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INTERPRETATION OF TUBERCULIN REACTIONS IN POPULATIONS WITH A HIGH PROPORTION OF BCG-VACCINATED PERSONS *

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SYNOPSIS

In recent years there has been an apparent increase in the frequency with which inconsistent results are obtained in the routine tuberculin-testing carried out at the Central Tuberculosis Dispensary in Copenhagen. The author describes an investigation which was undertaken to find out the cause of these conflicting results. In this study, about a thousand non-tuberculous people, many of whom had previously been vaccinated with BCG, were tested by one of two different techniques. In another similar group of people, 300 tuberculin reactions were each read independently by three nurses.

The pattern of tuberculin sensitivity observed among the non-vaccinated differed from that observed among the vaccinated. Whereas the reactions of the former could, with fair accuracy, be classified as " positive " or " negative " according to their size, those of the latter showed a unimodal distribution by size, so that any such classification was necessarily arbitrary. Moreover, it was found that many of the vaccinated individuals tended to give positive and negative reactions alternately to successive tests, owing to random variations in the testing techniques.

The author concludes that it is impracticable to divide BCG-vaccinated people into " positives " and " negatives ", and draws a parallel with populations in tropical countries, where the presence of " non-specific " sensitivity renders tuberculin-testing unreliable as a diagnostic tool.

The investigation described in this paper was undertaken in an attempt to solve what appeared to be a practical, technical problem encountered at the Central Tuberculosis Dispensary in Copenhagen (Københavns Kommunes Centralstation for Tuberculosebekæmpelse) during the routine intradermal tuberculin-testing of groups of healthy persons.

Tuberculin-testing has been used very extensively at the Dispensary for screening out recently infected persons. If a person was found to have converted from the tuberculin-negative to the tuberculin-positive state

* This paper is the fourth in a series on quantitative aspects of the intradermal tuberculin test in humans. The earlier papers are listed among the references (Guld; [2, 3] WHO Tuberculosis Research Office [18]).

(that is, to react to tuberculin after having been a non-reactor the previous year), he would then be closely examined for possible disease, and steps would be taken to find the source of infection. It is most annoying, from a technical point of view, when in such a case a repeat tuberculin test, carried out in the course of the medical examination, is found to give a negative result. Owing to an apparent increase, over the last few years, in the frequency of such inconsistent results, the Dispensary's medical staff wished to have the matter investigated. It was taken for granted that the result of one or the other of the tests would have to be wrong in any such case: that a person could not very well be tuberculin-positive and tuberculin-negative at the same time.

The routine testing at the Dispensary consisted of an intradermal injection of 3 tuberculin units (TU), followed, if the reaction to this test was considered negative, by a second injection of 10 TU. Readings of the reactions were made 3 or 4 days after the injection; the diameter of induration was usually measured and recorded, a diameter of 10 mm or more being taken as the definition of a positive reaction. The main purpose of the present investigation was to find the factor, or factors, responsible for the failures described. A secondary purpose was to find out whether a single intradermal test with 5 TU could safely and efficiently replace the two-dose procedure.

Material and Methods

The population for the main study numbered nearly a thousand persons and was drawn from groups of non-tuberculous people whose yearly routine examination at the Copenhagen Tuberculosis Dispensary happened to fall due during two weeks in April 1954. This population consisted of personnel from an automobile factory and two insurance companies, and persons from a cripples' home. The majority were adults; 5% were below 15 years of age and 3% above 60. Following a working rule of the Dispensary, only non-vaccinated persons who had shown a " positive " reaction less than 5 years earlier were exempted from the tuberculin-testing.

In the main study each person was tested according to one of two different procedures: some persons were first given a 3 TU test and then, if the reaction, when read 3 days later, measured 13 mm or less, a second test of 10 TU in the other arm; the others were given a 5 TU test the first time and, if the reaction was found, 3 days later, to be 15 mm or less, a second test of 5 TU. The criteria prescribed for the second tests represent a compromise; on the one hand, there was the fear of provoking too many severe reactions with the second test and, on the other, the wish to extend the duplicate testing to as many as possible of those with reactions falling above conventional borderlines between " positive " and " negative ". Persons to be tested were allocated alternately to one or the other testing

procedure in the order in which they presented themselves at the testing table. The nurses who read the reactions did not know which doses of tuberculin had been used, either in general or for the particular person; nor did they know the criteria for giving the second test. They dictated their estimate of reaction size to a secretary, and the person was then sent to another table where the second test was or was not given, according to the criteria outlined above. The second test was read 3 or 4 days later, by a nurse with no knowledge of the tuberculin dose given or the size of the first reaction.

The testing and reading in the main study were done by a team of five nurses from the WHO Tuberculosis Research Office, all with long training in careful intradermal testing. The readers were known, from several series of independent dual readings, to agree rather closely in their performance. The tests were given with tight syringes, and the dose was measured according to the calibration of volume on the syringe. The tuberculin dilutions were prepared by Statens Seruminstitut, Copenhagen, from the PPD preparation RT XXII (0.000013 mg or 1/75 000 mg in 0.1 ml considered equivalent to 1 TU). The first tests were given alternately in the right and in the left arm; the second tests were usually given in whichever arm had not received the first injection. The reactions were palpated, and the transverse diameter of induration was measured with a millimetre ruler.

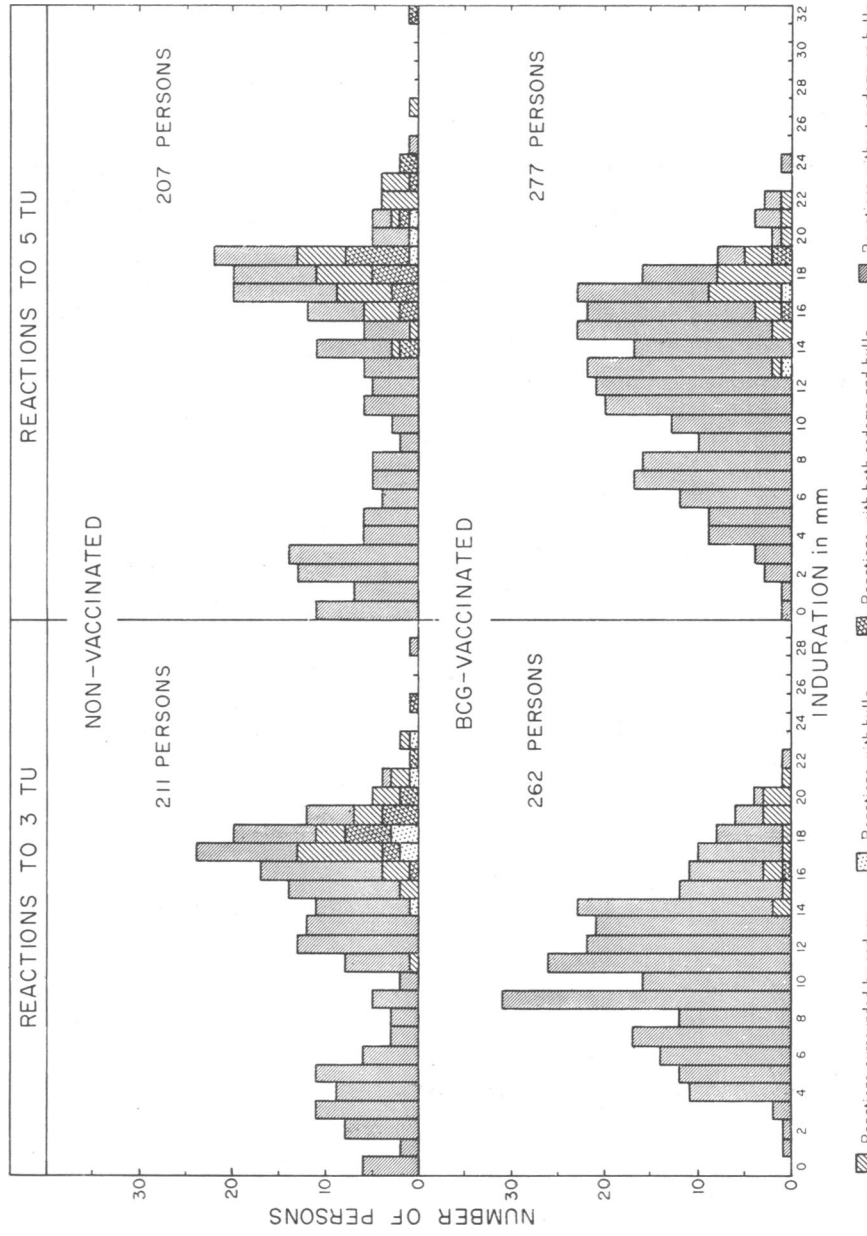
An additional study was made to investigate the consistency with which the size of a tuberculin reaction could be measured. Three hundred reactions in persons tested routinely in the Dispensary, 3 or 4 days earlier, were read independently by three persons. Five nurses from the Dispensary took turns in making the first and third readings, while the second reading was always done by one nurse from the Tuberculosis Research Office. The second and third readers always dictated their estimates of reaction size to a secretary and did not see the results obtained by the two other readers, either before or after their own reading.

A third study was carried out to investigate the possibility that repeated yearly testing in the same site might influence the response to the test. To a group of 70 male and female workers the routine test of 3 TU was given alternately in the left and in the right arm; the left arm represented the routine testing site, while the right arm represented a site not ordinarily used for testing.

Results

The tuberculin reactions to the first test in each person are presented as histograms in Fig. 1, separately for 3 TU (left), 5 TU (right), non-vaccinated persons (above), and BCG-vaccinated persons (below). For each of the four groups of persons the reactions are classified by diameter of induration;

FIG. 1. DISTRIBUTION OF TUBERCULIN REACTIONS BY SIZE (DIAMETER OF INDURATION IN mm) IN BCG-VACCINATED AND NON-VACCINATED PERSONS, FOR TUBERCULIN DOSES OF 3 TU AND 5 TU



two other characteristics are shown by different shading—namely, bullous reactions and reactions surrounded by oedema.

The distributions of reactions in non-vaccinated persons indicate the existence of two groups or kinds of reactions, one with a peak at 2-4 mm and another dispersed around a central value of 16-18 mm. In BCG-vaccinated persons the distributions of reactions are quite differently shaped, with a flat top at 10-17 mm and little or no indication of the existence of more than one kind of reaction.

TABLE I. DISTRIBUTION OF NON-VACCINATED PERSONS ACCORDING TO THEIR REACTIONS TO 3 TU AS FIRST TEST AND TO 10 TU AS SECOND TEST *

Reaction to second test: 10 TU (diameter of induration in mm)	Reaction to first test: 3 TU (diameter of induration in mm)																									
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	>24
0	2	.	2	2	1	1	.	.	.	.	.	.	.	.												
1	1	.	.	.	.	1	.	.	.	.	.	.	.	.												
2	2	1	1	1	1	.	.	.	.	.	.	.	.	.												
3	.	.	.	3	.	1	.	.	.	.	.	.	.	.												
4	1	1	2	3	1	.	1	.	.	.	.	.	.	.												
5	.	.	.	.	1	2	.	.	.	.	.	.	.	.												
6	.	.	1	.	2	.	.	.	.	.	.	.	.	.												
7	.	.	.	.	.	1	1	.	.	.	.	.	.	.												
8	.	.	.	1	1	.	.	.	.	.	.	.	.	.												
9	.	.	.	.	.	.	.	1	.	.	.	1	.	.												
10	.	.	.	.	1	.	.	.	.	.	.	.	.	.												
11	.	.	.	1	.	.	.	.	1	.	.	.	.	.												
12	.	.	.	.	.	1	.	.	.	.	.	1	.	.												
13	.	.	.	.	.	1	.	1	1	1	.	1	.	.												
14	.	.	.	.	.	1	.	.	1	.	.	.	.	1												
15	.	.	.	.	.	.	.	.	.	1	.	.	1	1												
16	.	.	.	.	.	1	1	1	.	.	.	.	3	1												
17	.	.	.	.	.	.	.	.	.	1	1	2	2	2												
18	.	.	.	.	.	.	.	.	.	2	.	1	1	2												
19	.	.	.	.	.	.	1	.	.	.	1	.	3	.												
20	.	.	.	.	.	.	.	.	.	.	.	1	.	.												
21	.	.	.	.	.	.	.	.	.	.	.	.	.	.												
22	.	.	.	.	.	.	.	.	.	.	.	.	.	2												
23	.	.	.	.	.	.	.	.	.	.	.	.	.	.												
24	.	.	.	.	.	.	.	.	.	.	.	1	2	.												
25	.	.	.	.	.	.	.	.	.	.	.	.	.	.												
No 2nd test	.	.	2	.	1	1	2	.	.	.	.	.	1	3	11	14	17	24	20	12	5	4	1	2	.	2
Total	6	2	8	11	9	11	6	3	3	5	2	8	13	12	11	14	17	24	20	12	5	4	1	2	.	2

* The second test was given to persons with a reaction to the first test of 13 mm or less.

TABLE II. DISTRIBUTION OF BCG-VACCINATED PERSONS ACCORDING TO THEIR REACTIONS TO 3 TU AS FIRST TEST AND TO 10 TU AS SECOND TEST *

Reaction to second test: 10 TU (diameter of induration in mm)	Reaction to first test: 3 TU (diameter of induration in mm)																									
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	>24
0	•	•	•	•	•	•	•	•	•	•	•	•	•	•												
1	•	•	•	•	•	•	•	•	•	•	•	•	•	•												
2	•	•	•	•	1	•	•	•	•	•	•	•	•	•												
3	•	•	•	•	•	1	•	•	•	•	•	•	•	•												
4	•	•	•	1	•	•	•	•	•	•	•	•	•	•												
5	•	•	•	•	•	•	•	•	•	•	•	•	•	•												
6	•	•	•	•	•	•	3	•	•	•	•	•	•	•												
7	•	•	•	•	•	•	•	•	•	•	•	•	•	•												
8	•	•	•	•	•	•	•	•	•	2	•	•	•	•												
9	•	1	•	•	•	•	2	1	•	1	•	•	•	•												
10	•	•	•	•	•	•	1	•	1	2	•	•	•	•												
11	•	•	•	1	2	•	•	•	•	1	•	1	•	•												
12	•	•	•	•	1	•	•	1	1	2	•	2	1	1												
13	•	•	•	•	1	2	•	1	1	2	•	3	1	2												
14	•	•	1	•	1	2	2	3	•	3	•	6	1	1												
15	•	•	•	•	3	•	1	3	1	3	1	4	4	•												
16	•	•	•	•	•	2	3	2	2	6	3	3	3	7												
17	•	•	•	•	2	•	•	4	2	2	5	1	3	1												
18	•	•	•	•	•	3	•	•	•	1	2	2	2	2												
19	•	•	•	•	•	•	1	•	•	1	1	•	4	5												
20	•	•	•	•	•	1	•	1	1	1	1	1	•	2												
21	•	•	•	•	•	•	•	•	2	•	1	2	2	•												
22	•	•	•	•	•	•	1	•	•	•	•	•	•	•												
23	•	•	•	•	•	•	•	•	•	•	•	•	•	•												
24	•	•	•	•	•	•	•	•	•	•	•	•	•	•												
25	•	•	•	•	•	•	•	•	•	•	•	•	•	•												
No 2nd test	•	•	•	•	•	1	•	1	1	4	2	1	1	•	23	12	11	10	8	6	4	1	1	•	•	•
Total	•	1	1	2	11	12	14	17	12	31	16	26	22	21	23	12	11	10	8	6	4	1	1	•	•	•

* The second test was given to persons with a reaction to the first test of 13 mm or less.

On the average, reactions to 5 TU were larger than reactions to 3 TU, though not very much; and the frequency of bullous or oedematous reactions was only slightly higher with the stronger dose.

Persons reacting with 13 mm or less to 3 TU were given a second test of 10 TU, and correlations of their reactions to the two tests are shown in Tables I and II. The two tables very clearly confirm the impression given by Fig. 1 that there are two kinds of non-vaccinated people but only one kind of BCG-vaccinated. There is a group of persons among the non-

TABLE III. DISTRIBUTION OF NON-VACCINATED PERSONS ACCORDING TO THEIR REACTIONS TO 5 TU AS FIRST TEST AND TO 5 TU AS SECOND TEST *

Reaction to second test: 5 TU (diameter of induration in mm)	Reaction to first test: 5 TU (diameter of induration in mm)																									
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	>24
0	3	2	4	3	·	·	·	·	·	·	·	·	·	·	·	·										
1	·	1	1	·	1	·	·	·	·	·	·	·	·	·	·	·										
2	5	2	2	1	·	1	·	·	·	·	·	·	·	·	·	·										
3	1	1	1	6	3	·	·	·	·	·	·	·	·	·	·	·										
4	1	1	2	3	·	·	·	·	·	·	·	·	·	·	·	·										
5	·	·	1	·	·	1	2	1	·	·	·	·	·	·	·	·										
6	·	·	·	·	2	·	1	·	1	·	1	·	·	·	·	·										
7	1	·	·	·	·	1	·	1	1	·	·	1	·	·	·	·										
8	·	·	·	·	·	1	·	1	·	1	·	·	·	·	·	·										
9	·	·	·	·	·	·	·	1	1	·	·	·	1	·	1	1										
10	·	·	·	·	·	1	·	·	·	·	·	1	·	1	·	1										
11	·	·	·	·	·	·	1	1	2	·	·	·	2	·	2	1										
12	·	·	·	·	·	·	·	·	·	1	·	·	·	1	2	·										
13	·	·	·	·	·	·	·	·	·	·	1	2	1	·	·	1										
14	·	·	·	·	·	·	·	·	·	·	·	·	·	·	2	·										
15	·	·	·	·	·	·	·	·	·	·	·	1	·	2	2	1										
16	·	·	·	·	·	·	·	·	·	·	·	·	·	·	2	1										
17	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·										
18	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·										
19	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·										
20	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·										
21	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·										
22	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·										
23	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·										
24	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·										
25	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·										
No 2nd test	·	·	2	1	·	1	·	·	·	·	1	1	1	2	·	·	12	20	20	22	5	5	4	4	2	3
Total	11	7	13	14	6	6	4	5	5	2	3	6	5	6	11	6	12	20	20	22	5	5	4	4	2	3

* The second test was given to persons with a reaction to the first test of 15 mm or less.

vaccinated (Table I, upper left) that did not react more strongly to 10 TU than to 3 TU; these people had either no reactions at all or, more frequently, reactions of 1-5 mm, and it seems a reasonable inference that they are not sensitive to the doses of tuberculin used in the present study. On the other hand, all the persons with reactions larger than 5-6 mm to 3 TU had still larger reactions to 10 TU; these people, apparently, are tuberculin-sensitive. The BCG-vaccinated persons (Table II) presented a uniform kind of sensitivity as compared with the non-vaccinated, only three persons (1% of

the vaccinated population) having small reactions to both tests. Almost everybody reacted more strongly to 10 TU than to 3 TU, and the few exceptions are undoubtedly the outcome of " experimental errors " (to be discussed later).

The two reactions in each person might be thought to be surprisingly uncorrelated; in Table II, for example, persons with a reaction of 9 mm to 3 TU are seen to have had reactions ranging in size from 8 mm to 20 mm to the 10 TU test. To understand this feature it is not necessary to postulate any kind of biological variation from person to person in ability to show

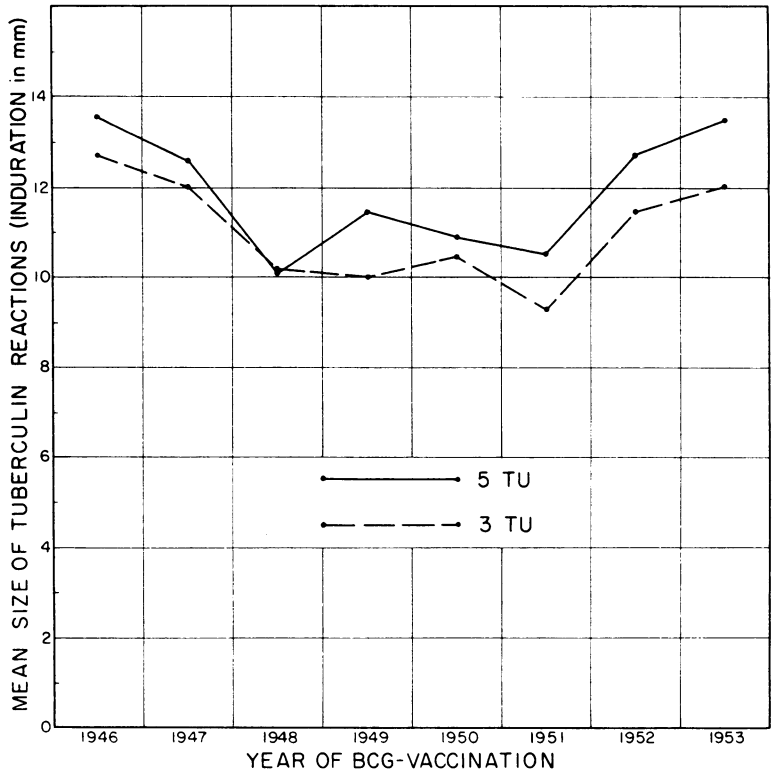
TABLE IV. DISTRIBUTION OF BCG-VACCINATED PERSONS ACCORDING TO THEIR REACTIONS TO 5 TU AS FIRST TEST AND TO 5 TU AS SECOND TEST *

Reaction to second test: 5 TU (diameter of induration in mm)	Reaction to first test: 5 TU (diameter of induration in mm)																									
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	>24
0	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.										
1	.	1	1	.	.	.	.	.	.	.	.	.	.	.	.	.										
2	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.										
3	.	.	.	1	.	2	1	.	.	.	.	.	.	.	.	.										
4	1	.	1	.	3	1	2	.	1	.	.	.	.	.	.	.										
5	.	.	.	.	1	1	1	1	1	.	.	.	2	.	1	1										
6	.	.	.	1	1	1	1	1	.	2	.	.	2	.	1	.										
7	.	.	1	1	1	.	3	.	3	2	2	3	1	2	1	.										
8	.	.	.	1	1	.	1	2	1	.	3	4	1	3	.	1										
9	.	.	.	.	.	.	.	3	3	.	3	2	2	3	1	2										
10	.	.	.	.	.	.	.	1	.	.	1	2	2	2	2	2										
11	.	.	.	.	.	.	.	3	1	2	3	2	1	2	1	1										
12	.	.	.	.	.	1	.	.	2	1	.	2	1	1	5	6										
13	.	.	.	.	.	1	.	1	.	1	.	1	.	1	3	3										
14	.	.	.	.	.	.	.	1	1	.	1	2	2	2	1	3										
15	.	.	.	.	.	.	1	.	.	1	.	1	3	1	.	.										
16	.	.	.	.	.	1	.	.	1	.	.	.	.	2	.	.										
17	.	.	.	.	.	.	.	1	.	.	.	.	.	1	.	1										
18	.	.	.	.	.	.	1	.	1	.	.	.	1	.	1	1										
19	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.										
20	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.										
21	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.										
22	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.										
23	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.										
24	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.										
25	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.										
No 2nd test	.	.	.	.	1	1	1	2	1	1	.	1	2	1	.	2	22	23	16	8	2	4	3	.	1	.
Total	1	1	3	4	9	9	12	17	16	10	13	20	21	22	17	23	22	23	16	8	2	4	3	.	1	.

* The second test was given to persons with a reaction to the first test of 15 mm or less.

relatively stronger reactions with increasing doses of tuberculin. A single Mantoux test is an inaccurate gauge of sensitivity, as will be seen from Tables III and IV, where results are shown for persons tested twice with 5 TU (all persons tested the first time with 5 TU and having a reaction to this dose smaller than 16 mm were tested once more with the same dose).

FIG. 2. MEAN SIZE OF TUBERCULIN REACTIONS TO 3 TU AND 5 TU N BCG-VACCINATED PERSONS, ACCORDING TO YEAR OF BCG-VACCINATION



The two tables illustrate the inaccuracy inherent in intradermal testing, even when the testing is done with care, perhaps with more care than could be afforded in most dispensary, clinic or mass campaign work. Note, for example, that vaccinated persons reacting with 8 mm to the first 5 TU test had reactions ranging from 4 mm to 18 mm to the second test with the same dose.

Even though the correlation in Tables II and IV is somewhat poor, it is clear that some persons tend to react more strongly than others; in other words, even though vaccinated persons do not fall into two distinct groups

as do the non-vaccinated, some may be more and some less sensitive to tuberculin. One cause of variation in sensitivity from person to person is indicated in Fig. 2, where the average reaction size in vaccinated persons is given separately by year of BCG-vaccination. There is an apparent trend indicating variation with time in some factor—such as potency of vaccine, for example.

Correlation with earlier tests

Fig. 3 and 4 show the correlation between the present results of testing and the results of earlier tuberculin tests in the same persons, as recorded by the Dispensary during previous years. Only persons tested within the

FIG. 3. DISTRIBUTION OF REACTIONS TO 5 TU IN THE PRESENT STUDY, FOR PERSONS WITH A RECORD OF TUBERCULIN-TESTING IN PREVIOUS YEARS

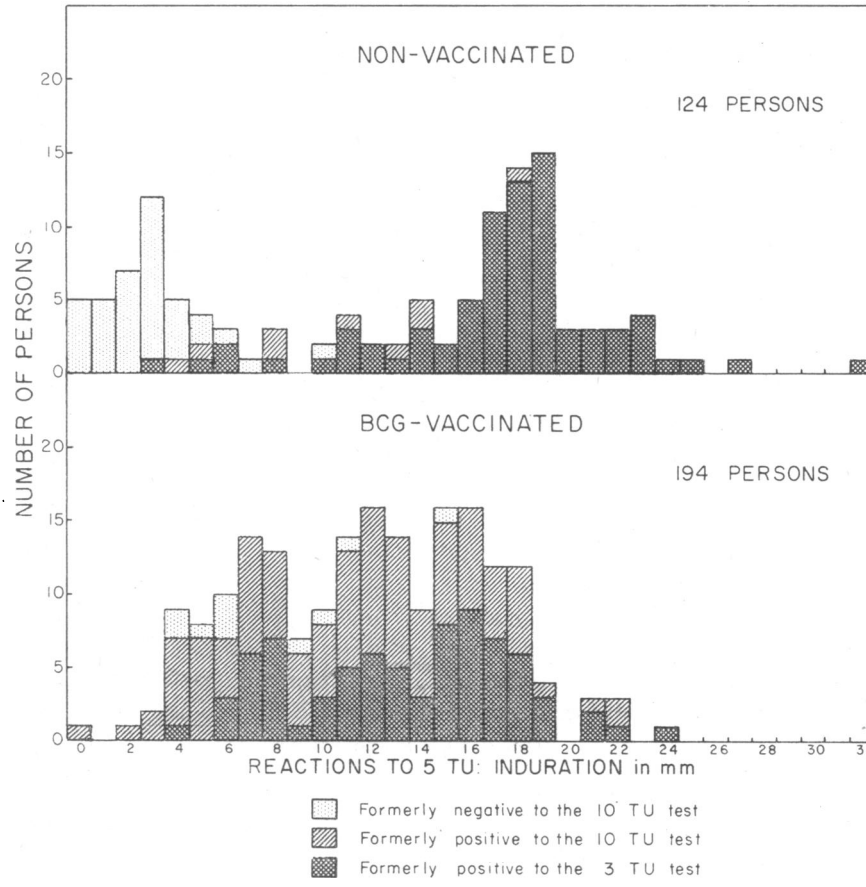
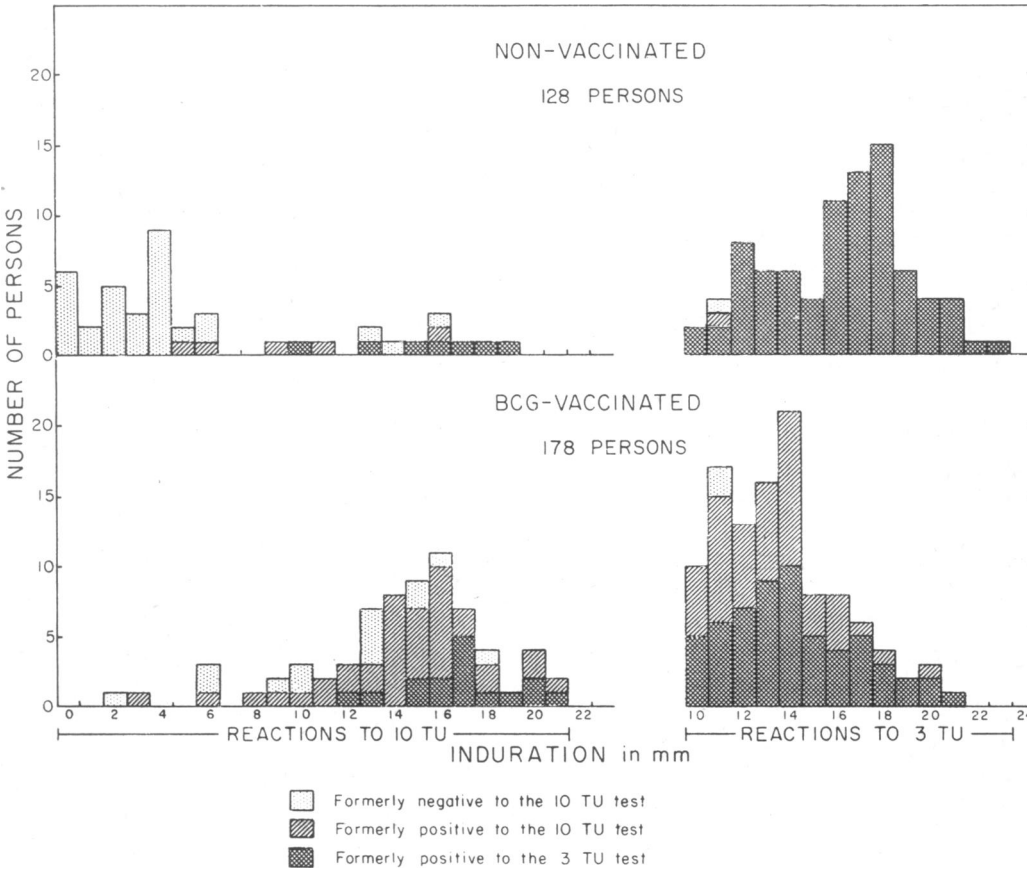


FIG. 4. DISTRIBUTION OF REACTIONS TO 3 TU (OR, IF THE REACTION TO 3 TU IS 9 mm OR LESS, TO 10 TU) IN THE PRESENT STUDY, FOR PERSONS WITH A RECORD OF TUBERCULIN-TESTING IN PREVIOUS YEARS



last five years are included, and the result of the last previous test is classified in one of three categories: " positive to the 3 TU test ", " positive to the 10 TU test ", and " negative to the 10 TU test ", where " positive " means a reaction size of 10 mm or more. The results of testing obtained in previous years are shown in Fig. 3 and 4 by heavy shading of former " positives " and light shading of former " negatives ".[a] Persons tested with 5 TU in the present study are shown in Fig. 3, with non-vaccinated persons in the upper histogram and BCG-vaccinated ones in the lower. The persons

[a] The category " formerly negative to the 10 TU test " is more sparsely represented here than at the time of the previous testing: those who at that time were offered, and did accept, BCG vaccination because of a " negative " response to the test are not included in Fig. 3 and 4. It may also be noted that the last previous test in BCG-vaccinated and in " negative " persons is in general more recent than the last previous test in " positive ", non-vaccinated persons, since the latter are not routinely tested every year. However, neither of these biases would seem to invalidate the main arguments.

are distributed in the histograms according to the size of their present reactions to 5 TU.

Fig. 3 confirms in practice what one would expect from Tables I-IV: the classification of a non-vaccinated person as reactor or non-reactor is reproduced quite well from one year to another; but BCG-vaccinated persons seem to be classified as the wind blows. Or rather, persons with somewhat weak sensitivity are called now " positive ", now " negative "; and most BCG-vaccinated persons have a somewhat weak sensitivity, whereas non-vaccinated persons mostly have either strong sensitivity or none at all.

Similar features are apparent in Fig. 4, which gives reactions for the persons tested in the present study with 3 TU and, if " negative " to this test, with 10 TU. The distribution of persons with a reaction of 10 mm or more to the 3 TU test is shown on the right in Fig. 4; the distribution of persons with a weaker reaction to this test is shown on the left, according to their reactions to the 10 TU test.

Among the BCG-vaccinated in Fig. 3 and 4, there are in all 26 persons " formerly negative to the 10 TU test ", and of these, 15 now show reactions of 10 mm or more. According to traditional concepts, this implies an unbelievably high " conversion rate ", around 50%. Among the non-vaccinated there are 5 " converters " out of 69 former " negatives ". However, none of the 20 " converters " attain the reaction size 16-18 mm that is the characteristic average for infected persons. All of them respond to repeated tuberculin testing, not as if any one among them had become infected with tuberculosis between the two testing periods, but as if they have a low degree of allergy that may or may not be revealed by any single test. Conversely, one is not going to be surprised if some of those found " positive " the previous year and " negative " this year are once more found " positive " next year.

Duplicate reading of reaction size

Results of independent readings of the same reactions by different nurses are correlated in Tables V-IX. The readings were carried out on 300 persons, some BCG-vaccinated and some not, routinely tested at the Dispensary with 3 TU or 10 TU.

Ninety-two reactions to 3 TU in non-vaccinated persons are distributed, in Table V, according to two estimates of reaction size: one made by a nurse from the Tuberculosis Research Office and the other made by one of five experienced nurses from the Dispensary (each having read about one-fifth of the reactions). Similar distributions are shown in Table VI for reactions to 10 TU in non-vaccinated persons (presumably " negative " to a previous 3 TU test); Tables VII and VIII show the readings of reactions to 3 TU and 10 TU in BCG-vaccinated persons.

TABLE V. DISTRIBUTION OF 92 REACTIONS IN NON-VACCINATED PERSONS TESTED WITH 3 TU, ACCORDING TO TWO INDEPENDENT ESTIMATES OF SIZE

Reaction as read by TRO nurse (diameter of induration in mm)	Reaction as read by Dispensary nurses (diameter of induration in mm)																									Total
	0		2		4		6		8		10		12		14		16		18		20		22		24		26		28		30	
0	2																													2
	2																													2
2	1																													1
	2																													2
4	2																													2
	2																													2
6			1																											1
					1																									1
8	1																													1
					2	2					1																			5
10							1																							1
									1				1																	2
12	1										1																			2
											1																			1
14							1				1		2	2		1														7
											1	1	1										1							4
16	1										3		2	1	1															8
											1					1	1													3
18													2	2	2	1	1		1											9
													2				1				1									4
20													4		1	1		1	3		3				1					14
															2	1						1								4
22																					1		1							2
																							1							1
24									1								1				2									4
																			1		1									2
26																														
28																									1					1
30																					1						1			2
32																														
34																													1	1
																						1								1
36																														
Total	14		1	3	2		1	2	1		5	6	13	5	4	6	4	2	5		8	2	4		1	1		1		1	92

As seen in any of the four tables, for all kinds of reactions the nurse from the Tuberculosis Research Office tended to give larger estimates of reaction size—on the average 4-6 mm larger—than the nurses from the Dispensary; in addition, there are considerable random deviations from this average. Apparently, such uncertainty in estimating the reaction size would account for a great deal of the total variability observed in duplicate testing (Nissen Meyer et al.[10]).

The classification of reactions as either " positive " or " negative " seems once again to be reasonably consistent where non-vaccinated persons are concerned and quite impossible for BCG-vaccinated. That the Dispen-

sary nurses actually tried to classify the vaccinated into " positives " and " negatives " (limit: less than 10 mm) is indicated by the conspicuous gaps at 9 mm in Tables VII and VIII. This dichotomy is not reflected in the readings of the nurse from the Tuberculosis Research Office and, what is even more convincing, when the Dispensary nurses read the same reactions twice (see Table IX), such a large proportion of the reactions of intermediate size were reclassified the second time that it can only be assumed that the dichotomy was entirely arbitrary in each case.

Accelerated reactions

In Tables VII and VIII a number of persons are recorded by the Dispensary nurses as having no reactions at all, although the nurse from the Tuberculosis Research Office found reactions from 10 mm to 20 mm in

TABLE VI. DISTRIBUTION OF 33 REACTIONS IN NON-VACCINATED PERSONS TESTED WITH 10 TU, ACCORDING TO TWO INDEPENDENT ESTIMATES OF SIZE

Reaction as read by TRO nurse (diameter of induration in mm)	Reaction as read by Dispensary nurses (diameter of induration in mm)																													Total
	0		2		4		6		8		10		12		14		16		18		20		22		24		26		28	
0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
2	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
	2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
4	3	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	4
	3	.	1	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	5
6	1	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
	.	.	.	1	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
8	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	1	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
10	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
12	2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
14	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
16	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
18	.	.	.	.	.	.	1	.	.	.	1	.	.	.	1	1	.	.	.	.	.	.	.	.	.	.	.	.	.	4
	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	1
	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
22	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	1
	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	1
24	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
26	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	1
Total	13	.	2	2	1	2	1	1	.	.	2	.	1	.	3	3	1	.	.	.	.	.	.	.	.	1	.	.	.	33

size. Actually, these reactions were very soft and flat, and they were probably not missed but regarded as " false " or " non-specific " by the Dispensary nurses. There is a plausible explanation for such reactions: it is known (Heaf;[5] Ikegami;[6] Lind;[7] Terada;[13] WHO Tuberculosis Research Office[18]) that when the same skin site is used more than once for intradermal testing, the later reactions will reach their maximum size sooner and disappear sooner than those at a " new " site. The large, soft reactions found in the present case could be such accelerated reactions about to disappear at the time of reading, as it has been a rule in the Dispensary to test BCG-vaccinated persons every year and always in the same site, the mid-dorsal aspect of the left forearm.

The existence of such modified sensitivity in a localized area of skin was demonstrated in a group of 70 male and female workers, all of whom had been tested at least once before in the last few years. These persons were

TABLE VII. DISTRIBUTION OF 80 REACTIONS IN BCG-VACCINATED PERSONS TESTED WITH 3 TU, ACCORDING TO TWO INDEPENDENT ESTIMATES OF SIZE

Reaction as read by TRO nurse (diameter of induration in mm)	Reaction as read by Dispensary nurses (diameter of induration in mm)																								Total
	0	·	2		4		6		8		10		12		14		16		18		20		22		24	
0	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
2	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
	2	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	2
4	2	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	2
	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
6	1	·	·	·	1	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	3
	·	·	1	1	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	3
8	1	·	·	1	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	3
	1	·	·	·	·	1	1	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	4
10	3	·	·	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	4
	·	·	·	·	·	·	·	1	1	·	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	3
12	·	·	·	·	·	1	·	·	2	·	1	1	·	·	·	·	·	·	·	·	·	·	·	·	·	5
	2	·	·	·	·	1	2	1	·	·	2	2	2	·	·	·	·	·	·	·	·	·	·	·	·	12
14	1	·	·	·	·	·	·	·	1	·	·	1	2	·	·	·	·	·	·	·	·	·	·	·	·	5
	·	·	·	·	·	·	1	1	·	·	4	3	·	·	·	·	·	·	·	·	·	·	·	·	·	9
16	·	·	·	·	·	·	1	·	·	2	1	2	1	·	·	·	·	·	·	·	·	·	·	·	·	7
	2	·	·	·	·	1	·	·	·	·	1	·	1	·	·	·	·	·	·	·	·	·	1	·	·	6
18	·	·	·	·	·	·	·	·	·	·	·	·	·	1	1	·	·	·	·	·	·	·	·	·	·	2
	·	·	·	·	·	·	·	·	·	·	·	1	1	1	·	·	·	1	·	·	·	·	·	·	·	4
20	2	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	1	·	·	·	·	·	·	·	·	3
	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	1	·	1	·	·	·	·	·	·	·	2
22	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	1	·	·	·	·	·	·	·	·	·	1
24	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
Total	17	·	1	3	3	5	4	5	4	·	11	9	8	3	1	2	1	2	·	·	·	·	1	·	·	80

given a routine test of 3 TU alternately in the usual site on the dorsal aspect of the left forearm and in the corresponding site on the right forearm. The reactions were read 6 hours after the tests had been given and again after an interval of 4 days. The testing as well as the reading was performed by nurses from the Dispensary.

TABLE VIII. DISTRIBUTION OF 94 REACTIONS IN BCG-VACCINATED PERSONS TESTED WITH 10 TU, ACCORDING TO TWO INDEPENDENT ESTIMATES OF SIZE

Reaction as read by TRO nurse (diameter of induration in mm)	Reaction as read by Dispensary nurses (diameter of induration in mm)																									Total
	0		2		4		6		8		10		12		14		16		18		20		22		24		26	
0	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
2	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	1	•	1	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	2
4	1	•	•	1	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	2
	2	•	1	•	1	•	1	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	5
6	2	•	•	3	•	2	1	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	8
	1	•	•	1	•	1	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	3
8	1	•	•	1	1	1	•	1	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	5
	•	•	•	•	1	2	3	1	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	7
10	•	•	•	•	•	•	1	1	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	2
	1	•	•	•	•	•	•	•	1	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	2
12	•	•	•	•	•	1	1	1	•	•	•	2	•	•	•	•	•	•	•	•	•	•	•	•	•	5
	2	•	•	•	•	•	•	1	1	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	4
14	•	•	•	•	•	•	2	•	1	•	2	•	1	•	•	•	•	•	•	•	•	•	•	•	•	6
	1	•	•	•	•	1	•	•	1	•	5	•	1	•	•	•	•	•	•	•	•	•	•	•	•	9
16	1	•	•	•	•	•	•	•	•	•	3	•	2	1	•	1	•	•	•	•	•	•	•	•	•	8
	1	•	1	•	•	•	1	•	•	•	1	3	•	•	•	•	•	•	•	•	•	•	•	•	•	7
18	•	•	•	•	•	•	1	•	•	•	1	•	•	1	2	•	•	•	•	•	•	•	•	•	•	5
	•	•	•	•	•	•	•	•	•	•	2	•	1	•	1	1	1	•	•	•	•	•	•	•	•	6
20	•	•	•	•	•	•	•	•	•	•	•	1	1	•	•	1	•	•	•	•	•	•	•	•	•	3
	•	•	•	•	•	•	•	•	•	•	1	•	•	•	•	•	•	•	•	•	•	•	•	•	•	1
22	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	•	•	•	•	•	•	•	•	•	•	•	•	•	1	•	•	•	•	•	•	•	•	•	•	•	1
24	•	•	•	•	•	•	•	•	•	•	•	•	•	1	•	•	•	•	•	•	•	•	•	•	•	1
	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	1	•	•	•	•	1
26	•	•	•	•	•	•	•	•	•	•	•	•	•	•	1	•	•	•	•	•	•	•	•	•	•	1
Total	14	•	3	6	3	8	11	5	4	•	14	7	6	4	4	3	1	•	•	•	1	•	•	•	•	94

The results for persons tested in the right arm are shown in Table X and those for persons tested in the left arm in Table XI. Each table correlates the reaction size 6 hours after testing with that 4 days after testing. There is a striking contrast between the reactions in the right arm, with a " normal " pace of development, and the accelerated reactions in the left arm, many of which were smaller at 4 days than at 6 hours.

TABLE IX. DISTRIBUTION OF 174 REACTIONS IN BCG-VACCINATED PERSONS TESTED WITH 3 TU OR WITH 10 TU, ACCORDING TO TWO INDEPENDENT ESTIMATES OF SIZE

Reaction as read by Dispensary nurses (diameter of induration in mm)	Reaction as read by Dispensary nurses (diameter of induration in mm)												Total
	0	2	4	6	8	10	12	14	16	18	20	22	
0	18	6	2	2	2	1							31
2	2	1	1										4
	2	1	2	2	1	1							9
4	3		2	1									6
	1	2	2	1	1	3	1	1					13
6			1	1	2	1	1	2	1	1	1	2	15
	1				1	1	3	2		1	1		10
8					1	1	4			1	1		8
10	1			1	2	1		1		6	6	5	25
	1		1	1			2	1		4	3	1	16
12						1		2		1	1	4	14
								1			1	2	7
14										2	1		5
										1	1	2	5
16											2		2
												2	2
18													
20													
												1	1
22										1			1
Total	29	10	6	11	12	9	12	10	1	15	14	17	174

Reaction as read by Dispensary nurses (diameter of induration in mm)	0	2	4	6	8	10	12	14	16	18	20	22	Total
0	6	2	2	2									12
2	1		1										2
	1	2	2	1	1								7
4			2	1									3
	2	2	1	1	3	1	1						11
6			1	1	2	1	1	2	1	1	1	2	13
				1	1	3	2		1	1			9
8				1	1	4			1	1			8
10			1	2	1		1		6	6	5	1	23
		1	1		2	1		4	3	1	2		15
12					1		2		1	1	4	1	10
						1			1	2		1	5
14								2	1		1		4
									1	1	2		4
16										2			2
											2		2
18													
20													
												1	1
22										1			1
Total	9	5	5	5	8	5	4	6	6	7	4	2	76

Discussion

Evaluation of naturally acquired tuberculin sensitivity

Results of cutaneous tuberculin-testing are almost always expressed in terms of *tuberculin-positive*, meaning definite response to tuberculin because of tuberculous infection, or *tuberculin-negative*, meaning the absence of such a response in persons who have not been infected with *Mycobacterium tuberculosis*. This *all-or-none* terminology reflects what must have been a basic feature of tuberculin sensitivity at the time and in the populations where tuberculin-testing was first carried out systematically: European countries in the early part of the present century. The soundness of this practice—but also its severe limitations—has been confirmed in recent

TABLE X. DISTRIBUTION OF 35 TUBERCULIN REACTIONS IN THE RIGHT FOREARM (UNUSUAL TEST-SITE) ACCORDING TO SIZE, 6 HOURS AND 4 DAYS AFTER INJECTION *

Reaction size 6 hours after testing (diameter of induration in mm)	Reaction size 4 days after testing (diameter of induration in mm)																							Total
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	
0	2	•	1	2	2	•	2	1	1	•	4	2	1	1	2	1	•	•	•	•	•	•	1	23
1	•	•	•	•	•	1	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	1
2	1	•	•	•	•	1	1	•	•	•	1	•	1	•	2	•	•	•	•	•	•	•	•	7
3	•	•	1	•	•	•	•	•	•	•	•	•	•	2	•	•	•	•	•	•	•	•	•	3
4	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
5	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
6	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
7	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	1	•	•	•	•	•	1
8	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
9	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
10	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
11	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
12	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
13	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
14	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
15	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
16	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
17	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
18	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
19	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
20	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
21	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
22	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Total	3	•	2	2	2	2	3	1	1	•	5	2	2	3	4	1	•	1	•	•	•	•	1	35

* This table illustrates the normal development of tuberculin reactions at a skin site not previously used for testing.

years by extensive investigations of the prevalence and character of tuberculin sensitivity.

Tuberculin sensitivity due to infection with *M. tuberculosis* seems to be surprisingly uniform, being of the same or nearly the same strength in tuberculous patients and in healthy persons, and also in different races and on different continents (Palmer & Bates; [12] WHO Tuberculosis Research Office [14]). This sensitivity is so uniform that a single test performed with reasonable accuracy and at a suitably selected dosage (an intradermal 5 TU test is the best known example) will give a perceptible reaction in practically every infected person and yet give few reactions so strong as

to be really inconvenient. Anergy after infection is found so rarely that individual workers feel justified in publishing reports on such cases (moribund patients, patients with measles, etc.) and is certainly not so frequent as to detract seriously from the value of routine tuberculin-testing.

It is not surprising that a number of percutaneous tests—von Pirquet, Moro, Trambusti, Heaf and many others—have worked quite well in the past, in spite of the ill-defined dosage of ill-defined tuberculin products: the reactions as seen from day to day must have been quite a reliable guide to correct dosage, in that when nearly all the persons tested have either moderately strong reactions or no reactions at all, i.e., when dubious reactions are scarce, it is fairly certain that practically every infected person will be revealed by the test in question.

TABLE XI. DISTRIBUTION OF 35 TUBERCULIN REACTIONS IN THE LEFT FOREARM (USUAL TEST-SITE) ACCORDING TO SIZE, 6 HOURS AND 4 DAYS AFTER INJECTION *

Reaction size 6 hours after testing (diameter of induration in mm)	Reaction size 4 days after testing (diameter of induration in mm)																							Total
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	
0	1	·	1	1	1	1	·	·	1	·	·	·	·	·	·	1	·	·	·	·	·	·	·	7
1	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	1
2	1	·	·	·	·	·	·	·	·	·	·	2	·	·	·	·	1	·	·	·	·	·	·	4
3	·	·	·	·	·	·	·	·	·	·	·	·	·	1	·	·	·	·	·	·	·	·	·	1
4	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
5	·	·	·	·	·	1	1	·	·	·	·	·	·	·	1	·	·	·	1	·	·	·	·	4
6	·	·	·	·	·	·	·	·	·	·	·	·	1	1	·	·	·	·	·	·	·	·	·	2
7	·	·	·	·	·	·	·	·	·	·	·	1	·	·	·	·	·	·	·	·	·	·	·	1
8	·	·	·	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	1
9	·	·	1	1	·	·	·	·	·	·	·	1	·	·	·	·	·	·	·	·	·	·	·	3
10	·	·	·	·	·	·	·	·	·	·	1	·	·	·	·	·	·	·	·	·	·	·	·	1
11	·	·	·	1	·	·	·	·	·	·	·	·	·	·	1	·	·	·	·	·	·	·	·	2
12	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
13	·	·	·	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	1
14	·	·	·	·	·	·	·	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	1
15	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	1
16	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
17	·	·	1	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	1
18	1	1	·	·	·	·	·	·	·	·	·	1	·	·	·	1	·	·	·	·	·	·	·	4
19	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
20	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
21	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
22	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
Total	5	1	3	5	1	2	1	1	1	·	1	5	1	2	2	2	1	·	1	·	·	·	·	35

* This table illustrates the accelerated development of tuberculin reactions at a skin site previously used for testing.

We may conclude that it is quite permissible to use the term " tuberculin-positive " in the double sense of (1) a definite response to the kind of tuberculin test that is in local use, and (2) a person showing such a response because of tuberculous infection, and to use the term " tuberculin-negative " correspondingly; that is, it is permissible to do this in populations where the only source of tuberculin sensitivity is infection with *M. tuberculosis*.

Evidence collected during recent years strongly suggests that other sources of natural sensitivity do exist. Such non-specific (non-tuberculous) sensitivity is usually found to be weaker than ordinary sensitivity and does not present a serious problem when very weak. In certain regions of the USA, for example, sensitivity not due to tuberculous infection (Palmer [11]) has been revealed by the use of an intradermal 250 TU test; and it seems that the problem is best dealt with by not using such high doses of tuberculin, or by not calling persons " tuberculin-positive " when they react only to such high doses. But the presumably non-specific sensitivity found in most parts of South-East Asia (WHO Tuberculosis Research Office [14, 15]) presents a serious problem, because it is not very much weaker than the sensitivity due to tuberculous infection; the reactions due to the two kinds of sensitivity overlap, so that even with the " best " limit in terms of reaction size the discrimination will be poor. Worse still, it would seem impossible in practice to keep up any " best " limit when no class of typically " positive " reactions stands out as a guide to correct dosage of tuberculin and stable reading of reactions. In such populations there is little point in calling a person " tuberculin-positive " or " tuberculin-negative ", because whatever the formal definition and whatever the practice, the classification will correspond poorly to biological reality, and will therefore be a dubious guide to action.

Evaluation of tuberculin sensitivity in groups of BCG-vaccinated persons

Difficulties of a similar kind are met with when tuberculin reactions in a BCG-vaccinated population are classified as " positive " and " negative ". BCG-induced sensitivity varies quantitatively from person to person over a potentially very wide range, from what is scarcely revealed by an intradermal 100 TU test to a sensitivity about as strong as that found in infected persons. Nowhere on this continuous scale of sensitivity is there a natural limit between a successful, satisfactory vaccination on the one hand, and an unsuccessful, unsatisfactory vaccination on the other. The unfounded, yet almost universal, practice of setting up arbitrary limits between " positive " and " negative " (and believing in them) seems to be a source of confusion and misinterpretation in this field.

That tuberculin sensitivity caused by BCG vaccination is a matter of degree rather than a quality present or absent has been demonstrated in previous publications from the Tuberculosis Research Office (Edwards,

Palmer & Magnus; [1] WHO Tuberculosis Research Office [16]). In the latter report, the results of a follow-up examination of 6000 schoolchildren were summarized as follows:

" Tuberculin sensitivity produced by BCG is not the kind of response that may logically be described as ' positive ' or ' negative '. Rather, vaccination always produces, or increases, sensitivity to tuberculin, although, with some vaccines and in some persons, the degree of sensitivity produced may be low. BCG-induced allergy can best be described by the distribution of the sizes of the tuberculin reactions and summarized by the mean and standard deviation of the distribution."

The present results, obtained in adults rather than in children, seem to fit this description quite well: the distribution of reactions by size, summarized perhaps as mean size and standard deviation, would seem to reflect something that does actually occur in nature, whereas " percentage positive " is an estimate of something that does not exist.

" Estimates " of percentages of " positives " may of course be made by defining some arbitrary limit between " positives " and " negatives ", in terms of a certain reaction size for a certain tuberculin dose. It is also true that such percentages will give some information on the degree of sensitivity, but this information is less precise than that contained in the average reaction size, even in the most favourable case when the percentage is about 50. (The variance of the mean of a normal distribution is two-thirds of the variance for the median.) A percentage close to either 0 or 100 yields far less information than does the corresponding average reaction size: two groups of BCG-vaccinated persons may both be " almost 100% positive " and yet one of the groups may show considerably larger reactions (stronger sensitivity) than the other.

Uncontrolled variability in results of testing

There are several well-known reasons, and probably a number of unknown, why two tuberculin tests given to the same person in the same way should not give the same result. With the intradermal technique there are such sources of variability as inaccurate standardization of tuberculin, instability of tuberculin dilutions (Guld et al.; [4] Magnus et al. [9]), inaccuracy in measuring the volume of dilution injected (Guld [3]), variability in estimating the size of the reaction, etc. These sources of error should all be considered if a greater accuracy in the performance of tuberculin-testing is aimed at.

In addition, the sensitizing effects of intradermal testing should be kept in mind: the sensitization of the local area of skin (as described above), as well as the general " boosting " effect on waning sensitivity (Magnus & Edwards; [8] Magnus [a]).

[a] See article on page 249 of this number of the *Bulletin*.

Tuberculin-testing as a diagnostic tool

It is commonly believed that a BCG-vaccinated person may eventually " revert to the tuberculin-negative state " and will then remain " negative " until sensitized once more. If this were true, or essentially true, the observation of a second " conversion ", without intervening revaccination, would imply the incidence of virulent infection.

The idea that a positive reaction, when preceded by a negative, almost always signifies a " conversion " and only quite exceptionally an " error " (provided the testing is done with reasonable care and accuracy) was probably correct when and where it was first used, not because testing was done more accurately at that time but because the presence or absence of sensitivity due to " natural " (virulent) infection is not easily mistaken when it is the only existing kind of sensitivity. " Errors ", that is, uncontrolled variability in the results of testing, will be of minor significance so long as the individuals to be divided into two classes do really belong to two distinct categories, infected and non-infected. The same variability, due to the same uncontrolled factors, will be vastly more impressive when the population to be divided does not consist of two categories, but of one only (namely, vaccinated persons), especially if the arbitrary definition of a limit happens to be close to the average value of the sensitivity of the population. Thus, when a BCG-vaccinated person is found to react to tuberculin, though recorded as a non-reactor the previous year, it is very likely that this " change " is due to random fluctuations in the outcome of the tuberculin test rather than to any true increase in sensitivity to tuberculin.

There is another popular belief about the nature of BCG-induced sensitivity: that tuberculin reactions due to BCG are very different from those due to virulent infection. And it is true (under most circumstances) that tuberculin reactions in vaccinated persons are typically smaller and softer than reactions in naturally infected persons so that it is often possible to make a fair guess about the source of allergy of a given reaction. But many reactions are not typical, and systematic guesswork of this kind will result in a moderate proportion of mistakes. As was illustrated earlier, many vaccinated persons give, sometimes, reactions so strong that they are confused with reactions due to tuberculous infection. Repeated testing in such persons will, quite automatically, yield a heavy rate of false " conversions ".

A small number of presumably non-vaccinated persons in this study seem to present similar problems (see Table III and Fig. 4). These are quite possibly unrecognized and forgotten BCG-vaccinated cases, and the frequency of such cases will necessarily increase in the coming years. When systematic BCG-vaccination of the child population has been carried out for many years, it is very likely that a person will, in fact, have been BCG-vaccinated, even if he maintains in good faith that he never was; thus any " conversion " in a " non-vaccinated " person will be much more likely to be due to unrecognized vaccination than to virulent infection.

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RÉSUMÉ

Depuis quelques années, les réactions tuberculiniques de routine, appliquées à des sujets apparemment bien portants, en vue de dépister d'éventuelles infections récentes, ont donné une proportion anormale de résultats aberrants. Il est déroutant de constater chez une même personne, au cours d'une brève période, une réaction à la tuberculine, tantôt positive, tantôt négative. L'auteur a cherché les causes de ces résultats inconstants lors de l'estimation de la sensibilité à la tuberculine d'une population danoise composée d'adultes non tuberculeux, comprenant une forte proportion de sujets vaccinés au BCG.

Les résultats obtenus chez des sujets non vaccinés ont confirmé l'opinion selon laquelle l'infection tuberculeuse a pour conséquence une sensibilité à la tuberculine uniformément élevée, contrastant avec l'absence de sensibilité qui caractérise, en Europe, les individus non infectés et non vaccinés. Lorsqu'il s'agit du classement qualitatif des personnes soumises au test en « positives » ou « négatives », une certaine inexactitude — inévitable dans les estimations quantitatives du degré de sensibilité à la tuberculine — n'a que peu d'importance. Ce classement conventionnel a une base réelle et pratique indiscutable lorsqu'il s'agit de personnes non vaccinées, en Europe.

La sensibilité à la tuberculine des sujets vaccinés au BCG répond à un schéma très différent. On observe chez eux des réactions de toutes intensités entre « positif » et « négatif », allant de la réaction à 100 UT à peine visible à une réaction à peu près aussi forte que celle que provoque le bacille tuberculeux lui-même. Dans ces conditions, les différences quantitatives inévitables observées dans la mesure de l'intensité de la réaction tuberculinique revêtent une importance considérable. Des tests successifs chez une même personne vaccinée au BCG peuvent être interprétés soit comme « négatifs » soit comme « positifs », cela simplement à la suite de variations imprévisibles dues à l'action de facteurs incontrôlables dans la technique du test. Il s'ensuit que l'on risque d'en tirer des conclusions erronées: dans certains cas, on estimera que la sensibilité induite par la vaccination a diminué puis disparu; dans d'autres cas, on pensera qu'il s'agit d'une surinfection—selon la direction dans laquelle la variation s'est produite. Le classement des individus vaccinés au BCG en « positifs » et « négatifs » ne correspond dès lors plus à la réalité et n'a pas de signification pratique. L'auteur établit un parallèle avec les constatations faites dans les populations tropicales, chez lesquelles la présence d'une sensibilité non spécifique à la tuberculine fait obstacle au diagnostic par les tests tuberculiniques.

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