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Observations concerning the use of BCG

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OBSERVATIONS CONCERNING
THE USE OF
BCG

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Donald M. Fitch, M.D., Chairman
Senior Thesis Committee

Re: Senior thesis, Byron V. Toot

Dear Doctor Fitch:

Enclosed with this letter please find the original senior thesis of student Byron V. Toot entitled "Observations Concerning the Use of BCG".

I have acted as advisor for senior student Toot in his consideration of BCG vaccine and its potential use among medical and paramedical personnel. Mr. Toot has done considerable reading on this subject and on your perusal of the thesis you will see that he has done considerable individual thought concerning this matter. I believe this is a creditable job and I find the format and the data contained acceptable to me. The views the student has reached concerning the use of BCG vaccine are not necessarily my own; however, I believe the student has sound basis for the opinions he has given in his paper.

H. W. McFadden, Jr., M.D.
Professor and Chairman
Department of Medical Microbiology

HWMcF/llr

F O R E W A R D

This paper is not intended to be a comprehensive review of available literature as one might expect from its title. Rather, it is an attempt to correlate the information found in the literature with the current state of tuberculosis vaccination and skin testing among medical and nursing students at the University of Nebraska College of Medicine.

The impetus for this study was the result of a strong but transient interest in BCG vaccination by the graduating class of 1967. In my opinion, this interest was the result of courses in Preventive Medicine and Public Health taught by Dr. Carl J. Potthoff, then-Professor and Chairman of that department. Although never strongly advocating its use, he presented enough stimulus to our curiosity that a small group within the class asked the Student Health physician for BCG vaccinations at our own expense. This 'small group' eventually grew to number approximately one-half the class.

Through the further cooperation of Dr. Haskell Morris and Mrs. Laurine Burke, R.N., of the Student Health department, I have been able to extract from their records the results of Mantoux testing among the medical students of the last ten graduating classes, as well as the same information concerning the School of Nursing. Unfortunately, not all records were complete so that some 'classes' consisted of fewer students that were actually graduated in that year. Other

obvious reasons for variability were also noted, such as drop-outs, graduate students, transfer students, et cetera.

Among the smaller licenses I have taken with this paper, I have also claimed a larger one--- I have reserved the right to add my <u>own</u> opinion to that of the others from time to time.

I thank Dr. Harry W. McFadden, Professor and Chairman of the Microbiology department, for his patient counseling and guidance in the preparation of this paper. I would also like to acknowledge Dr. Carl Potthoff for his interest and for sharing his opinions and views with me.

B.V.T.

I N T R O D U C T I O N

The history of BCG vaccine is rather short but shrouded in continuing controversy. The Bacillus Calmette-Guérin is a living, attenuated, bovine strain of tubercle bacillus. This strain was first isolated in Paris as a very virulent organism for animals and then attenuated by serial passage in artificial media for a period of thirteen years.

By 1921, Calmette and Guérin were satisfied that they had produced an attenuated bacillus, but they delayed the announcement and the distribution of cultures to other laboratories until about 1924. During the period from 1921 to 1928, large numbers of experiments were conducted to try to cause reversion of this attenuated bacillus to its original virulent characteristics. All attempts in this direction failed.

In 1930 the vaccine received a setback from which it has never fully recovered: Two hundred and fourty children received it as an orally administered vaccine and seventy-two of them died. A full-scale investigation revealed that the BCG strain was not the cause. A contaminating strain in the administered culture was positively identified by growth and color-producing characteristics.

In reading the literature, it seems improper to speak of

a single BCG vaccine, but rather to consider them as a group of vaccines, having varying degrees of virulence and invasiveness. Therefore, the literature may show that in Scandinavia, a BCG vaccine produced a certain amount of hypersensitivity and a certain amount of immunity but it is virtually impossible to duplicate their results. In this country there are several sources of BCG vaccine that a laboratory may acquire or a physician may use. The one most commonly used is prepared in Chicago by the Tuberculosis Research Institute. However, a strain is also produced in Philadelphia which is different from the Chicago strain, and in Canada two strains are available, one from the Connaught Laboratories in Toronto and one from the University of Montreal.

The strain that is prepared in Chicago is probably as pure and reliable a strain as one can obtain. This depends on the fact that the cultures are not made by transferring from one culture medium to another. Rather, a mother strain has been prepared and then a large quantity of it freeze-dried and stored in the frozen state. Each new batch of BCG vaccine is cultured from this lyophilized, frozen strain.

The use of BCG vaccine has been worldwide, especially finding favor in Europe. More recently, workers in India and Africa have begun mass immunization programs in an attempt to reduce the morbidity and mortality rates from tuberculosis, especially in infants. Here in the United States, its use has been more slowly adopted. Twenty years ago, the United States

Public Health Service called together an advisory group when European nations were adopting mass BCG vaccinations as part of tuberculosis control programs. That 1946 panel recommended against BCG use in the United States until large-scale controlled trials were conducted. USPHS advisory groups since then have urged that BCG vaccination be limited to special groups. The National Tuberculosis Association, the American Thoracic Society, the American Medical Association, and the USPHS are in favor of BCG vaccination for:

1. Children living in areas where the incidence of tuberculosis among young people is high;
2. Professional and other persons whose work involves a high risk of exposure;
3. Members of households unavoidably exposed to infectious cases in the home, and
4. Inmates and personnel of institutions in which tuberculosis is found to be present.

These limitations express the caution felt in this country toward BCG vaccination. Although I must agree to the use of such caution, expecially in light of the apparently conflicting results in the literature, I cannot agree with the slowness with which we have progressed in planning and especially supporting large-scale trials.

Early workers were not able to provide enough controls to their studies to convince the general medical population of the advantages of BCG. However, through increasing govern-

mental interest of the Scandanavian countries as well as that of Great Britain, large-scale trials were begun. In 1956 a committee of the Medical Research Council of Great Britain reported on the early results of a carefully controlled clinical trial of vaccines in the prevention of tuberculosis among adolescents (ages 14½ - 15) in urban industrial areas. Of this group, fourty percent were already tuberculin-positive before the trial. The use of BCG vaccine resulted in a reduction of eighty-two percent in incidence of disease in the first two and one-half years of follow-up study.[20] This study is considered to be the major supportive work by those in favor of the use of BCG vaccine.

Apparently prompted by this study, investigators in the USPHS published in 1958 the results of two separate community trials in this country.[15] One took place in Puerto Rico where children between the ages of one and eighteen were vaccinated with BCG. The other trial included two counties, one each in Georgia and Alabama, which were chosen because "they were representative of many communities in this country which had the same problem". A total of approximately two hundred fifty-thousand people were included in these studies with follow-up observations being made for the next six to seven years after vaccination. Their results show that there was actually a low incidence, and that this was falling to a level of hardly more than one new 'positive' per one thousand population per year. The risk of becoming an active case was also found to be much greater for those with positive skin tests than those

who were initially negative. They concluded, therefore, that, even with the use of BCG, no more than a ten percent reduction in incidence could have been accomplished while the use of the skin test as a screening tool would be sacrificed. This would prevent the early use of chemotherapy in those who might have been in the 'positive' group and therefore those who apparently have the greatest risk of active disease. Like others, they believe that the low infection rates are a direct result of successful application of other methods of control---case-finding, isolation, and treatment. As could be anticipated, this report serves as the main argument of those against BCG, especially since it was done here in the United States.

An editorial in the British Medical Journal[22] points out that, in the case of the United States where the conversion rate is low, the tuberculin test is likely to become of increasing importance as an indicator of natural infection. It may come to be used not so much to identify negative reactors preparatory to vaccination as for the detection of those who are positive as a result of natural infection and thus may require periodic x-ray examinations or chemoprophylaxis.

It is interesting that Rosenthal and his workers[16,17,18] are not given as much weight among the medical community as might be possible. Although his efforts have been among the most early and, unfortunately, poorly controlled, I feel his enthusiasm has repressed his acceptance rather than his efforts themselves. One of his broadest trials[16] used a series

of one thousand seven hundred sixteen BCG-vaccinated and one thousand six hundred sixty-five nonvaccinated infants, all born at the Cook County Hospital in Chicago between February, 1937 and February, 1948. They were followed until February, 1960(twenty-three years). Among the vaccinated there were a total of seventeen cases of tuberculosis (0.43/1,000/year) and sixty-five cases among the nonvaccinated (1.7/1,000/year), a reduction of seventy-five percent ($p < 0.001$)

C L I N I C A L I N V E S T I G A T I O N

The interest in BCG vaccination among my class (77 students) led to a total of thirty-five intradermal vaccinations of BCG in late May, 1965. All those wishing to be vaccinated were given Mantoux skin tests two weeks prior. Only those who were negative to intermeadiate-strength PPD-S were allowed to be vaccinated with BCG. Eight weeks later, in early August, skin testing was again performed on the arm opposite the BCG site. This second Mantoux was to confirm the 'take' (a change from negative to positive) as directed by the protocol accompanying the BCG vaccine. Only two 'failures' were found for a 5.7% failure to convert from negative to positive. This figure compares to other data where the rates varied from two percent to as high as twenty-six percent[4,7,18] The two students were not vaccinated again.

On this campus, there are only two recorded instances

where BCG vaccination was used: Four students in the class of 1955 and those above. Apparently all were vaccinated with the vaccine from the Tuberculosis Research Institute in Chicago using the intradermal technique. Later work has shown that, using the multiple-puncture technique, the draining ulcer which is a frequent result of the former form of vaccination could have been avoided.[10] The appearance of this 'ulcer' and its persistence(up to six weeks) was a surprise to all, although it was not found in all cases. It was probably this response which prevented the two failures from accepting re-vaccination.

Because the USPHS definition of 'high-risk' includes medical and paramedical personnel and students, I attempted to confirm that we are indeed in that category. I skin-tested all patients with whom I came into contact during one of my clerkships. The sample was chosen from the Douglas County Hospital over a period of ten weeks. Patients were tested upon their admission whenever possible without regard to their reasons for admission. Of the sixty-six patients seen during this period, seventeen had positive skin reactions to intermeadiate-strength PPD-S, approximately a twenty-five percent incidence of positive reactors. There is no doubt that the sample is biased in the direction of the 'typical county patient' but---it <u>is</u> this skewing of the curve which leads to the consideration of BCG vaccination in the first place. I think it is obvious to all that this incidence was several-fold greater than that found in the general population.

If the medical student is in the high-risk group, what are his chances of converting from negative to positive as he passes through four years of medical school? Some authors have placed the conversion rate as high as 10-20% 5%.[17,18] On this campus, the range is from two to thirty-one percent(see Appendix A). Considering the range of conversions in all graduating classes over the last ten years:

	% Graduating Class with Positive Mantouxs
as Freshmen	3.9 - 17.0 (range)
" Sophomores	4.7 - 31.4
" Juniors	2.6 - 42.9
" Seniors	6.6 - 48.6

To date, there have been four students in the nonvaccinated group(class of 1967) who have become tuberculin-positive. In other words, approximately 5.3% of the initially-negative as Freshmen have converted naturally.

It is now known that vaccination with BCG does not provide life-long immunity. Its protection will usually become 'attenuated' as evidenced by the reversion of the skin test back to negative. This usually takes place two to four years after vaccination requiring re-vaccination if continued protection is desired.[4,16,17,20] Of the four students of the class of 1955 who received BCG, only one was still positive at the end of four years. Unfortunately, no values are presently available for the class of 1967 concerning reversion rates.

D I S C U S S I O N

It should be obvious to the reader that there is a moderate lack of agreement among many of the authors. And there can likewise be no doubt as to the irregular results coming from well-controlled trials. But what of the medical student as compared to the general population? Can high-risk justify irregular success at preventing active tuberculosis?

Dickie[7] at the University of Wisconsin has shown a marked reduction in morbidity following vaccination in nursing and medical students. One of 106 vaccinated medical students acquired pulmonary findings while six of fourty-four nonvaccinated students developed pulmonary lesions requiring hospitalization. In the same study, the morbidity among student nurses was 8.9% during the ten-year period before immunization. After the vaccination program had started, there were no cases reported among the vaccinated.

Abruzzi and Hummel[1] collected reports from sixty-two medical schools in the United States. Nineteen of them used BCG in their tuberculosis control programs. Of the 4,400 students vaccinated, only three contracted the disease.

Those who oppose the use of BCG feel that the loss of the tuberculin skin test as a diagnostic tool is a prime consideration. That is, once a natural conversion occurs in an unvaccinated patient, further tests are indicated at once if the presummed disease is to be evaluated before it is possibly lethal. Without this guideline, they say, chemotherapy is

usually too late. On the other hand, is it not better to prevent the disease in at least eighty-five percent of those exposed that to treat it once it is present? Even if the conversion occurs, x-rays as well as other culture studies are necessary before the diagnosis is made. Therefore, is not the skin test just one of a series of tests rather than a 'diagnosis'?

It has been pointed out that the incidence of tuberculosis was declining without BCG---but it was also declining before chemotherapy was as available as it is today. And now that the incidence is low, is vaccination justified at all? Advocates point out that widespread vaccination is not the goal, but rather it is to be used in those high-risk groups previously mentioned.

It is interesting that, during the writing of this paper, the BCG Advisory Panel of the U.S. Communicable Disease Center met in Atlanta and revised its recommendations concerning the use of BCG as follows:

> "Individual Use: BCG should be used for the uninfected individual or small groups of uninfected individuals living in unavoidable contact with one or more uncontrolled infectious persons who cannot or will not obtain or accept supervised treatment.
>
> Group Use: Based on available data, there is no epidemiological indication for the use of BCG on a group or community basis in the United States.

In particular, BCG is not recommended for medical and paramedical personnel and students, or for employees and inmates of penal and mental institutions, because the knowledge of tuberculin conversion, if it occurs, is essential so that chemoprophylaxis may be instituted and the infectious source identified and treated."[19]

It would appear then, that the prophylactic use of BCG has been restricted even further in the United States. And yet, there is implied even in the above restrictions, a confirmation of its efficacy in those instances where exposure is certain and unavoidable. It is indeed unfortunate that, given a tool which could successfully place tuberculosis on the list of controlled diseases for the medical student, we must now turn our back on it.

Consider these points:

1. BCG is always successful in reducing the incidence of active tuberculosis in a range of from ten to eighty-five percent.
2. A high rate of conversion to positive occurs with a single vaccination, approaching 98%.
3. There is usually a reversion back to negative in two to four years.
4. The multiple-puncture vaccination prevents the former subjective complaints about 'ulcer' formation.
5. Medical students have a higher-that-average

natural conversion rate, from five to twenty-five percent on this campus, indicating a higher-than-average exposure to questionably inactive cases of tuberculosis.

6. Workers have shown a reduction of morbidity to less than two percent using BCG among medical students.

To me, this evidence cannot be disregarded. I must make a plea to routinely offer to vaccinate all medical students with BCG upon their entrance to medical school. They may be followed as before, if desired, with yearly chest films and Mantoux testing. Those who revert to negative may be re-vaccinated, especially if they have the majority of their clinical years yet to be completed. Should they revert in their senior year, a strong appeal should be made to have them accept one more immunization, to 'carry them through their internship', so to speak.

Above all, these students must be given the opportunity to apply the very basis of the practice of medicine--prevention. This opportunity is available only through the cooperation and education of those responsible for their continued interest and participation in the fields of medical practice.

A P P E N D I X A

	1966(76)		1965(76)		1964(73)		1963(68)		1962(62)	
	#	%	#	%	#	%	#	%	#	%
Freshmen	3	3.9	7	9.2	9	12.3	4	5.9	9	14.5
Sophomores	7	9.2	9	11.8	14	19.2	5	7.4	10	16.1
Juniors	2	2.6	9	11.8	15	20.5	8	11.8	12	19.4
Seniors	5	6.6	9	11.8	15	20.5	9	13.2	12	19.4

	1961(43)		1960(35)		1959(48)		1958(37)		1957(43)	
	#	%	#	%	#	%	#	%	#	%
Freshmen	2	4.7	6	17.1	5	10.4	6	16.2	2	4.7
Sophomores	2	4.7	11	31.4	6	12.5	9	24.3	4	9.3
Juniors	4	9.3	15	42.9	8	16.7	11	29.7	5	11.6
Seniors	10	23.3	17	48.6	12	25.0	14	37.8	7	16.3

	1956(41)		1955(42)		1966(18)*		1965(33)*		1964(23)*	
	#	%	#	%	#	%	#	%	#	%
Freshmen	7	17.1	3	7.1	0		0	0	2	8.7
Sophomores	8	19.5	3	7.1	0		3	9.1	2	8.7
Juniors	9	22.0	5	11.9	0		3	9.1	2	8.7
Seniors	10	24.4	5	11.9	0		4	12.1	2	8.7

* Nursing School Graduates

Note: From the text,

Conversion rate = (% positive as Seniors) — (% positive as Freshmen)

B I B L I O G R A P H Y

1. Abruzzi, W.A. Jr.; Hummel, R.J.: Medical Progress, Tuberculosis. Incidence among American medical students, prevention and control and the use of BCG, New Eng J Med 248:727-729 (April 23) 1953.

2. Anderson, A.S.: Case against BCG, Brit Med J 1:1423-1430 1959.

3. Barclay, W.R.: BCG vaccination, Ped 24:478-481(September) 1959.

4. Blackman, N.S.; Shelly, J., and Hoyt, E.K.: BCG vaccination of student nurses: A ten-year experience, Dis Chest 38:157-161 (August) 1960.

5. Brown, J.A.K., and Stone, M.M.: BCG vaccinations of children against leprosy: First results of a trial in Uganda, Brit Med J 5478:7-14 (January 1) 1966.

6. Comstock, G.W.: BCG, Neither neglected nor always useful, Maryland Med J 13:69-71 (December) 1964.

7. Dickie, H.A.: Tuberculosis in student nurses and medical students at the University of Wisconsin, Ann Institut Med 33:941-959 (October) 1950.

8. Dubos, R.: Acquired immunity to tuberculosis, Amer Rev Resp Dis 90:505-515 (October) 1964.

9. Finland, M.: Tuberculosis mortality and morbidity and the problem of BCG vaccination in the United States, New Eng J Med 261:699-702 (October 1) 1959.

10. Griffith, R.H.: Multiple puncture BCG vaccination, Postgrad Med J 40:74-77 (February) 1964.

11. Hyde, L.: Stability of tuberculin reaction, Dis Chest 45: 72-74 (January) 1964.

12. Irvine, K.N. and Barr, A.: Conversion after freeze-dried BCG, Brit Med J 5395:1424-1425 (May 30) 1964.

13. Johnson, R.N.; Ritchie, R.T. and Murray, I.H.F.: Declining tuberculin sensitivity with advancing age, Brit Med J 5359:720-724 (September 21) 1963.

14. Morgen, W.K.C.: Bacillus Calmette Guerin, Maryland Med J 13:80-82 (July) 1964.

15. Palmer, C.E.; Shaw, L.W. and Comstock, G.W.: Community trials of BCG vaccination, Amer Rev Tuber 77:877-907 1958.

16. Rosenthal, S.R., et al.: BCG vaccination against tuberculosis in Chicago, Ped 28:627-641 (October) 1961.

17. Rosenthal, S.R., et al.:BCG vaccination and tuberculosis in students of nursing, Amer J Nurs 63:88-93 (June) 1963.

18. Rosenthal, S.R., et al.: Tuberculin reaction trends and BCG vaccination--Special reference to young adults(medical students), Arch Environ Health(Chicago) 11:794-803 (December) 1965.

19. BCG Advisory Panel of the United States Communicable Disease Center, JAMA 198:7:49 (November 14) 1966.

20. BCG and vole bacillus vaccines in prevention of tuberculosis in adolescents: First(progress) report to the Medical Research Council by the Tuberculosis Vaccines Clinical Trials Committee, Brit Med J 1:413-427 1956.

21. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life, Brit Med J 5336:973-978 (April 13) 1963.

22. Vaccination against tuberculosis in childhood. An editorial, Brit Med J 1:1534-1536 1956.