Controlled Trial of BCG Vaccination in a School Population

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THE ROLE of BCG vaccination in tuberculosis control programs has been cloaked with controversy almost since the day in 1921 when BCG was first administered to a human subject (*1*). Although some aspects of the problem have been clarified by controlled field trials of vaccination, divergent conclusions have been reached regarding its usefulness. This is well illustrated by two of the most recently reported trials, one involving a quarter of a million participants in Puerto Rico and the southeastern United States, and the other, 56,700 subjects in Great Britain (*2,3*). Both reports agreed that the risk of developing tuberculosis was considerable among reactors to a low dose of tuberculin. But for nonreactors, the British found a high risk of developing disease and substantial protection from vaccination, while the American trials led to the opposite conclusions, namely, that the risk for nonreactors was low and that the benefits conferred by vaccination were too slight to counterbalance its disadvantages. Nevertheless, midst the welter of conflicting findings and opinions, there appears to be growing acceptance of the view that BCG vaccination should not be used in populations whose risk of becoming infected with *Mycobacterium tuberculosis* is slight (*4–7*).

The validity of this view is illustrated by the results of a controlled trial of BCG vaccination among the school population of Muscogee County, Ga., begun in April 1947. Observations during the ensuing 12 years show that the infection rate in the community has been low and diminishing, that reactors to a low dose of tuberculin ran the greatest risk of developing tuberculous disease, and that BCG vaccination had no demonstrable effect on the tuberculosis problem.

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Procedures

The tuberculin testing and BCG vaccination procedures have been described (*8*). Briefly, all participants were tested with 5 T.U. of PPD, and the nonreactors to this dose were tested with 100 T.U. of PPD. The PPD was supplied by the State Serum Institute of Copenhagen, Denmark, and was designated as lot RT 18. Throughout this report, reactors are defined as persons with 5 millimeters or more of induration to the specified dose of PPD. To allay concern on the part of parents and teachers, reactors to the 5-T.U. dose were advised to have a chest X-ray. No further followup examinations were advised for reactors with negative chest X-rays because it was then generally believed that their risk of developing tuberculosis was slight.

Because a negative reaction to the 100-T.U. dose was considered to be a necessary prerequisite for vaccination in 1947, all nonreactors to the 5-T.U. test were given the larger dose. For those who reacted to the 100-T.U. test, nothing more was advised. Nonreactors were divided into two groups on the basis of their birth year. One group was vaccinated and the other was left unvaccinated as a con-

trol. The vaccine, supplied by Dr. S. R. Rosenthal of the Research Foundation, Chicago, Ill., was administered by multiple tangential acupuncture on the third or fourth day after preparation.

Six months later, 70 percent of the vaccinated students were retested with 5 T.U. and 100 T.U. of PPD. At that time 45 percent were reactors to the 5-T.U. dose, and 93 percent reacted to the 5- or 100-T.U. doses. The nonreactors to the 100-T.U. dose were revaccinated.

Cases among the study population were identified through the normal casefinding and reporting facilities in the county. The mechanics of case identification were simplified by combining tuberculosis control and research activities in the metropolitan area into a single facility, the Muscogee County Tuberculosis Study (*9*). Because of the extensive casefinding conducted in this area and the highly cooperative attitude of the local physicians, it is very unlikely that important cases of tuberculosis have been missed among the resident population even though no effort was made to examine each participant periodically. The records of persons classified as tuberculosis cases or suspects were matched with a master index file which contained the tuberculin and vaccination status of participants in the 1947 trial. The 1947 tuberculin and vaccination status was not recorded on the clinic case records.

The Study Population

Approximately 16,000 children were enrolled in the schools of Muscogee County in 1947. The study population is restricted to 11,262 children whose 5-T.U. tests were read at 48 hours. These children came from all grades of the city, county, and parochial school systems. All but 1.5 percent were between the ages of 5 and 19 years, the average age being 11.4 years. The subdivision of this population into study categories is shown in table 1. Of the total, 1,492, or 13 percent, had positive reactions to 5 T.U. of PPD.. Another 3,768, one-third of the study population, were classified as reactors to the 100-T.U. dose. The 5,261 nonreactors to both doses were to be divided into two roughly equal groups, one to be vaccinated and the other to be left unvaccinated as controls. However, 422 were classified as "irregulars" since they did not qualify for the vaccinated or control groups for such reasons as refusal to accept vaccination if offered or medical contraindications to vaccination.

There was a marked difference between the two races with respect to tuberculin sensitivity to the 5-T.U. test. Only 8 percent of the white children were classified as reactors to 5 T.U. compared with 26 percent of the Negro children. The distribution of the 5-T.U. reaction sizes is shown for each race in the chart Three-fifths of the Negro reactors but only two-fifths of the white reactors had 10 mm. or more of indura-

Table 1. Composition of study population, by tuberculin and vaccination status and race, Muscogee County, Ga.

Tuberculin and vaccination status	Both races		White		Negro	
	Number	Percent	Number	Percent	Number	Percent
5-T.U. tests						
Completed tests	11, 262	100. 0	7, 767	100. 0	3, 495	100. 0
Reactors	1, 492	13. 2	590	7. 6	902	25. 8
Nonreactors	9, 770	86. 8	7, 177	92. 4	2, 593	74. 2
100-T.U. tests						
Completed tests	9, 029	80. 2	6, 675	85. 9	2, 354	67. 4
Reactors	3, 768	33. 5	2, 606	33. 6	1, 162	33. 2
Nonreactors	5, 261	46. 7	4, 069	52. 4	1, 192	34. 1
Controls	2, 341	20. 8	1, 818	23. 4	523	15. 0
Vaccinees	2, 498	22. 2	1, 948	25. 1	550	15. 7
Irregulars	422	3. 7	303	3. 9	119	3. 4

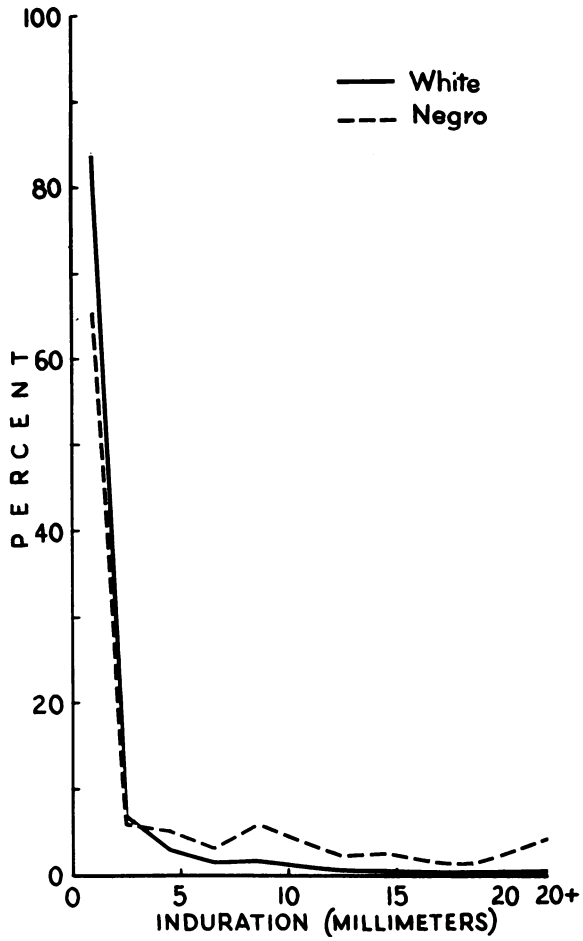
tion. A surprising finding at the time was that the proportion of the study population reacting only to the 100-T.U. dose was similar for whites and Negroes. In addition, while the frequency of reactions to the 5-T.U. test, particularly those of 10 mm. or more, were in line with other indices of the tuberculosis problem in the two races, those to 100 T.U. were not. The failure of the 100-T.U. reactions to reflect the extent of the tuberculosis problem in the various subgroups of the community was one of the early clues to the existence and high prevalence of nonspecific tuberculin sensitivity in the southeastern United States (*10*). Because of the use of the 100-T.U. dose, only one-half of the white children and one-third of the Negro children were eligible for vaccination.

Estimating the Infection Rate

One reason for selecting Muscogee County, Ga., as the site for a field study of tuberculosis and BCG vaccination was the belief that the tuberculosis problem in this area is not too different from that of the United States as a whole. However, weak sensitivity to tuberculin, especially that elicited only by the 100-T.U. dose, was prevalent to an unusual degree. Subsequent studies have shown that most of this weak sensitivity can be attributed to sources other than *M. tuberculosis* (*11–13*). This has an important bearing on the use of conversion rates as an index of the risk of acquiring specific tuberculous infection. In this area, it now appears that most of the reactions to 5 T.U. of PPD with induration less than 10 mm., and some of the larger reactions as well, are caused by an agent other than *M. tuberculosis* (*14*). Consequently, in this paper, a conversion will be defined as a reaction to the 5-T.U. dose which changes from less than 5 mm. to more than 10 mm. of induration. It is believed that the conversion rate, so defined, will approximate the tuberculosis infection rate reasonably well.

The infection rate in the school population in this area can be estimated from the results of two tuberculin surveys in the school system subsequent to the 1947 BCG trial. The first was the 1950 BCG trial, in which 5 T.U. of PPD (RT 19–20–21) was used (*2*). The second survey in 1957 covered all junior and

Percentage distribution of the study population by initial reaction to 5 T.U. of PPD, by race, Muscogee County, Ga.



senior high schools in Muscogee County and in Russell County, Ala. (the county adjoining Muscogee County to the west and part of the same metropolitan area). The tuberculin used in the second survey was also 5 T.U. of PPD (RT 19–20–21). At the time of testing and reading, the observers did not know the tuberculin and vaccination status of the children in the 1947 or 1950 trials.

In the spring of 1950, 1,379 controls from the 1947 trial were tested. All of these 1,379 subjects had less than 5 mm. of induration to both 5- and 100-T.U. tests in 1947. Three years later, 0.9 percent of the whites and 4.9 percent of the Negroes had reactions larger than 10 mm. to the 5-T.U. dose (*8*). This is equivalent to an average annual infection rate of about 0.3 percent for whites and 1.7 percent for Negroes.

Too few controls from the 1947 program were tested in 1957 to yield reliable results. However, 611 students who were controls in the 1950 trial were retested in April 1957. At that time, 1.3 percent of the white controls and 4.7 percent of the Negro controls had converted from less than 5 to more than 10 mm. of induration to 5 T.U. of PPD. This is equivalent to an average annual infection rate of 0.2 percent for whites and 0.7 percent for Negroes.

These infection rates have been calculated as an average over a period of years. They were lower in the second period than in the first. Therefore, it is not unreasonable to assume that they have been decreasing over the entire 10-year period, and that the rate for 1957 was about 0.1 percent per year for whites and 0.3 percent for Negroes. The rate for whites is essentially the same as that estimated for white naval recruits from all sections of the United States (*15*). It appears likely that the risk of becoming infected with *M. tuberculosis* in Muscogee County is not too different from the average risk in the country as a whole, and that the risk in Muscogee County, again like most other parts of the Nation, is not only low but has been diminishing.

Table 2. Comparison of controls and vaccinees, Muscogee County, Ga.

Characteristic	Controls	Vaccinees
Number	2, 341	2, 498
Race (percent):		
White	77. 7	78. 0
Negro	22. 3	22. 0
Sex (percent):		
Male	48. 1	45. 6
Female	51. 9	54. 4
Mean age (years)	9. 7	9. 6
Initial reaction to 5 T.U. of PPD (percent):		
No reaction	83. 3	84. 1
Erythema only	12. 0	11. 7
1–4 mm. induration	4. 7	4. 1
Initial reaction to 100 T.U. of PPD (percent):		
No reaction	49. 0	48. 2
Erythema only	34. 7	36. 9
1–4 mm. induration	16. 3	14. 8
Participation in 1950 BCG program (percent)	58. 9	57. 9

Comparison of Controls and Vaccinees

The similarity of the vaccinated and control groups with respect to certain characteristics is shown in table 2. Controls and vaccinees were almost identical in their race, sex, and age composition. Their initial sensitivity to both doses of tuberculin was likewise almost the same. The similarity of their participation in the 1950 trial suggests that both groups remained in the community and participated in subsequent community programs to almost the same extent. Consequently, there is no reason to believe that the procedure for allocating some persons eligible for vaccination to the control group and others to the vaccinated group was not successful in producing two essentially similar subgroups of the study population.

Cases of Tuberculosis

In the 12-year period, April 1, 1947, through March 31, 1959, 44 members of the study population were classified as tuberculosis cases or suspects. As can be seen in table 3, most of them were among the reactors to 5 T.U. of PPD. Of the total group of 44 cases, one was known to the Muscogee County tuberculosis study prior to the 1947 trial; 4 others were later classified as nontuberculous. These five persons have been excluded from the study group of cases. Also excluded are four persons classified as suspected cases of tuberculosis. The only evidence shown by three of them was an indeterminate shadow on the chest X-ray which was not characteristic of tuberculosis. The fourth suspect, who was a reactor to the 5-T.U. dose in 1947, had disease of a submental lymph node, from which acidfast bacilli were demonstrated by smear on one occasion. Cultures were negative, and the clinical course was not characteristic of tuberculosis.

Restricting the cases to the 35 persons whose tuberculosis was classified as definite and who

Table 3. Final classification of participants classified at some time during the study as tuberculosis cases or suspects, by 1947 tuberculin and vaccination status, Muscogee County, Ga.

Classification	Total	Reactors, 5 T.U.	Nonreactors, 5 T.U.			
			Not tested, 100 T.U.	Reactors, 100 T.U.	Nonreactors, 100 T.U.	
					Controls	Vaccinees
Participants ever classified as tuberculosis cases or suspects	44	28	3	7	2	4
Cases known prior to 1947 program	1	1	0	0	0	0
Later discharged as nontuberculous	4	2	[1] 1	1	0	0
Suspected cases	4	1	0	1	0	2
Definite cases	35	24	2	5	2	2

[1] Also diagnosed prior to 1947 program.

were first diagnosed after the program started removes four cases from the 5-T.U. reactors, two from the 100-T.U. reactors, none from the controls, and two from the vaccinees. The net effect of these exclusions is to decrease the relative magnitude of the tuberculosis problem among reactors as compared with nonreactors, and also among vaccinees as compared with controls.

The type and stage of disease of the study group of cases is shown in table 4, according to the organ and degree of most serious involvement. Of the 35 definite cases, 28 were solely or predominantly pulmonary tuberculosis, and 7 nonpulmonary; 20 of these definite cases had one or more bacteriological examinations reported as positive for acidfast bacilli. There were no significant differences between the subgroups of the study population with respect to the proportion of cases bacteriologically confirmed.

Most of the definite cases had serious disease. Twenty of them had had either advanced pulmonary disease or serious forms of nonpulmonary tuberculosis. In addition, 20 of the 35 had positive bacteriological examinations, 15 by smear and culture of sputum specimens, 4 only by culture of sputum, and 1 only by cul-

Table 4. Classification of cases, by tuberculin and vaccination status, Muscogee County, Ga.

Tuberculosis classification	Total	Reactors, 5 T.U.	Nonreactors, 5 T.U.			
			Not tested, 100 T.U.	Reactors, 100 T.U.	Nonreactors, 100 T.U.	
					Controls	Vaccinees
Total	35 (20)	24 (13)	2 (1)	5 (3)	2 (2)	2 (1)
Pulmonary	28 (20)	20 (13)	1 (1)	4 (3)	2 (2)	1 (1)
Far advanced	9 (9)	[1] 5 (5)	1 (1)	2 (2)	1 (1)	
Moderately advanced	9 (8)	6 (5)		1 (1)	1 (1)	1 (1)
Minimal	6 (3)	5 (3)		1		
Primary	4	4				
Nonpulmonary	7	4	1	1	0	1
Meningeal	1	[1] 1				
Bone and joint	1	1				
Lymph node	1	1				
Pleurisy with effusion	4	1	1	1		1

[1] 1 death from tuberculosis in each of these two groups.

NOTE: Numbers in parentheses indicate those with bacteriological examinations positive for acidfast bacilli.

Table 5. Treatment advised for definite cases, by tuberculin and vaccination status, Muscogee County, Ga.

Treatment advised	Total	Reactors, 5 T.U.	Nonreactors, 5 T.U.			
			Not tested, 100 T.U.	Reactors, 100 T.U.	Nonreactors, 100 T.U.	
					Controls	Vaccinees
Total	35	24	2	5	2	2
Hospitalization	21	14	1	3	2	1
Home treatment	2	1	0	0	0	1
None	12	9	1	2	0	0

ture of gastric washings. The severity of disease is also reflected in table 5, which shows that 21 cases were advised to be treated in a tuberculosis hospital. All but one (a control) accepted this advice. Most cases occurred at a time when there were enough hospital beds for sick and infectious patients, but not enough to hospitalize cases of doubtful clinical significance.

On the whole, the outcome for these cases was quite favorable, as shown in table 6. Almost all were entirely well and leading normal lives on October 1, 1959. Two were still under treatment and 2 had died, both prior to the availability of isoniazid. One fatal case occurred in a Negro girl with far advanced pulmonary tuberculosis diagnosed in January 1951, who died in December 1951. The other was in a white girl whose primary lesion was detected a few weeks after the program started. She developed tuberculous meningitis and died in March 1948. There were no significant differences between reactors and nonreactors with respect to the treatment advised or the outcome of disease.

The year in which the definite cases were first recognized is shown in table 7. Among 5-T.U. reactors, 80 percent were diagnosed in the first 5 years following the initiation of the trial, compared with only 1 of 11 cases occurring among nonreactors to the 5-T.U. dose. Among nonreactors to the 100-T.U. dose, all four cases came to recognition in the last 6 years of the observation period.

Among the 5-T.U. reactors, five cases were diagnosed in the first month after the trial started, all as a result of chest X-rays advised for reactors to the first tuberculin test. All but one of the remaining cases among 5-T.U. reactors and all but one of the nonreactors to 5 T.U. had one or more negative chest X-ray examinations prior to the date of diagnosis. Consequently, 28 of the 35 cases represent recognizable disease known to have developed after the initiation of the trial. Rates based on these 28 cases give a minimum measure of incidence,

Table 6. Health and treatment status on October 1, 1959, of definite cases, by tuberculin and vaccination status, Muscogee County, Ga.

Health and treatment status	Total	Reactors, 5 T.U.	Nonreactors, 5 T.U.			
			Not tested, 100 T.U.	Reactors, 100 T.U.	Nonreactors, 100 T.U.	
					Controls	Vaccinees
Total	35	24	2	5	2	2
Dead from tuberculosis	2	2	0	0	0	0
Disabled, under treatment	1	0	0	1	0	0
Well, under treatment	1	1	0	0	0	0
Well, no treatment	31	21	2	4	2	2

Table 7. Year in which definite cases of tuberculosis were first recognized by tuberculin and vaccination status, Muscogee County, Ga.

Year of recognition	Total	Reactors, 5 T.U.	Nonreactors, 5 T.U.			
			Not tested, 100 T.U.	Reactors, 100 T.U.	Nonreactors, 100 T.U.	
					Controls	Vaccinees
Total	35	24	2	5	2	2
1st	5	[1] 5				
2d	2	2				
3d	4	4				
4th	4	[2] 4				
5th	5	4		[2] 1		
6th	1		1			
7th	3	1			2	
8th	5	2	1	2		1
9th	2			1		
10th	2	1				1
11th	2	1		1		
12th	0					

[1] All diagnosed in April 1947.
[2] One case who did not have a negative chest X-ray at least once prior to diagnosis.

or the "development" of new cases of disease. Rates based on the total group of 35 cases reflect newly "reported" tuberculosis.

Newly Reported Cases of Tuberculosis

The average annual rate of newly reported cases among the total study population was 26 per 100,000, as shown in table 8. The rate for 5-T.U. reactors was tremendously higher than for nonreactors, 134 for reactors and only 9 for nonreactors. No significant differences were noted among nonreactors to 5 T.U. according to their sensitivity to the 100-T.U. dose. The rates among controls and vaccinees were the lowest observed and were essentially the same.

The degree of sensitivity in 1947 to 5 T.U. of PPD appeared to be closely related to the tuberculosis case rate. This is shown in table 9. Persons with no induration to the 5-T.U. test had the lowest rates, whereas persons with 10 mm. or more of induration had extremely high rates. The case rate among Negroes was appreciably higher than among whites at all levels of initial sensitivity to tuberculin, the difference being most marked among students

Table 8. Cases of definite tuberculosis among participants and average annual rates per 100,000 population, by tuberculin and vaccination status, Muscogee County, Ga.

Item	Total	Reactors, 5 T.U.	Nonreactors, 5 T.U.			
			Not tested, 100 T.U.	Reactors, 100 T.U.	Nonreactors, 100 T.U.	
					Controls	Vaccinees
Participants	11, 262	1, 492	741	3, 768	2, 341	2, 498
Definite cases	35	24	2	5	2	2
Average annual rates per 100,000.	25. 9	134. 0	22. 5	11. 1	7. 1	6. 7

NOTE: 422 nonreactors to 100 T.U. classified as "irregulars" had no cases of tuberculosis and, although included in the total, are not shown separately in the table.

Table 9. Tuberculosis case rates among participants, by race and size of reaction to 5 T.U. of PPD, Muscogee County, Ga.

Induration to 5 T.U. (mm.)	Both races			White			Negro		
	Population	Cases		Population	Cases		Population	Cases	
		Number	Rate [1]		Number	Rate [1]		Number	Rate [1]
Total	11, 262	35 (7)	25. 9	7, 767	5 (2)	5. 4	3, 495	30 (5)	71. 5
0	7, 090	7 (1)	8. 2	5, 265	1	1. 6	1, 825	6 (1)	27. 4
1–4	2, 680	4	12. 4	1, 912	0		768	4	43. 4
5–9	698	5	59. 7	337	1	24. 7	361	4	92. 2
10 and greater	794	19 (6)	199. 0	253	3 (2)	98. 8	541	16 (4)	246. 4

[1] Average annual rate per 100,000.

NOTE: Numbers in parentheses are persons without negative X-rays prior to diagnosis.

with little or no induration to the initial test. For possible application to tuberculosis control programs, it is worth noting that children with 5-T.U. reactions of 10 mm. or more comprised only 7 percent of the total study population, but yielded 54 percent of the total cases over the 12-year period. During the first 5 years of observation, the same 7 percent yielded 80 percent of the cases.

Even though there were very few cases among nonreactors to the 5-T.U. dose, their known characteristics were examined to see if any hint of a high-risk subgroup could be detected. Aside from the fact that 10 of the 11 cases were in Negroes, this effort was not successful. There was no suggestion that the tuberculosis case rate was related to initial age, sex, place of residence, or socioeconomic status as judged by housing characteristics in 1946.

Known Incidence of Tuberculosis

As noted previously, 28 of the cases among the study population had had at least one negative chest X-ray examination prior to the date of diagnosis of tuberculosis. These cases, whose disease is known to have developed after the start of the trial, may be used to measure the incidence of tuberculosis among the study population.

It is also possible to estimate the proportion of the study population remaining in the community during the 12-year observation period. In 1954, a 2 percent sample of the 1946 census

Table 10. Incidence of new cases of definite tuberculosis per 100,000 person-years experience at stated ages, by reaction to 5 T.U. of PPD, Muscogee County, Ga.

Age group (in years)	Reactors			Nonreactors		
	Person-years experience	New cases		Person-years experience	New cases	
		Number	Rate [1]		Number	Rate [1]
Total	13, 400	18	134	89, 000	10	11
5–8	400	0		7, 500	0	
9–12	2, 000	2	100	20, 700	0	
13–16	4, 200	5	120	28, 400	2	7
17–20	4, 100	8	197	21, 600	4	19
21–24	2, 300	3	130	9, 200	4	44
25–28	500	0		1, 800	0	

[1] Cases per 100,000 person-years.

population was drawn for a survey of blood pressure levels in Muscogee County (*16*). From that sample, the proportion of the population remaining in the metropolitan area 8 years later was calculated. Over the initial age span of 5 to 18 years, which includes almost all of the present population, it was found that older children had left the community to a somewhat greater extent than younger children, and whites somewhat more than Negroes.

Applying the race-age specific rates of emigration to the study population allows an estimate of the number of children remaining in the community at the end of each year of the observation period. From such a tabulation, it is then possible to estimate the number of person-years of experience contributed by members of the study population for each year of age.

If the newly developed cases are allocated to the year of age at which they were first diagnosed, an estimate of the incidence rate for successive age groups can be developed. This is shown in table 10 for reactors and nonreactors to 5 T.U. of PPD during the age span 5 to 28 years of age.

The incidence rate for reactors to the 5-T.U. dose is 134 per 100,000 person-years of observation, slightly more than 12 times that for nonreactors. For both reactors and nonreactors, higher rates are observed in the older age groups. This finding is consistent with observations of other workers that the years of late adolescence and early adult life comprise one of the periods of greatest risk from tuberculous disease (*17–19*).

Discussion

The findings of this study support the conclusions of subsequent controlled trials of BCG vaccination in Puerto Rico, Georgia, and Alabama (*2*). The most striking finding of those trials, and of the present trial as well, was that persons who were reactors to 5 T.U. of PPD had the greatest risk of developing tuberculosis. A corollary to this finding is that nonreactors to the 5-T.U. dose had such a low risk of developing tuberculosis that there is serious question about the need for vaccination of nonreactors in this country. So low is this risk in the present study that after observing nearly 10,000 children for a period of 12 years, only 10 cases of tuberculosis are known to have developed.

Although too few cases were observed among controls and vaccinees to attempt any assessment of the efficacy of vaccination among nonreactors, it is obvious that vaccination was not completely effective. Nor could failure be attributed to lack of trying. The vaccinees were retested 6 months after vaccination. At that time, 45 percent reacted to the 5-T.U. dose and 93 percent to the 100-T.U. dose. Those who had less than 5 mm. of induration to 100 T.U. were revaccinated. In the 1950 BCG trial, 42 percent of the vaccinees were again vaccinated, partly because of loss of allergy and partly because only the results of the 5-T.U. test were used in 1950 to select persons for vaccination. Although postvaccinal allergy in this trial was not nearly as marked as has been reported by others (*20*), the tuberculin sensitivity of the vaccinated group was increased appreciably by vaccination. It should also be kept in mind that there is far from universal agreement that ability of a vaccine to confer protection is necessarily dependent on its ability to produce strong allergy.

It is of some interest to note the postvaccinal allergy of the two cases which occurred among the vaccinees. Initially, neither of them had any reaction (erythema or induration) to 100 T.U. of PPD. Six months after vaccination, one subject still had no reaction to the 100-T.U. test. He was revaccinated and following this showed 15 mm. of induration to 100 T.U.; in 1950, he had 4 mm. of induration to the 5-T.U. test. The other subject had 12 mm. of induration to the 5-T.U. test 6 months following vaccination but was not tested in 1950.

Unfortunately, there were also too few cases among nonreactors to the 5-T.U. dose to cast much light on the attractive hypothesis that the agent responsible for low-grade tuberculin sensitivity in the southeastern United States also confers some resistance to tuberculosis, possibly by acting as a sort of natural vaccination (*21*). This may be so, but a higher attack rate than that observed among nonreactors in Muscogee County or a much larger study population would be necessary to test this hypothesis.

The conditions of the present trial are closer to the BCG trial conducted by the British Medical Research Council (*3*) than any controlled trials previously reported. Both populations were of school age, and although the British participants were initially 4 years older on the average than the Muscogee County children, the latter have been followed 5 years longer. The British students have been followed to an average age of 22 years, the Muscogee children to an average age of 23 years. In addition, like the British procedure, reactors to the 100-T.U. dose of PPD were excluded from both the control and vaccinee groups. Although chest X-rays were not routinely used in screening the Muscogee County participants, it is possible to classify all but two cases according to their initial X-ray status. Exclusion of the five cases diagnosed within a month of the initial tests and of the two cases without negative X-rays prior to diagnosis yields a group of cases reasonably similar to those developing among participants in the British trial.

Thus it is reasonable to compare the number of new cases observed during the first 8 years of the Muscogee County trial with the number expected had the rates among British participants for the first 7½ years applied to the Muscogee population. Although one could hardly expect exact agreement, one might anticipate that observed and expected numbers would be of the same order of magnitude if environmental conditions were reasonably similar. Conversely, if observed and expected numbers differed grossly, one might suspect that the characteristics of the two trial populations were dissimilar in some important respect.

Among reactors to the 5-T.U. dose in Muscogee County, 16 new cases are known to have developed in the first 8 years, where 12 would have been expected at the British incidence rates (with allowance for differences in tuberculosis risks for subjects with differing degrees of sensitivity to the 5-T.U. dose). This is quite close agreement, and suggests that the risk for British and Muscogee low-dose reactors is generally similar.

On the other hand, where 2 cases had been observed in the first 8 years among unvaccinated controls, 34 would have been expected had the British rates applied. This is quite a striking difference and not likely to be explained by differences in age or race composition, case-finding procedures, or population losses. In fact, it is difficult to explain this difference in observed and expected cases on any basis except that the risk of infection for British school leavers must be very much higher than the risk in Muscogee County and in most parts of the United States.

Among the nonreactors to 5 T.U. who reacted to the 100-T.U. dose, 2 cases were observed; application of British rates indicates that 23 would have been expected. Although some of the 100-T.U. reactors in Muscogee County were vaccinated in 1950, the reduction in tuberculosis attributable to vaccination is too low in this population to account for much of the difference in observed and expected numbers. The simplest explanation is again that the infection rate from *M. tuberculosis* in British cities must have been much higher than in Muscogee County.

Among vaccinees, no cases were observed in the first 8 years. British experience suggests that six cases should have been expected.

It is of course possible that some of the differences between observed and expected numbers might arise from the application of British rates during late adolescence to Muscogee County children in a period of life when they would not be expected to have reached their age of greatest risk. However, table 7 shows that observation of cases for 4 more years, to the point where the age difference between the two study populations is no longer marked, does not increase the number of cases appreciably. Even comparing cases observed during 12 years with those expected during 8 years, had the British rates applied to this population, leaves considerable similarity for low-dose reactors (18 observed, 12 expected), and marked disparity for low-dose nonreactors with completed 100-T.U. tests (8 observed, 63 expected).

Comparison of the results of these two trials suggests that the risk of infection must have been many times higher in Great Britain than in the United States. This has a direct bearing on the need for vaccination in the two areas, since it seems obvious that the need for vaccination varies directly with the likelihood of becoming infected. No matter how effective a

vaccine may be, vaccination can have little impact on the tuberculosis problem when the risk of infection is as low as it is in most of this country today. Whether or not BCG can be expected to reduce morbidity rates among nonreactors in this country in areas where infection rates may still be high is a moot question. Certainly the low protection observed in the southeastern United States and in Puerto Rico gives little hope that BCG vaccination could be a useful tool elsewhere in this country (*2*).

One finding of this study relates to casefinding activities among school populations. The incidence of tuberculosis among the total study population was clearly too low to warrant any consideration of periodic chest X-ray examinations, and the infection rate has become too low to warrant annual tuberculin testing. However, the initial testing with 5 T.U. of PPD did delineate a high-risk group, namely, students with 10 mm. or more of induration. These students comprised only 7 percent of the population examined in 1947. Initially and in the ensuing 5 years, 80 percent of the cases were found among this small segment of the initial population. This finding strongly suggests that the currently popular tuberculin testing programs among school populations must be carefully done in all respects in order to define as sharply as possible the small group at greatest risk. Further, it appears that this small group should be kept under surveillance with annual chest X-rays for at least 5 years after a strongly positive tuberculin reaction has been discovered. Studies done elsewhere indicate that examination of all household associates of very young, strongly positive tuberculin reactors is a productive method of detecting cases of active tuberculosis and an important facet of tuberculin testing programs (*22*).

In areas where the infection rate is low, it seems that repeated tuberculin testing of entire school populations on an annual basis may well be inefficient since so few newly infected students could be discovered each year. In such areas, it would appear more reasonable to test the school population on entrance to school, and again during adolescence.

These recommendations would have sounded completely unrealistic in 1947. At that time, it seemed most important to find some way of protecting the currently uninfected population from the presumed high risk of developing disease soon after infection had occurred. The healthy reactor then was viewed as having passed safely through the period of appreciable risk. Today, as a consequence of a number of studies on tuberculosis infection and incidence rates, it is recognized that tuberculosis among the currently uninfected population in the United States is not of critical importance, but rather that the already infected population is the important seedbed of future disease. As a result of this knowledge, it is now clear that in addition to efforts designed to identify infectious cases and to prevent them from creating new reactors, it is essential to discover some effective means of preventing the development of disease among apparently healthy reactors, thereby sterilizing the present seedbed of disease before another crop of tuberculosis cases can be germinated.

Summary

In April 1947, a controlled trial of BCG vaccination was initiated in the school population of Muscogee County, Ga. A total of 11,262 children had completed tests with 5 T.U. of PPD, and the nonreactors were tested with 100 T.U. The nonreactors to both doses were divided into two similar groups; one group was vaccinated with BCG and the other left unvaccinated as controls.

In the ensuing 12 years, 35 definite cases of tuberculosis were diagnosed among the study population, 24 among 5-T.U. reactors, 2 among 5-T.U. nonreactors who were not tested with 100 T.U., 5 among 100-T.U. reactors, and 2 each among controls and vaccinees. Three-fifths of the cases had clinically serious disease; a similar proportion were bacteriologically confirmed. There was no significant variation in type or extent of disease among the various tuberculin-vaccination subgroups of the study population. Most of the cases among 5-T.U. reactors were diagnosed during the first 5 years of observation; the few cases among nonreactors to 5 T.U. of PPD were scattered through the last 8 years of observation.

The average annual case rate for 5-T.U. reactors was 134 per 100,000; for nonreactors to 5 T.U. it was only 9 per 100,000. For both

controls and vaccinees, the rate was 7 per 100,000. There was a marked direct correlation of the tuberculosis case rate with size of reaction to the 5-T.U. dose, ranging from 8 per 100,000 among those with no induration to 199 among those with 10 mm. or more of induration. The incidence of new disease was highest in late adolescence and early adult life.

In this area of low tuberculosis infection rates, it was not possible to demonstrate any benefit from BCG vaccination during 12 years of observation.

The results of the 5-T.U. tests delineated a high-risk group, namely students with 10 mm. or more of induration. These reactors comprised only 7 percent of the study population, but furnished 80 percent of the cases during the first 5 years of observation.

It is suggested that in areas of low infection rates, which comprise most of the United States today, tuberculosis control programs among school populations might profitably be limited to periodic tuberculin testing surveys, with careful followup of reactors to a low dose.

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