Vaccination on Lepromin Sensitivity

Children attending 11 primary day schools were tested with lepromin, tuberculin, or both. Their ages ranged from 5 to 16, and the age distribution in corresponding classes was similar. The allocation of children to the experimental series was either by school or by class to obtain comparable groups.

Some children received both test injections at the same time; others at intervals. The lepromin used was a 1 in 20 depot preparation, except where stated that it was 1 in 100. It was given by the multipuncture route. The tuberculin P.P.D. was obtained from The State Serum Institute, Copenhagen. It was administered as a Mantoux test (using 5 TU), or by the Heaf multipuncture method. The children chosen for vaccination were those reacting with less than 10 mm. infiltration to the Mantoux test, or with less than Grade II to the Heaf, the assumption being that small and intermediate responses were not generally due to infection with the tubercle bacillus (WHO, 1959). The expression tuberculin negative in this report implies only that the response was less than the standard defined above. The BCG used was the Glaxo freeze dried preparation.

The first part of this work and its results can be summarised as follows:

<i>Group A</i>	Percentage of lepromin positives in 472 children none of whom had had any test except the single lepromin test now given:	56 %
<i>Group B</i>	Percentage of lepromin positives in 255 children none of whom had had any previous test and who now were given the Heaf tuberculin and depot tests together:	59 %
<i>Group C</i>	Percentage of lepromin positives in 124 children none of whom had had any previous test except the Heaf tuberculin test 5 weeks earlier:	55 %
<i>Group D</i>	Percentage of lepromin positives in 179 children who had been Mantoux tested 6 months earlier with BCG vaccination of the tuberculin negatives:	86 %
<i>Group E</i>	Percentage of lepromin positives in 148 children who had been Heaf tuberculin tested 5 weeks earlier with BCG vaccination of the tuberculin negatives:	87 %

The tuberculin tests made at the time of the lepromin tests, or earlier, had no significant effect on the lepromin results. The 851 children in Groups A, B and C had a lepromin positive rate of 57 %.

In the schools where the tuberculin negatives had been BCG vaccinated, the lepromin positive rates were the same whether the lepromin tests were made one month or six months after vaccination.

They were higher by 29% than in comparable groups of children, in which the tuberculin negatives had not been vaccinated. It did not appear to matter whether the Mantoux or Heaf standard was used.

(The difference between Groups A and B is 3%; less than the Standard Error of 3.8: that between Groups B and C is 4%, less than the Standard Error of 5.4. Neither of these differences is significant. The tuberculin could have had no effect. The difference between Groups B and D is 27% nearly 7 times the Standard Error: that between Groups A, B and C taken together and D and E combined is 29%, nearly 10 times the Standard Error. These differences are therefore significant. The BCG vaccination was responsible for the change.)

In 316 children belonging to Groups D and E the tuberculin test was repeated. Of these 234 had been tuberculin negative. After BCG vaccination 231 became tuberculin positive. The results are given below:

*Comparison of Lepromin and Tuberculin Results*

<i>Tuberculin test used</i>	<i>Group F Lepromin result in natural tuberculin positives</i>		<i>Group G Lepromin result in converted tuberculin positives</i>		<i>Lepromin result in persistent negatives</i>	<i>Total</i>
	+	—	+	—		
Mantoux	40	13	105	9	0	169
Heaf	23	6	107	10	0	147
Total	63	19	212	19	0	316
	82		231		3	

*Group F* The percentage of lepromin positives among the naturally occurring tuberculin positives (63/82) was: 77%

*Group G* The percentage of lepromin positives among the BCG converted tuberculin positives (212/231) was: 92%

(If the Mantoux and Heaf groups are separated there is little difference, e.g., percentage of lepromin positives in the natural tuberculin positives: Mantoux 75%, Heaf 79%; percentage of lepromin positives in the BCG'd tuberculin positives: Mantoux 92%, Heaf 91%.)

*Group H* In 615 other children in comparable age groups the percentage of lepromin positives among the natural tuberculin positives (289/400) was: 72%

*Group J* If groups F and H are taken together the percentage of lepromin positives among the natural tuberculin positives (352/482) was: 73%

In none of this work was there any interference by a previous lepromin test. The lepromin positive rate was significantly higher among the tuberculin negatives who converted after BCG than among those who were already tuberculin positive.

(The difference between Groups F and G is 15%, 3 times the Standard Error of 5; that between Groups J and G is 19%, 7 times the Standard Error of 2.7. These differences are significant. The BCG vaccination was responsible for the change.)

#### **4. Strength of the Lepromin Response**

Of 644 children, none of whom were vaccinated:

40% were lepromin negative,

36% were lepromin positive Grade I

24% were lepromin positive Grade II or stronger.

Of 281 other comparable children, whose tuberculin negatives were BCG vaccinated:

10% remained lepromin negative,

32% became lepromin positive Grade I,

58% became lepromin positive Grade II or stronger.

The BCG vaccination was not only followed by a significant increase in the number of reactors, there was also a significant increase in the strengths of the reactions. This confirms the observations of Convit (1956).

#### **5. Comparison of 1:20 and 1:100 depot lepromin**

Six hundred and fifteen children were Heaf tuberculin tested. They were also lepromin tested with 1 in 20 depot lepromin; 274 others were Heaf tuberculin tested but a lepromin test was made with 1 in 100 depot lepromin. 65% of the 615 and 66% of the 274 were tuberculin positive.

The 1 in 20 lepromin discovered 59% positive reactors, the 1 in 100 lepromin only 45%. The stronger antigen is thus more efficient in provoking a reaction in those who have any capacity to respond. The diluted antigen on the other hand makes a clear cut distinction between those who would react satisfactorily to normal antigen and those whose response would be negative or inadequate. Where the supply of antigen is limited, a multipuncture depot lepromin test, using a concentration weaker than 1 in 20, will safely indicate those who need further protection.

#### **6. Lepromin results according to age**

The following table gives the percentage of lepromin positives and negatives in each two year age group. (It is difficult to assess the ages of children with greater exactness.)

<i>Ages</i>	<i>Percentage Positive</i>	<i>Percentage Negative</i>
5 and 6	29	71
7 and 8	46	54
9 and 10	56	44
11 and 12	62	38
13 and 14	71	29
15 and 16	78	22

The positive reactor rate increases steadily with age; it has not yet been established among any group older than age 16. The reactor rate after BCG was 86%–87%. It might have been higher had the lepromin tests been read again after the 21st day. (In one group it was 92%.) It follows that any measure that will increase the lepromin positive rate from 29% at ages 5 and 6 to 86% (which had not been reached in this series at age 16) is worth considering. It could certainly do no harm.

### Conclusions

1. The test injection of tuberculin did not affect the response to lepromin whether given previously or at the same time.
2. In comparable groups, the lepromin reactor rate after BCG vaccination of the tuberculin negatives was 29% higher than in the controls who had only the one lepromin test. The same results were obtained one month after BCG vaccination as after six. The difference between the control and vaccinated groups is significant and is due to the vaccination.
3. The lepromin reactor rate among those who became tuberculin positive after BCG vaccination was significantly higher than among the naturally occurring tuberculin positives. Sensitivity probably includes more than one or two elements. The BCG vaccination was responsible for the change.
4. BCG not only increases the lepromin reactor rate; it increases significantly the number of strong reactors.
5. A less concentrated antigen can be used where it is desired only to distinguish weak or negative reactors from those whose response is adequate.
6. The lepromin reactor rate varies from 29% at ages 5 and 6 to 78% at ages 15 and 16. BCG vaccination produces within one month a rate which would not otherwise be reached for many years.
7. Doubt has been thrown on the part played by BCG in producing lepromin conversion because lepromin injected intradermally in much larger doses than were used in this work can itself sensitise. This work was so planned however that the test injection could not contribute to the sensitivity that developed.

8. In the anxiety to establish the respective parts played by the injection of lepromin and BCG vaccination the importance of the sequence 'lepromin test plus vaccination plus lepromin test' may have been overlooked. The synergic or adjuvant actions of the lepromin and BCG may produce more lepromin conversions than either could alone. The subject should be explored more fully with the object of producing a combined technique that will deal with those who are persistently lepromin negative. The value of BCG is not lessened because lepromin itself helps to sensitise.
9. This work confirms the advantages of the multipuncture depot lepromin test. In one group the used injection apparatus produced a series of positive results on the arms of each volunteer without the application of fresh antigen to the skin.

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