

POST-VACCINATION ALLERGY ELEVEN YEARS AFTER BCG VACCINATION

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In South India the risk of being infected with tubercle bacilli is greatest at the age of 10 to 19 years. If BCG vaccination is given in the pre-school or during the first school years, the post-vaccination allergy should be maintained at a fairly high level for a period of up to 10 to 15 years. Is it possible that BCG-induced allergy can last that long? In Danish children BCG allergy has been maintained at a high level for 5 years (WHO Tub. Res. Office 1956). The two BCG assessment teams which carried out retests in India in 1954 and 1955 respectively found also BCG induced allergy at a moderate level in children vaccinated 4 years earlier (WHO Tub. Res. Office, 1955 and 1957). At Madanapalle, presence of BCG allergy could be demonstrated after an interval of 4 years (Frimodt-Moller, 1960). Kul Bushan (1960) examined between August 1955 and October 1958 the post-vaccination allergy in school children in 129 different localities throughout India. The interval between vaccination and retests ranged from 1J months to 3J years, the average being 13 months. The mean size of indurations during the first 6 months was 13.0mm., during the second half year 11.5mm., during the third half year 11.2 mm., during the fourth half year 12.8 mm., and after 2-3 J years 12.1 mm.

Our experience with BCG vaccination at Madanapalle dates back to 1948 when a high proportion of the town population was tuberculin tested and nearly all tuberculin negative persons vaccinated (Frimodt-Moller, 1949). In 1950 the village population of 37,000 within 10 miles of Madanapalle was submitted to a community-wide survey by tuberculin tests and X-ray.

The first place to be surveyed was Vayalpad, a small town of 5,500 inhabitants. During the summer of 1950 all persons reacting with less than 6 mm., to 1 and 10 TU were offered BCG vaccination. In 1961, i.e., 11 years later, a series of tuberculin tests was carried out in the Board High School at Vayalpad. Fifty-five per cent of the school children were found to have been vaccinated earlier, and many of these as far back as 1950. The present report describes the results of these retests.

THE MATERIAL

The main purpose of the tuberculin testing of the school children at Vayalpad was to compare the effect of two different tuberculins: the new standard tuberculin, RT 23, issued since 1958 by the State Serum Institute, Copenhagen, and their former standard tuberculin, RT 19-20-21, which had been used all the previous years by the Madanapalle Tuberculosis Field Research Station. The RT 23 was given in doses of 1 TU with Tween 80 and the RT 19-20-21 in doses of 5 TU without Tween 80. The school children were tested simultaneously with both tuberculins, the sites on right and left arms being alternated from child to child. It was found that the RT 23 produced smaller reactions than the RT 19-20-21, particularly in the lower range of reaction sizes (Frimodt-Moller *et al*, 1961).

The findings given here relate only to the reactions following tests with RT 19-20-21.

There were 387 children in the five forms of the school. Their ages ranged from 9 to 22 years (92 per cent ranged between 11 and 18 years), the mean being 13.8 years. In 342 of the 387 children the tests were given and read (at 48 hours). The readings were done independently by three different readers without their knowing which tuberculin had been used at each site of reaction (the readings of the senior reader are given here).

The transverse diameter was measured on a transparent millimeter scale and dictated to an assistant. After the last reader had finished his readings the left shoulder was examined for presence of vaccination scars. The diameters of these in millimeters were also noted. Afterwards the cards with the names of the children and of their father, or guardian, their age and full address were matched against the files of index cards and household registers maintained at the office of the Research Unit.

It was found that 186 children belonged to the Madanapalle Survey Area whereas 156 children belonged to villages outside the Survey Area. Vayalpad lies in the periphery of the Madanapalle Survey Area, so many of the school children are drawn from the neighboring

Villages on that side of Vayalpad which has not been included in the Madanapalle Study Population. It was found that of 165 children showing BCG scars 74 belonged to the villages outside our Survey Area. They had been vaccinated, probably in 1956 or 1957, by the Andhra Government BCG Campaign team and not by ourselves. Three of these children had fresh scars after vaccination done by the Mass Campaign team four months earlier during its second tour of the area, but the rest had been vaccinated 4 or 5 years earlier.

Of the 186 children belonging to the Madanapalle Survey Area, individual records were found in 162 but could not be found in 24, owing to changes of address. The records of the 162 give detailed information of previous tuberculin tests, BCG vaccination and MM X-ray findings. It was found that 98 had been vaccinated by our own teams, 69 of these in 1950 and the rest during 1951-55. Of the 98 vaccinated, 76 showed BCG scars while 22 showed no scars (several had shown scars at the inspections one or two years after vaccination). Of 64 children known not to have been vaccinated none showed BCG scars. Thus 22 (or 22.5 per cent) of the vaccinated would not have been recognized as vaccinated had the records not been available; they would therefore have appeared among the children presumed not to have been vaccinated.

Of the 156 children belonging to villages outside our Survey Area, 74 showed typical BCG scars and 82 no scars. It must be assumed that some children previously vaccinated but showing no scars must be among the 82 presumed not to have been vaccinated. As these children had been vaccinated only 4-5 years earlier the proportion who had lost their scars might not be so high as found in the group vaccinated 10-11 years earlier.

RESULTS

Sixty-nine of the children tested in 1961 had been vaccinated in 1950. The frequency distribution of the diameter of their indurations is shown in Fig. 1. Ignoring some 20 per cent of the children showing reactions of less than 4 mm., the rest are grouped according to a normal distribution around a mode of 11 mm, or so. This suggests that the majority of the children vaccinated eleven years earlier possess a moderately high level of allergy. Whether all this can be ascribed to the BCG vaccination or can be due to other sources of tuberculin

sensitivity can be studied by comparing their reactions with those found in children who were not vaccinated.

In Fig. 2 the results in all the children belonging to the Madanapalle Survey Area have been shown. In the distribution shown in the upper part of the graph, besides the 69 vaccinated in 1950 another 29 who were vaccinated between 1951 and 1955 have been included, as well as 15 with BCG scars whose records could not be found. The mean interval between vaccination and retest for those for whom the date of vaccination is known was 10.6 years. The lower part of the graph shows the distribution of 73 persons of which 64 had not been vaccinated and 9 whose records could not be found but who showed no scars.

The findings in the non-vaccinated children show that their reactions can clearly be divided into two groups, one with reactions ranging from 10 to 26 mm., forming a normal distribution around a mode of 17 or 18 mm., and another with reactions ranging from 2 to 10 mm. Evidently, the group with large reactions represents children with a specific sensitivity caused by infection with tubercle bacilli while the other group with small reactions have a low degree of sensitivity which probably is caused not by tubercle bacilli but by some other type of bacilli. The non-vaccinated children show therefore a pattern of tuberculin sensitivity which is in conformity to what has been found many times before in many places of India and other tropical and semi-tropical areas.

The vaccinated have reactions which correspond to a level of allergy midway between the 'specific' and the 'non-specific' levels and is different from either two. It is, therefore, reasonable to ascribe this sensitivity to the allergy produced by the BCG vaccination. It can therefore be concluded that the effect of the vaccination ten to eleven years earlier is still in existence.

Before discussing whether other factors have modified the pattern on tuberculin sensitivity in the vaccinated group, the results obtained in the children from the villages outside the Madanapalle Survey Area may be studied. Fig. 3 shows the distribution of reactions in 74 children with typical scars and 82 without scars. As mentioned, these children had been vaccinated by the Government BCG vaccination team in the Mass Campaign in 1956-57,

TABLE I
Results of 342 Mantoux Tests in Vayalpad Board High School, March 1961

Indurations to 5 TU in mm	Children from Madanapalle Survey Area						Children from villages outside the Survey Area	
	Vaccinated (98)		Not vaccinated (64)		No data (24)		Vaccination scars	
	Present	Absent	Present	Absent	Present	Absent	Present	Absent
0	6	4	.	14	3	2	9	18
1	.	.	.	3	.	.	1	4
2	4	2	.	11	1	.	6	12
3	7	1	.	2	3	1	9	8
4	1	1	.	6	1	.	3	4
5	5	2	.	3	.	.	5	4
6	1	1	5	1
7	6	2	.	3	.	.	5	2
8	7	2	.	1	1	.	6	.
9	2	1	.	1	1	.	4	2
10	3	.	.	.	1	.	4	.
11	5	1	.	.	1	1	1	2
12	3	2	.	3	1	.	2	3
13	6	4	3
14	4	.	.	1	.	.	3*	2
15	3	1	.	3	.	.	2*	1
16	4	1	.	2	.	.	2	1
17	3	2	.	3	.	1	1	6
18	1	.	.	2	.	1	1*	2
19	2	.	.	2	1	.	.	2
20	1	.	.	1	1	2	.	1
21	.	.	.	1	.	.	.	1
22	1	.
23	.	.	.	1	.	.	.	2
24	2	.	.	1	.	.	.	1(30 mm)
Total	76	22	0	64	15	9	74	82
	186						156	

One child in each group had been vaccinated only 4 months earlier.

i.e., only 4-5 years earlier. The pattern of reactions in both groups is very similar to that found in the children from the Survey Area just described. The children, presumably not vaccinated, have also two types of reactions—one with large reactions and another with small or no reactions. The vaccinated show reactions intermediary in size between the other two. Compared with the children belonging to the Madanapalle Survey Area the level of post-vaccination allergy seems to be very much of the same order—if anything, perhaps slightly lower. There does not appear to be any essential difference between the type of allergy produced by the vaccination done by the Madanapalle Research team and that produced

in the Mass Campaign. As the Madanapalle material is supported by previous data, it forms the basis for the further analysis.

DISCUSSION

In his report on retests done between 1955 and 1958 Kul Bhushan presents a diagram showing the frequency distribution of reactions in well over 18,000 school children. It shows a normal distribution with a mode around 13 mm. It differs from the present findings by showing very few children with really small reactions. His distribution for the children classified as 'positive' has a mode of about 19 mm. The reactions in the vaccinated are, therefore, in general about 6 mm. smaller than

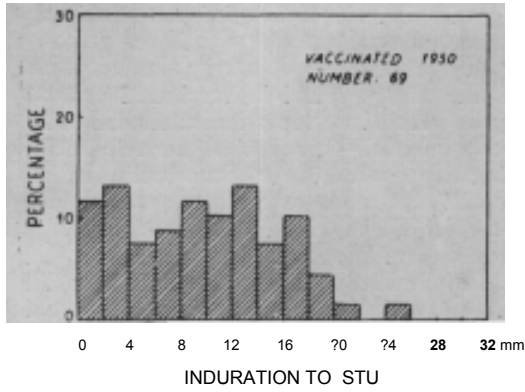


FIG. 1

1. Frequency distributions of diameters of indurations to 5 TU at retests in 1961 of children vaccinated in 1950.
2. Frequency distributions of diameters of indurations to 5 TU at retests in 1961 of children tested initially in 1950-55 by the Madanapalle Research Unit.
3. Frequency distributions of diameters of indurations to 5 TU at tuberculin tests in Vayalpad 1961 of children belonging to villages outside the Madanapalle Study Area. Previous vaccinations done by the Andhra Government BCG Mass Campaign Teams in 1956-57.
4. Hypothetical distributions of children vaccinated by the Madanapalle Research Unit 1950-55 according to size of their indurations to 5 TU at retests in 1961.

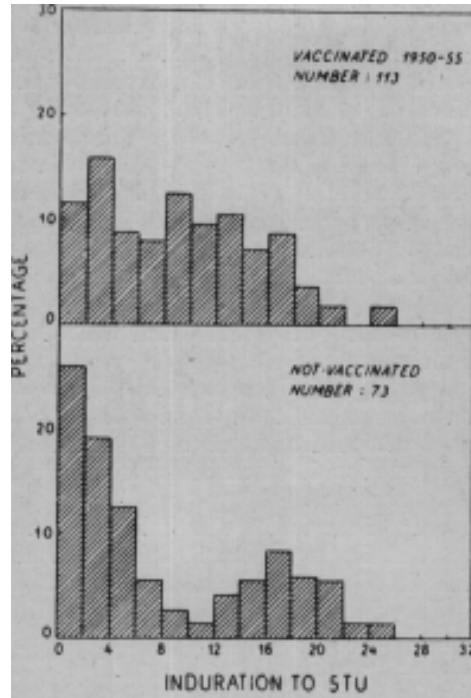


FIG. 2

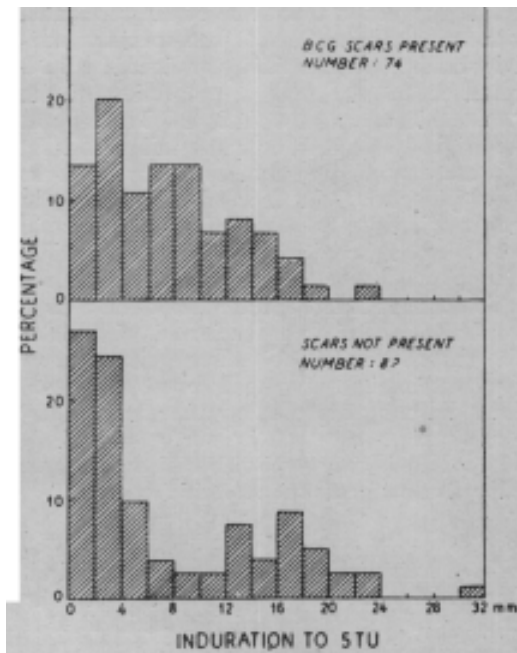


FIG. 3

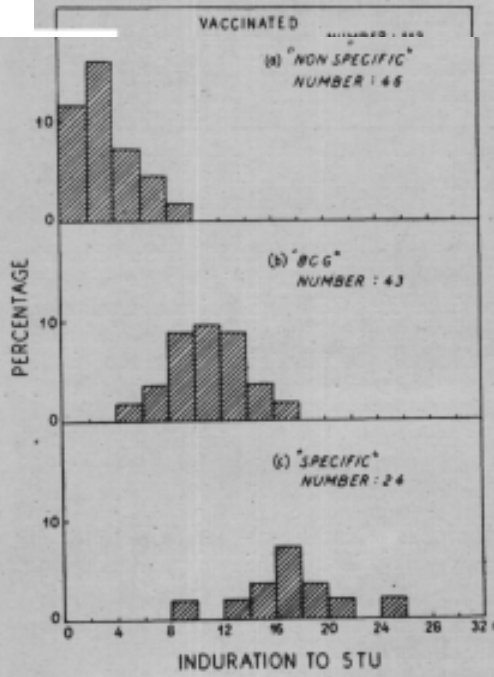


FIG. 4

those observed in the children with specific sensitivity. The corresponding diameter for the present material are 11 and 17 mm. with a difference of also 6 mm. The reason for the reactions in the Madanapalle material being a little smaller is probably due to a difference in reading between the two readers. There appears, however, to be a significant difference in the shape of the distributions in the two materials. Considering that Kul Bushan's retests took place much sooner after vaccination—in 72 per cent of his examinations within the first 12 months—than ours which were done after an interval of ten to eleven years, it is not surprising that there are differences. It would be strange if during such a long period some of the children in our material had not been infected with tubercle bacilli and some had lost some of their allergy by waning.

A study of the findings in India and other Asian countries as well as in Africa and the Middle East by the BCG assessment teams of the WHO Tuberculosis Research Office, Kul Bushan's and our own findings leads to the conclusion that the allergy induced by BCG vaccination in India is generally not so high as found in naturally infected persons. In terms of tuberculin reactions the BCG allergy is usually found midway between that obtained in naturally infected and that found in persons with 'non-specific' low-grade allergy. Each type of allergy is characterized by normal distributions, of tuberculin reactions placed at different points on the scale of indurations. There may be some overlapping but not so much that they coalesce. From the shape of the right tail corresponding to the larger reactions the whole distribution can often be reconstructed.

Assuming that reactions of 17 mm. or more represent the specific sensitivity only we can isolate from the BCG distribution a number of reactions corresponding to children infected with tubercle bacilli (Fig. 4, group *(c)*). Similarly, assuming that the new right hand tail of the remaining bulk of reactions is due to BCG allergy only, we can isolate the 'pure' BCG reactions by forming another normal distribution around a mode of 11 mm. Such a distribution is shown in Fig. 4 under *(b)*. We are now left with a third distribution of small reactions as shown under *(a)* in Fig. 4. They resemble very much the distribution among the unvaccinated (Fig. 2) attributed to the 'non-specific' allergy,

By this kind of reasoning it is not our aim to estimate the exact number of children possessing this or that sort of allergy, but to stress that the allergy found in vaccinated persons may be affected by super-infection with other types of bacilli—the classical tubercle bacilli which step up the degree of tuberculin sensitivity and the unknown bacilli responsible for 'non-specific' allergy. This 'non-specific' allergy may be found in persons who either never did acquire any allergy after BCG or if they did had lost it all, or most of it, so that they could get a low-grade allergy if subsequently infected with the unknown type of bacilli.

As for the incidence of children presumably infected with tubercle bacilli, it was found that among 64 non-vaccinated whose records are available 53 had been tuberculin tested when the vaccinated had their pre-vaccination test. Nine of the 53 showed large reactions at the initial test. Of the other 44 who would be classified as 'tuberculin-negative', 8 showed now large reactions, i.e., a conversion rate of 18 per cent. In comparison we have estimated above that about 24, or 21 per cent, of the vaccinated had acquired so high an allergy that it could be due to an infection with tubercle bacilli (group *(c)* in Fig. 4). It is therefore quite probable that the rate of infection has been about 20 per cent over a period of 10-11 years, or roughly 2 per cent per year.

The suggestion that some of the vaccinated with small reactions have a 'non-specific' sensitivity rather than a sensitivity produced by BCG would mean that only a proportion of the vaccinated still possess their BCG allergy at the original level. How many this would be, it is not easy to say—perhaps it may be about 60-70 per cent. The lack of BCG allergy in the remainder has been offset to a certain extent by the acquisition of the 'non-specific' allergy.

To sum up: There is little doubt that a large proportion of children vaccinated with BCG still possess their BCG allergy eleven years after vaccination. A small proportion who either did not get any allergy after the vaccination, or might have lost it later on, may have been infected with atypical bacilli which have induced a low-grade 'non-specific' allergy.

SUMMARY

Post-vaccination retests in school children after an interval of eleven years show that the majority of the vaccinated has maintained a

level of allergy comparable to that found one year after vaccination. It is possible that some of the children whose allergy has waned have been reinfected with atypical bacilli

setting up a low-grade, 'non-specific' sensitivity. Other children show levels of allergy suggesting - that they have been infected with tubercle bacilli setting up a high degree of allergy.

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