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Method of use and indications for BCG vaccine

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TABLE OF CONTENTS

I. INTRODUCTION

BCG vaccine was first used in humans in 1921. Since that time, controversy has existed concerning the use of this agent. Few topics have engendered so much divergent opinion in the field of medicine. Professional views have varied from adversely critical to enthusiastic or skeptical. Over the last decade, many revealing studies involving BCG have been published. It was felt, that at this time, a review article on the subject would be a useful writing. This paper will briefly outline the history of the Calmette Guerin bacillus, indicate the theory of its application, discuss the leading controversial papers, present possible indications for usage and make clear the technique of BCG vaccination.

II. HISTORY OF BCG VACCINATION

In 1882, Koch isolated the causative organism of tuberculosis which, unquestionably, was once the greatest single cause of death and disease.[16] Since that time, a specific immunizing procedure against tuberculosis has been sought. Nocard isolated a virulent bovine tubercle bacillus from a case of heifer mastitis.[35] Originally, 1/10,000 mg. of this culture killed a guinea pig in sixty days. The strain was commonly used in experiments at its place of discovery, the Pasteur Institute of Lille, and at first was known as "souche lait Nocard".[3] In 1908, it was noted that when a drop of beef bile was added to the culture, in the grinding process, the bile acted as a soap and facilitated the preparation of a finely divided emulsion for experimental purposes. Eventually, a

method was evolved of cooking potatoes in a solution of beef bile containing glycerine. The potatoe surface, when kept moist with the same fluid media, would support the growth of the organism and caused the bacilli to be separated into disassociated and almost single units.[16] In the same year, Calmette and Guerin began subculturing the organism on this special media. Soon, the gross cultural characteristics of the bacillus changed, in that the colonies were no longer rough and dry but had acquired a smooth, moist, viscous quality. Testing of this new form, disclosed an original increase in virulence. However, after fifteen subcultures, a one milligram dose of the culture failed to produce any ill effects in guinea pigs.[35] Over the next thirteen years, the culture was transplanted two hundred and thirty times, by Calmette and Guerin, and characterization of the bacilli revealed that they had retained their original cultural, tinctorial and antigenic properties. They would still produce a potent tuberculin preparation. However, the culture, now called BCG, would not produce progressive disease in animals as susceptible to tuberculosis as guinea pigs. This attenuation probably occurred as the result of mass mutation or selective growth of attenuated forms, due to the action of the bile media.[16] Guerin, a veternarian, began immunization studies in small laboratory animals, then in cattle and finally in monkeys and apes. After numerous experiments it was established that the "virus fixe" or attenuated organism did not produce progressive disease in animals but that it would protect against natural infection by virulent

tubercle bacilli.[33] Calmette and Guerin were still reluctant to use the organism in humans. However, in 1921, they allowed Weil-Halle to initiate human innoculation by the oral route.[33] Fruitlessly, from 1921-1928, large numbers of experiments were conducted as an attempt to revert the bacillus to its original virulent state.[6] At this point, two events occurred which were to cause reluctance of use of BCG for years to come. In 1927, Petroff, reported that a BCG culture received directly from Paris would disassociate into rough and and smooth colonies and that the smooth form would, at times, cause progressive disease in guinea pigs.[12,16] This work has never been repeatable[38] and is generally held to be in error.[12,16,4] A second serious setback occurred three years later in Lubek, Germany. One half of all newborns in that city were innoculated orally at ten days of life with BCG. By January of 1931, seventy-five of the two hundred and and fifty "immunized" infants were dead from tuberculosis.[16] The German government organized an investigation of the incident. After five years of study, a report was published indicating that the BCG culture had been negligently contaminated by a strain of virulent human tubercle bacilli.[35]

Other attempts were made to produce a specific immunity against tuberculosis. Thus chemical fractions and metabolic by-products of tubercle bacilli, killed by chemical or physical agents, and viable related mycobacteria were frequently investigated.[4] Increased resistance to tuberculosis following the use of minute numbers of viable, virulent tubercle bacilli, has been observed. The

latter method involves considerable risk. It and all others, except for the use of attenuated strains were abandoned. The vole, or murine (field mouse), bacillus was discovered by Wells in 1937.[43] Until recently, it has not enjoyed popularity.[30] However a current study strongly suggests that it is as effecient as BCG in preventing tuberculosis.

Little use was found for BCG in the United States until 1945. The Scandinavian program and mass campaigns sponsered by UNICEF and WHO served to maintain some interest.[23] It has been variously estimated that over one hundred and fifty doses of vaccine have been given to the world population, including all age and socio-economic groups.[16,28,26] In many countries, such as Norway, Denmark, France, Japan and Brazil, BCG vaccination has become mandatory by law.[28]

Over the last fifteen years, several well controlled studies on the vaccine have been reported in the English literature. Many reports still indicate the controversial nature of the subject. A discussion of these studies and new advances in forms of vaccine and administration will be presented below.

III. INDICATIONS FOR THE USE OF BCG

Judicious application of a vaccine, or any drug, must be based on a consideration of the following inquiries. What is the basic theory involved? How effective is the desired action? Is there a need for the application in question? How safe is this agent? What are the related disadvantages and complications?

A. THEORY OF BCG VACCINATION

The basic theory supporting the use of BCG vaccine is that it produces an increased resistance against tuberculous infection. The exact mechanism of this effect is not known. Furthermore, the alleged increased resistance cannot be directly measured and is known only through clinical observation. A serological yardstick or some other test, to predetermine formed resistance is lacking and therefore another method has been substituted. A person who has not been infected with tubercle bacilli does not demonstrate skin sensitivity to tuberculoprotein. The first or primary infection is usually subclinical and is noted only through a positive tuberculin reaction. The primary infection is hazardous to some. BCG innoculation produces a primary, benign infection of the skin,[18] which remains localized in the skin or regional lymph nodes. Sensitivity to tuberculoprotein appears three to six weeks after BCG vaccination.[4] The great question arises as to whether or not the acquired skin sensitivity is accompanied by increased resistance to tubercular infection. Wallgreen supports BCG as providing resistance to tuberculosis, judging by clinical trials, and yet agrees that there is no true, direct, method to measure the resistance. Tuberculin testing measures only sensitivity to tuberculoprotein. Usually sensitivity and resistance appear and leave together, but one of the other may be present alone.[42] [3] Aronson states there is close but not absolute correlation between sensitivity and resistance.[21] Myers claims that sensitivity is independent of immunity and that one may develop in the

absense of the other. Allergy to tuberculoprotein has not been proved to indicate the presence of immunity, yet it is the production of such allergy, by BCG vaccination, and its indentification by the tuberculin test which is presently being used as a criterion of immunity.[21] Anderson[2] makes a strong case against BCG and notes that allergy to tuberculoprotein is not a sign of immunity but is a definite prerequisite to the development of clinical tuberculosis.

A study of these and other opinions indicates that the basic question to be answered is whether or not artificial acquisition of sensitivity to tuberculoprotein is accompanied by increased resistance to tuberculosis infection. In light of our lack of understanding in the basic mechanisms involved, this can only be solved by well controlled clinical trials of BCG vaccination.

B. EFFECTIVENESS OF BCG VACCINE

Many presentations of this subject have been made. In fact, the extensive series of laboratory and clinical studies far exceeds work done on other vaccines.[28] An attempt has been made to select papers from the literature which reflect the opposing opinions as to the effectiveness of BCG vaccine.

In 1950, a detailed, very well controlled, clinical trial of BCG and vole bacillus vaccination was undertaken by the Medical Research Council in England.[29,30] Although still in progress, two preliminary reports have been published. The first covers data from the initial two and a half years of study; the second entails five years of observations. The study group included 56,000 participants

of about fifteen years in age on entrance to the trial. Teenagers were choosen because of the increased tuberculosis risk in their age group. Boys and girls, with a wide range of social and economic backgrounds, were included from urban and suburban industrial areas with well developed health services and a relatively low incidence of tuberculosis. On the first examination, roentgenograms were taken. All those with signs of clinical tuberculosis or a history of recent contact were excluded. The remaining received tuberculin skin tests with a strength of 3 T.U., and then if negative, 100 T.U. The participants were automatically classified into five trial groups: tuberculin negative (to 100 T.U.) and left unvaccinated (13,300); tuberculin negative, Danish Fresh BCG vaccinated (14,000); tuberculin negative, vole bacillus vaccinated (6,700); tuberculin positive to 3 T.U. (16,000); and tuberculin positive to 100 T.U. but not to 3 T.U. (6,600). Those tuberculin negative, and thus eligible for vaccination, were allocated to the unvaccinated and to one of the two vaccinated groups by a random process. Three to five months later and thereafter at an approximate interval of fourteen months, the participants were re-examined by special study teams. Each periodic examination included roentgenograms, tuberculin tests, physical examination and inquiry. Other inquiries were made by mail. Medical records of the National Health Service, the Armed Forces and other established sources were sifted for additional developmental information on the participants. All definite and suspected cases of tuberculosis and all cases of

radiographic pulmonary abnormality, persisting for more than 14 days, were submitted to an independent assessor for diagnosis. To avoid bias, the examiner was kept unaware of the vaccination status of the suspect cases. Both published reports contain detailed, thorough, investigational comments into the possibility of bias among the study groups. The reader is impressed with the structure of the study, which deserves the frequently noted comment of "well controlled". In particular, it was quite well shown that the vaccinated and unvaccinated groups, who were originally tuberculin negative, were alike in all respects and had entered the trial at concurrent times. At the end of the five year period, there were 151 cases of tuberculosis among the tuberculin negative unvaccinated group (2.29/1,000) and 27 cases among the BCG vaccinated group (0.38/1,000). Thus, the BCG group had one sixth the incidence of tuberculosis as did the unvaccinated group. Statistically the chances of this occurring by accident are less than one in a million. The protective value of vole bacillus vaccination was similar. If, as believed, there was no bias in the structure of the trial, the percentage of reduction in the incidence of tuberculosis between the BCG vaccinated and the tuberculin negative control group was 83 percent. Allowing for chance fluctuations in the numbers of cases observed, it is still possible to say, with a high degree of confidence (99%), that the reduction afforded by BCG vaccination, in the tuberculin negative population of the study group was between 71 and 90 percent. To determine the protection afforded to the total

population by BCG vaccine, one must consider the cases of tuberculosis present and excluded before the start of the study and also the cases noted during the trial, among the tuberculin positive, non-vaccinated group. Allowing for the statistical effect of these cases, a fifty percent reduction would have been expected in the incidence of tuberculosis. The degree of protection noted was similar for pulmonary tuberculosis, tubercular pleural effusion and for hilar gland enlargement. However, four cases of tuberculous meningitis and four of miliary tuberculosis were found among the tuberculin negative, unvaccinated group and none were noted among the vaccinees. At the time of publication of the second report, there were indications that the protective value of the vaccine may extend to six and a half years. This study was well received by most authors.[23] However, Palmer criticizes the British study on the basis that due to frequent follow-up exams, the participants were reminded of their vaccination status and that this could have led to information, which could cause bias, being inadvertently transferred to the supposedly non-informed team physician and independent radiological assessor.[30] In the second British report, it is made quite clear that the majority of the participants were not aware of their tuberculin or vaccination status.[2] Anderson attacks the British trials on the basis that they relied of shadow casting lesions instead of bacteriological studies for the diagnosis of tuberculosis. He feels that the higher incidence of thoracic lesions in the control group could be partially due to erroneously grouping primary

pulmonary infiltrates with those of clinical tuberculosis.

In 1958, Palmer[23] published a progress report covering the first seven years of a large field trial of BCG vaccine, that was started in 1949, under the auspices of the United States Public Health Service. This is the most similar, recent, study comparable to the English trial. Two geographic locations were used; Puerto Rico, where the tuberculosis incidence is relatively high and Muscogee and Russell Counties in Georgia, where the racial adjusted tuberculosis mortality is slightly lower than that of the United States as a whole. In Puerto Rico, the study was conducted among school children ranging in age from one to eighteen years. No preliminary radiographic screening examinations were done. Intermediate PPD skin testing divided the final test group into 82,000 reactors and 110,000 nonreactors. The latter group was divided into vaccinees and controls. In Georgia, the preliminary examinations included tuberculin testing and chest roentgenograms. The participants included all age groups except that of under five years. There were 16,900 vaccinees and 17,200 controls. Fresh BCG vaccine, manufactured in the United States, was used in both the trials. No special follow-up examinations were utilized and detection of tuberculosis, among the trial population, was made only through established medical, and public health facilities. No source of bias was thought to exist between the vaccinated and unvaccinated groups. In Puerto Rico, the reduction in tuberculosis incidence between the originally tuberculin negative and vaccinated group and the tuberculin negative

unvaccinated participants was only thirty-one percent. A similar figure was noted in the Georgia trial; however it was not considered statistically significant due to the low numbers of people involved in the study. In both areas, the reduction in tuberculosis, attributable to the vaccine, as applied to the population as a whole was 9.3 percent. Considering both groups, there were 112,000 original tuberculin positive and 144,000 original tuberculin non-reactors. Seventy-five percent of the tuberculosis occurred in those who were initially tuberculin positive and inelegible for vaccination. Therefore, only twenty-five of the tuberculosis would have been prevented if the vaccine had been completely effective in all those innoculated. Furthermore, analysis revealed that the risk of tuberculosis is much higher to those who have a tuberculin reaction of over 10 mm, of induration, to Intermediate Strength PPD. Palmer felt that the low rate of tuberculosis among non-reactors was due to the low risk of acquiring new infections. Of interest, were his findings that the effectiveness of BCG against the more serious forms of tuberculosis such as fatal, far advanced, miliary, or meningeal tuberculosis and more benign forms were about the same.

Aronson[4] casts a doubt on Palmer's study by noting that there was no report concerning proof of the antigenicity of the vaccine used in the trials. Furthermore, the follow-up procedures and criteria for diagnosis varied from that used in other acceptable studies. He feels that the determination of the prophylactic value of an immunizing agent should be conducted in an area where the tuberculosis morbidity and mortality are high. Yet Muscogee

County is so free of tuberculosis that no tubercular deaths occurred among the vaccinated or control groups. Palmer, himself, admits that "in a county like Muscogee County there is not much tuberculosis that can be influenced by BCG or any other immunizing procedures". Aronson believes that, without proof of the vaccine's antigenicity, and in view of the methods utilized to find cases of tuberculosis, "the study must be considered inconclusive".

30

The British authors indicate that the Puerto Rico and Georgia trial results differed from theirs mainly in a lower protective efficacy of BCG and a much higher incidence of tuberculosis among those who were originally tuberculin positive. The possible sources of these discrepencies lie in rather obvious differences, between the two trials; in population studied, criteria for vaccination, vaccines used and methods of follow-up study. It is interesting to note that, in the British trial, fourty-four per cent of the cases of tuberculosis were detected by the special follow-up teams. On the average of every fourteen months, for the five years of study, ninty-four percent of the participants were examined radiographically. This would seem a much more accurate method of detecting cases than that of relying on the standard channels of tuberculosis reporting. Both Palmer and the British authors agree that their divergent results cannot be explained satisfactorily at this time. Each study is continuing. Perhaps complete data, rather than reports of samplings, will indicate

an answer.

4

Aronson has published a study with results that are quite significant. Between 1935 and 1938 initial tuberculin skin tests were conducted among 8420 American Indians ranging in age from one to sixty years. The participants were from eight different Indian tribes in five widely separate geographical areas (Arizona, Wyoming, North Dakota, South Dakota and Southeastern Alaska). These tribes were non-nomadic. Edonomic, social, and dietary patterns were fairly uniform for all those living on the same agency. At the beginning of the study and until after the late 1940's, economic conditions were low, housing was crowded and the morbidity and mortality from tuberculosis was high. The incidence of tuberculous infection, as judged by a positive tuberculin response was high and varied but little in five year age groups. The percentage of those who reacted to .00002 mg of PPD increased rapidly by age. Thus 12.7 percent positive reactions were found in those under five years of age while in those between twenty and twenty-four years of age ninty percent were reactors. All those who failed to react to 0.00002 mg and 0.005 mg of PPD were precisely divided at random into two groups. One group (1,551) received 0.1 mg or 0.15 mg of freshly prepared BCG vaccine intracutaneously and the other (1,457) received 0.1 ml of normal saline. Of those included in the study, eighty-five percent were examined roentgenologically shortly after they received their initial tuberculin test. Neither the controls nor the vaccinees were

isolated before or after the start of the study and their way of life was not purposely modified. Annually, from 1938 to 1944, and in 1947, the controls and vaccinees were revisited for tuberculin testing and roentgenograms. During the eleven years of the survey, the percentage of the vaccinees that were tuberculin tested annually ranged from 96.4 to 68.9 percent. Among the controls, similar figures ranged from 95.4 to 70.4. Over the same period, 97.4 to 69.9 per cent of the vaccinees received yearly chest roentgenograms while 96.8 to 72.1 percent of the controls were thus examined. Between 1936 and 1947, an average of 8.86 and 8.9 roentgenograms were taken of the vaccinees and controls respectively. The chest films were evaluated in three separate reviews. A BCG field unit radiologist made the first interpretations. To avoid bias, two further film surveys were made by radiologists completely ignorant of the study. The following observations were made:

interpretation of roentgenograms	percentages vaccinees	controls
1. abnormal films, all causes	16.7	31.2
2. characteristic of pulmonary tuberculosis	4.1	16.4
3. non-tuberculous pulmonary lesions	12.5	14.8
4. evidence of miliary tuberculosis	0.0	0.7

Over the eleven years, twelve tubercular deaths were noted among the vaccinees and in sixty-five of the controls. On this basis, Aronson[3] claims that hypersensitivity to tuberculin and resistance to tubercular infection have a close, but not absolute relationship. This concept is supported by the finding that tuberculin sensitivity,

among the vaccinees, persisted at the high levels of 93.3 per cent , one year after vaccination, and 90.2 percent eleven years later. Corresponding figures among the controls, who developed more tuberculosis, were quite low at levels of 12.7 and 41.7 per cent. In 1956, another survey was made among the participants and was restricted to determining the causes of mortality. The whereabouts of 99.7 per cent of the vaccinees and 99.4 per cent of the controls were determined. In all cases, substantiating clinical and medical records, in addition to the death certificates per se were required to prove cause of death. The following results were noted:

cause of death over 20 years	percentages vaccinees	controls
1. all causes	6.7	10.4
2. tubercular diseases	0.34	4.7
3. non-tubercular diseases	3.0	2.9
4. violence	2.9	2.9

Among the vaccinated, tuberculosis was responsible for 12.5 per cent of all deaths. A much higher figure of 45.3 was found in the controls. A specific inquiry, revealed no evidence that tuberculin hypersensitivity favors development of destructive forms of tuberculosis, even when the risk is high. Acute hematogenous forms of tuberculosis occurred, with but few exceptions, among the controls. Many of those had remained tuberculin negative on their last skin test or up to within one year of death. Ikezaki remarks, and it would certainly seem true, that this study has been universally accepted as proof of the efficacy of BCG vaccination for this racial

16

group of known high susceptibility to tuberculosis.

Rosenthal[34] has published a report on the effectiveness of BCG vaccination, involving five separate studies over a twenty year period. (1) Newborn infants at Cook County Hospital were innoculated on the second to fifth day of life with either fresh or dry BCG vaccine. They were first screened to determine a lack of tuberculosis contact in their families. There was a total of 3,841 vaccinees and 3,014 controls. It was felt that the vaccinees returned to an envoirnment with a relatively high incidence of tuberculosis since the tubercululin negative control children converted to positive at a rate of fourty-one percent, at eight to twelve months of age, and thirty percent at four and a half years of age. The infants were seen semi-annually for tuberculin tests, roentgenograms and physical examinations. About ninty percent of the population studied were Negro. At the end of a fifteen year continuous follow-up, comparasion of the vaccinated and control groups revealed a reduction of tuberculosis morbidity and mortality of seventy-five to eighty-nine per cent, respectively. (2) Newborn infants from various hospitals in the Chicago area were separated from tuberculous family contacts at birth and kept in foster homes for periods of up to four months. The length of isolation varied with the severity and relationship of the contact case. All vaccinations were done either at birth or up to three months of age. The children were returned to their own homes only after the source case was considered "closed". For twelve years, 276 vaccinees and 218 con-

trols were observed closely. Comparasion of the vaccinated and control group revealed a reduction of tuberculosis morbidity and mortality of 68 and 80 per cent respectively. Both studies also indicated that tubercular pulmonary infection was less extensive among those BCG vaccinated. Among those, substantial parenchymal infiltration occurred in only ten per cent. However, this was noted in one third of the controls. Of the twelve patients who died from tuberculosis in the control groups, of both series, eight had tuberculous meningitis which was verified by postmortem examination. This did not occur in the subjects who were successfully vaccinated. (3) The entire population of a housing project, situated in a high, tuberculosis-incidence area, were examined roentgenographically for tuberculosis. All tuberculin negative project children, up to 12 years of age were innoculated randomly with either BCG or saline. There were 777 vaccinated children and 1,875 nonvaccinated; all were Negros. For ten years, annual tuberculin testing of the children and roentgenographs of the entire population were repeated. No cases of tuberculosis were found among the vaccinated children, however there were nine cases of tuberculosis, including two fatalities, among the nonvaccinated. (4) At the Cook County Hospital in Chicago, 494 tuberculin negative student nurses, entering training, were divided into BCG vaccinated and control groups. Tuberculin tests and roentgenograms were repeated at six months intervals. Only the initally tuberculin positive and the vaccinated students were allowed to take a two months training tour in the tuberculosis hospital.

Over a twelve year period, the tuberculosis morbidity rate during training was 8.7 per thousand, among the 231 vaccinated nurses and 19.0 among the 263 controls. Despite the obvious defect of differential exposure, Rosenthal feels that significance remains, in that there are "unquestionably undiagnosed, active cases of tuberculosis in the general wards since roentgenograms are made of only a certain percentage of the patients on admission". (5) Over a 13 year period, medical students entering the University of Illinois were examined initially and at yearly intervals, with tuberculin skin tests and roentgenograms. There were 305, who were tuberculin negative and who received BCG vaccine; 298 who were tuberculin negative controls and 816 with positive reactions. A further 254 had an incomplete tuberculin reaction status. Respective to these groups, there were two cases of tuberculosis in the controls, four cases in the tuberculin positive group and four in the incomplete tuberculin group. No cases of tuberculosis were noted in the vaccinated group.

In 1953, Abruzzi[1] published a review article concerning BCG vaccine and the incidence of tuberculosis among American medical students. He first carefully reviewed the literature citing an increased indidence of tuberculosis among medical students as compared to other suitable groups of young adults. The Prophit Survey[10], summarizing most of the valid work on the subject up to 1948, indicates a tuberculosis rate three times higher in medical students than among suitable controls. Abruzzi's investigation was

based on a survey of 42,000 students from 62 American medical schools , representing 166,959 student years between 1940 and 1950. The investigation uncovered 557 cases of clinical tuberculosis or a case rate of 3.34 per thousand per year. The schools reported a total of three cases of tuberculosis among 4400 BCG vaccinated students. These three cases were all in students who had not converted to positive after vaccination.

Larber[20] has presented a study concerning newborn infants and children in close contact with tuberculosis. Between 1949 and 1952, 267 children, less than two years of age, were seen in a tuberculosis contact clinic. All newborns were BCG vaccinated with Danish Fresh BCG, intracutaneously, and isolated from their tubercular families until they were tuberculin positive. They were then returned home; irrespective of the condition of the contact case. All non-newborn contacts were isolated from their families for six weeks after a tuberculin negative skin test. They were then retested,and if still tuberculin negative were similarly vaccinated. These children were returned home after they converted to tuberculin positive. All of the tubercular index cases were household contacts with parents representing 47 per cent, grandparents 12.4 and other persons 40.6 per cent. By means of positive sputum cultures, four fifths of the index cases were classified as active at the beginning of the study. During the five year follow-up, 11.3 per cent of the index cases remained active. (The author mentions, citing Briggs (1955), that it is well known that inactive cases of tuberculosis

may cause fatal infections in children.) The participating children were examined once each year, more often if necessary. At the end of five years of follow-up, 264 of the original 267 were traceable. Of these, six had emigrated, ten were alive, well, and refused examination and 248 or 92.9 per cent were re-examined. Tuberculin testing revealed that 98 per cent were positive; four children were negative and were revaccinated with a positive response. Chest roentgenograms revealed only three cases suspicious of tuberculosis. These children developed pulmonary and hilar calcific formations, but no signs of progressive disease. Since there was evidence available that BCG innoculation would prevent tuberculosis, the physicians involved felt that they could not ethically withold vaccination from a portion of the participants. Thus, there are no controls in this study. However, the protective value of BCG is strongly suggested by the fact that, even in the face of such unfaverable conditions, none of the infants died of tuberculosis and only two contracted symptoms suggestive of the disease.

Sams[36] describes BCG vaccination in Japan during the postwar occupation. From the onset of military control, up to 1949, 31,000,000 persons were vaccinated with BCG. The mean annual tubercular death rate of 280 per 100,000 in 1945, decreased to 131 per 100,000 in 1948. Analysis of tubercular deaths, by age group, demonstrated that the entire reduction appeared in the age group given BCG. The tubercular death rate among the non-vaccinated group was not appreciably decreased during this period. Within the imm-

unized group, tuberculosis mortality was reduced by 88 per cent.

In November of 1953, an expert committee of the World Health Organization unanimously concluded that a "specific resistance to tuberculosis can be induced by artificial means (vaccination)"[14]. As will be discussed below, a special committee of the United States Public Health Service, in 1957, indicated that "BCG confers some protection against tuberculosis"[27]. A similar statement was issued by the American Trudeau Society in 1958.[50]

C. THE NEED FOR BCG VACCINATION IN THE UNITED STATES

Anderson has outlined what he and others believe to be the chief objections to the use of BCG in the United States.[2] It has been estimated that there is a backlog of 56,000,000 persons in this country harboring tubercle bacilli. By far, the majority of these are over fourty years of age. Under these conditions, the tuberculosis case rate cannot be expected to undergo a fast decline. However, he notes that in 1926, a study of grade school children, in cities of one half-million population, demonstrated a positive tuberculin rate of 47 per cent. In 1954, this same rate had dropped to 4 per cent. A similar study among junior highschool students revealed a decrease from 34.7 per cent in 1934 to 3.7 in 1957. He cites Palmer (1956) as studying tuberculin reactions in over 120,000 seventeen to twenty-one year olds, from 1949 to 1951, and finding a tuberculin positive reaction in 8.8 per cent. The group included U.S. Navy recruits from many locales and university students from seventeen states. Anderson feels that these figures,and others,

indicate that a marked decrease in the mortality and attack rate of tuberculosis will be noted in the United States as more and more new generations emerge. BCG will not be usuable on the 56,000,000 Americans already tuberculin positive and, if the aforementioned figures are accurate reflections, relatively few of the younger people can be expected to become infected.

In discussing the need for BCG vaccination in the United States, Raffel[26] mentions that the incidence of active tuberculosis has fallen little in the past quarter century, in contrast to the mortality rate. In 1930, the number of newly reported cases was 125,000 and in 1955 about 100,000. The latter figure is impressive, despite the increase in total population that has occurred. He strongly proposes that a definite need for BCG lies among specific high-risk groups and areas. Badger[5] concurs with Raffel in an extensive review article on tuberculosis. He believes that the present United States tuberculosis death rate of 8.41 per 100,000 is a "red Herring". The incidence of new cases each year (69,000), in its gentle downward slope, lags far behind the death rate. The prevalence of tuberculosis in 1956, as reported by the Public Health Service, was 250,000 inactive and 150,000 active cases.

Blomquist[7] has published a report noting how poorly the known cases of tuberculosis are being controlled in our country. In 1955, a nationwide, Public Health Service survey revealed that nearly half (45%) of all active cases were being cared for at home. Of these, 87 per cent were cases of far advanced

tuberculosis; in one half the suptum status was unknown and in the other half it was positive. Slightly over one third of the home care cases were receiving neither drugs nor supervised rest. Slightly less than 50% had been discharged from hospitals against medical advice.[13] A British editorial in discussing the value of BCG vaccine, lends added importance to these home care cases by pointing out that, as the net is closing around tuberculosis, the exposure to infection is more likely to come from an unsuspected, rather than a known, source and is therefore more difficult to prevent.

Childress[9] has estimated that 40,000 unknown tubercular patients are admitted to general hospitals in the United States each year.[22] In 1948, a study by Oatway indicated that only 247 out of 4539 general hospitals in this country did routine admission chest roentgenograms. Reflection on the aforementioned studies indicates that physicians, nurses, medical students and other hospital personnel are likely to be unknownly exposed to tuberculosis. Since the advent of isoniazid prophylaxis, special reference has been made, by many authors, to the question of what part BCG vaccination shoud play in the prophylaxis of tuberculosis in children.[19] Lichtenstein outlines the indications and technique of isoniazid prophylaxis in children, as made clear by a recent Public Health Survey on the subject. The Municipal Tuberculosis Sanitarium of Chicago has utilized this program, for children found in contact with active tuberculosis and for tuberculin converters, since the late 1950's. One difficulty noted, has been

the lack of cooperation of the parents in carrying out the treatment. The percentage of those children who finish the complete isoniazid therapy ranges from 40 percent in the slum areas to 75 percent in the low economic districts. Previously mentioned studies have discussed the effectiveness of BCG vaccination among high-risk infants and children and have demonstrated that the vaccine will prevent almost all cases of miliary and tubercular meningitis among children. Therefore, it would seem, that under special conditions, BCG vaccination deserves a place in the prophylaxis of tuberculosis in children.[11] Davison underscores this thought by pointing out that tubercular meningitis almost always occurs in those under three years of age and that only two cases of this disease progression have been reported in BCG vaccinated infants.[32] Rich raises an academic question by noting that vaccination of the newborn involves giving an antigen to those less capable of an antibody response than any other age group.[6] Barclay states that in his opinion, the prophylactic use of isoniazid cannot substitute for BCG vaccination as therapy for exposed children. This is particularly true for those in the low socio-economic group who are transients and escape vigilant medical observation. He agrees with Lichtenstein in that isoniazid therapy is frequently not carried out properly due to lack of cooperation of the parents. This same lack of cooperation lowers the value of the alternative procedure of frequent tuberculin testing. Interestingly enough, he notes that most physicians do not take the trouble to perform

tuberculin tests in their own immediate families. A single therapeutic procedure, such as BCG vaccination, is much more effective way of handling exposed children when there is doubt as to the continuity of other forms of management.[6]

Wallgreen[42] has delivered a summary of arguments against the mass use of BCG vaccination in countries where the morbidity and mortality from tuberculosis are low and declining. He maintains that the decline of tuberculosis in Scandinavia and the United States is not a result of BCG vaccination programs. Furthermore, the specific immunity produced by this vaccine has little or no effect on the degree of resistance to postprimary forms of tuberculosis and that the primary tubercular infection causes a degree of resistance higher than that resulting from vaccination. The protective value of the vaccine is predominantly against the serious, early, postprimary complications, such as miliary and meningeal tuberculosis, local progression of the primary infection and pleurisy. In countries such as the United States, he favors the use of the vaccine in specific high risk groups such as those with household tubercular contacts, medical and paramedical personnel and new military recruits. The best use of BCG, according to the author is in age groups with low natural resistance (infants, small children with a high risk of exposure).

In 1957, a special committee, formed at the request of the Surgeon General of the United States Public Health Service, reported[49] a new statement on the use of BCG vaccination as

a public health procedure and their recommendations on further research as to its value. In part, their review of accumulated evidence indicated the following: (1) BCG appears to be as safe as any other vaccine and does lead to some degree of increased resistance against tuberculous infection. (2) The beneficial use of this vaccine is restricted to those who are tuberculin negative. Recent studies have shown that tuberculosis is much more likely to develop among those tuberculin positive at the time of survey. Therefore those under the greatest hazard from tuberculosis are ineligible for vaccination. (3) Use of BCG vaccination results in the loss of the tuberculin test as an indicator of recent infection in the individual, as an index of infection in population groups, as a tool for locating sources of contagion, as a screening device in case finding to keep radiation hazard to a minimum and in the differential diagnosis between tuberculosis and other simulating diseases. (4) The use of BCG should be determined by the particular circumstances in the local community or population groups. (5) Large scale vaccination programs, including routine vaccination of the newborn are not indicated in this country. (6) The advantages of BCG innoculation outweigh the disadvantages for tuberculin negative persons who are exposed to a definite risk of infection. Under certain local circumstances, the following are examples of suitable subjects for BCG innoculation: (a) physicians, nurses, medical and nursing students, laboratory and other hospital employees. (Here, the report indicated that very little exposure

would occur if the hospital had established an adequate tuberculosis control program) (b) persons unavoidably exposed to continued contact with infectious cases of tuberculosis in the home. (c) personnel and inmates of institutions in which survey programs indicate a high risk exposure to tuberculosis. (7) Further new vaccination trials in this country are not recommended, but the studies already underway should continue as long as they provide useful information.[39] A statement along the same lines was released by American Trudeau Society in 1958.

D. THE SAFETY OF BCG VACCINE

Since BCG vaccine is a living attenuated form of a tubercle bacillus that originally caused progressive tuberculosis, some question has always existed as to its safety. The primary question has been as to whether or not the bacillus would revert to a virulent stage. As noted previously, early in the history of BCG use on humans, there were two incidents which made this thought even more plausible. However, evidence has been presented many times in the last two decades which attests to the safety of the vaccine.[3] The Aronsons have worked with BCG since 1928 and have observed fluctuations in the tuberculogenic property and variations in some of the biological characteristics of the culture. At no time have they observed progressive disease in guinea pigs; not even with intraperitoneal injection of as much as 30 mg. of the culture.[40] Vorwald exposed guinea pigs over a long period of time to inhalation of silica dust and demonstrated that BCG vac-

cination would then produce extensive pulmonary lesions. However, the cultures of bacilli obtained from the infected guinea pigs remained avirulent. Furthermore, these studies could not be verified, by Vorwold himself, in further experiments with guinea pigs, rabbits and dogs.[5] Anderson[9] mentions the work of Dubos (1949) in which three United States strains of BCG produced pulmonary lesions in mice. Rosenthal[5] notes, however, that "Dubos has stated to me that the low state of nutrition produced in his mice, in which BCG was invasive, was of such a degree that it would never be approached in human beings." From 1953 to 1955, there appeared in the Scandinavian literature, four reports of alleged, BCG-caused, tubercular fatalities in humans. The diagnoses were made on the basis of careful postmortem examinations.[9] However, in all the cases, tubercle bacilli were isolated which did not cause progressive disease in guinea pigs.[3] Ikezaki mentions the paper of Peterson (1955) which offers the explanation that these cases involved agammaglobulinemia or an equivalent state in which progressive disease developed from an avirulent, attenuated vaccine because the individuals lacked the ability to develop a resistance mechanism.[53] Irvine discusses this and remarks that even if the deaths were due to BCG, there would be only four recorded fatalities out of 145 million vaccinations that have been given. As a comparison, he mentioned 43 deaths, from smallpox vaccine alone, in England and Whales from 1940 to 1949. Other authors have commented on the safety of the vaccine.[49,35,32,50] A new form of BCG, the freeze-dried vaccine, maintains its stability for

many months.[36] This provides the necessary time, between preparation and distribution, for the complete standardization of the vaccine as to viability, potency, and safety.[5,35,36]

E. THE DISADVANTAGES AND COMPLICATIONS OF BCG VACCINATION

The primary disadvantage in the use of BCG vaccine is the loss of the tuberculin test and all of its attendant uses.[2] Anderson comments on this. The tuberculin test determines earlier than any other method when tubercle bacilli have entered the body. There are hopes of perfecting drugs which will kill all tubercle bacilli by reaching them when the lesions are still vascular. Early detection will be necessary for this application. Furthermore, he mentions Quaiser (1954) as indicating that the distinction between a tuberculin reaction due to vaccination and that of natural infection is impossible.[34] Rosenthal argues that in surveys, prior to 1940, only two active cases of tuberculosis were found among every 100 persons who reacted to the tuberculin test. Thus, the test was brought into disrepute for mass screening and the miniature roentgenogram has largely replaced the tuberculin test in survey studies. Furthermore, the test is a devious diagnostic route in comparison with the direct approach of roentgenography.[3] Aronson claims, that in general, the trained observer can differentiate between the tuberculin reaction following BCG vaccination and that following spontaneous infection with tubercle bacilli. The following differences are noted; (1) After BCG sensitization, a low level of sensitivity persists and 50 percent of the vaccinees

will react to 0.01 mg of O.T. or 0.00002 mg. of PPD. The other half will react to from 0.1 mg to 1.0 of O.T. or to 0.005 mg. of PPD. Whereas in those who have encountered a natural infection, 80-90 percent will react to 0.01 mg O.T. or 0.00002 mg. of PPD. (Rosenthal[34] agrees with these findings with the additional comment that the low level of tuberculin sensitivity in BCG vaccinees is not seen until a year or more after innoculation). (2) In the vast majority of vaccinees, the skin reaction is characterized by a diffuse, red or reddish-purple area, of about 8-20 cm diameter, associated with slight or ill defined edema or absense of any palpable edema. With increasing time, the zone of reaction becomes purplish and persists for several weeks. The local skin reaction of those infected naturally is a well defined area of redness and sharply defined, elevated, area of edema with induration measuring 1-2 mm in thickness and often associated with a central area of blanching, vesiculation or necrosis. (Rosenthal[34] states more definitely that tuberculin-caused vesiculation or necrosis is never seen in vaccinees.)

In discussing the possible loss of the tuberculin test, another article[28] on the subject agrees that, to the epidemiologist, the test is extremely useful in areas where the tuberculosis infection rate is low. However, in large cities where the tubercular infection rate is high, the determination, by means of the tuberculin test that the majority of the populace are positive, is of little value. It is strongly suggested that a possible 80 percent reduction in the incidence of tuberculosis, as indicated by the Brisish studies,

might more than compensate for the loss of the tuberculin test.
Raffel[26] discusses the objection of the loss of the tuberculin test as a case finding tool and notes that this argument is not valid, since recommendations for vaccination are only for those areas of high tuberculin positive incidence.

It is reasonable to suspect, and many authors have noted, that with the wrong attitude, BCG vaccination could encourage abandonment of the standard anti-tuberculosis control methods which have been primarily responsible for the waning of this disease in the United States.

The complications of BCG vaccination have been few.[29,30] In the British trials the complications attributable to the vaccine were; "a few" cases of shallow ulcer and delayed healing at the vaccination site, local cold abcesses and regional adenitis. Out of 14,000 vaccinees, there were three cases of erythema nodosum thought to be due to the vaccine.[18] Irvine has written on the medical management of these complications. For skin ulcers over 10 mm. in diameter and indolent lesions that are not healing well, he recommends dressing the wound twice a day with an ointment. Cold abscesses, localized at the vaccination site are best treated by a single aspiration. The most troublesome complication is a cold abscess in the regional lymph nodes draining the area of vaccination. This occurs mostly in children and is uncommon after the age of five years. Halving the innoculation dose in children has decreased the incidence of this complication without significantly effecting the conversion rate. Simple excision of such an abscess is strongly

contraindicated, in that the area may require months to heal. The best therapy is aspiration of the pus and replacement with 10-20 mg. of streptomycin. This may have to be repeated more than once. No specific therapy is indicated for erythema nodosum as it is usually brief and self limiting. Other vaccines should not be injected into the same extremity within six months of BCG innoculation, since this may provoke abscess formation.

IV. TUBERCULIN TESTING: BCG VACCINATION TECHNIQUE: AND RELATED INFORMATION

The following section deals with the procedural information necessary to the physician who is undertaking BCG vaccination.

A. TUBERCULIN TESTING

A knowledge of tuberculin testing is necessary to all who deal with BCG vaccination since only those who are tuberculin negative are eligible. Furthermore, the efficacy of the vaccination is noted through tuberculin conversion.

1. Types of tuberculin and equivalent dosages

Tuberculin is a soluble substance of the tubercle bacilli.[8] It is usually prepared from human tubercle bacilli. Two forms are currently in use. The first of these, Old Tuberculin (OT, TO), was made by Koch originally and consisted of a filtrate, of glycerol-broth culture of the bacilli, concentrated by evaporation on a water bath to about one tenth of its original volume. A derivative of tuberculin was isolated by Seibert using precipitation with trichloracetic acid. Originally designated SOTT

(synthetic medium old tuberculin tricholracetic acid precipitated) it is now known as PPD (purified protein derivative). OT is relatively unstable in its nexessary dilutions, while PPD, a dry powder is "dry-diluted" with lactose and is indefinitely stable. Different lots of OT have been noted to vary somewhat in activity, while the activity of PPD is relatively constant. PPD appears to be as satisfactory in action as OT and because of its stability and constant activity, is regarded by many as superior to OT.[8] The Research Foundation[31] states that OT should be used in testing for tuberculin sensitivity before and after BCG vaccination. However, at a recent meeting of the Skin Testing Committee of the American Trudeau Society and the National Tuberculosis Association (Feb. 1959) the discussion unofficially concluded that PPD is the tuberculin of choice for case-finding and with BCG vaccination.[37]

Varying terminology, in reference to tuberculin, is present in the current literature. Badger[5] has presented a table of approximate tuberculin equivalents based on comparative skin-testing potency:

Tuberculin Units	Strength	PPD-S* mg./dose**	Old Tuberculin mg./dose***	dilution
1	1st	0.00002	0.01	1:10,000
5	intermediate	0.0001	0.05	1:2,000
250	2nd	0.005	1.0	1:100

* International Standard Tuberculin (adopted by WHO 1952)
** based on milligrams of protein
*** based on 1 ml. of concentrated OT - 1000 mg.

(2) Methods of tuberculin application

Badger[5] has presented an interesting review of the different methods of applying tuberculin. The Von Piguet test involves scarification of OT into the skin. This approach is crude and of little present day value. The patch test (Volmer) has been used considerably in recent times, but a study by Waegele[41] has casted some doubt as to its reliability. He performed simultaneous intracutaneous (Mantoux) and patch tests on 855 school children. There were 196 positive tuberculin reactors as judged by the intracutaneous response. Of these, 83 were positive to both forms of the test, 113 were positive to the Mantoux and negative to the patch test, and three were positive to the patch and negative to the Mantoux test. Heaf has introduced a new multi-puncture skin test that is used widely in England.[18,5] Glycerinated PPD is spread on the skin and an automatic pistol-like device, manufactured by H. G. East Co., London, England, is pressed over the skin. As the trigger is pressed, a spring-loaded disc with six prongs automatically penetrate through the PPD solution and into the skin, to a depth of 2 mm. This test is read at seven days. It is comparable with the 100 TU Mantoux and has received favor, especially in working with young children, because of the ease of administration. Those who have attempted to perform an intracutaneous injection in a squirming infant will appreciate this technique. The intradermal (Mantoux) tuberculin test has been indicated as the technique of choice when working[25,37] with BCG vaccination. Properly performed, it consists of the

introduction of 0.1 ml. of tuberculin into the superficial layers of the skin; preferably utilizing a 26-27 gauge, 1 to 2 cm., short bevel needle[5] and a tuberculin syringe. The skin is drawn taut and the needle is inserted, bevel tip up, between the layers of the skin, at the juncture of the proximal and middle third of the volar forearm. Injection at the proper depth will produce a white, elevated area or wheal. When the first test dose has been administered too deep,[25] a second dose should not be given at that time. Tuberculin placed carelessly into the subcutaneous tissue, will produce no readable reaction.[31] The Research Foundation suggests that the site selected for injection should not be over a muscle belly, tendon, or vein. A small hollow area is preferred so that resistance from underlying structures will least obscure the induration resulting from the tuberculin reaction. Acute illness, skin disease or a Smallpox vaccination of less than one month old are contraindications to tuberculin testing.[25]

(3). Interpretation of the Intradermal Tuberculin Test

Interpretation of the Mantoux test is done at 48 to 72 hours following administration. All erythema is disregarded and the longest transverse diameter, at right angles to the axis of the arm, of edema or induration is measured in millimeters. If, as recommended for case-finding and with BCG vaccination, the dose has been 5 TU, the response is interpreted as follows:

"....induration of 10 mm or more in the intermediate, 5 TU strength is interpreted as a well defined, positive test.....induration of 6-9 mm constitutes a weak-positive result and is the area of uncertainty and disagreement in interpretation. Thus, 6-9 mm of induration may include a varying percentage of false-positive reactions from nontuberculous, atypical, acid-fast mycobacteria,varying in importance in different parts of the country....reactions in the range of 6-9 mm are associated with a lower risk, of developing tuberculosis or of having household contacts with active tuberculosis, than reactions of 10 mm or more of induration."[37] The test is negative if induration measures 5 mm or less.[25]

B. BCG VACCINATION

(1). Types of Vaccine

Several variations of BCG vaccine have been popular about the world at different times. At first, all strains were manufactured in the liquid form, which was stable for only approximately two weeks after manufacture.[25,18] With the intrc-duction of freeze-dried or lyophilized vaccine which has a storage life of from 12 to 20 months,[25] a product became available which could be completely standardized before release. This added safety factor has made freeze-dried vaccine almost a universal choice.

(2). Sources of Vaccine

Freeze dried BCG vaccine may be obtained in the United States from The Research Foundation, 70 West

Hubbard St., Chicago 10, Illinois. This laboratory is operated, in conjunction with the University of Illinois, under U. S. Government license. The Research Foundation claims to be the "only licensed BCG laboratory in this country"[24]. All vaccine produced in the laboratory meets standards, established by the National Institutes of Health[31], for viability, potency, sterility, identity and virulence. It is available on the request of any licensed physician, hospital, health department or similar authorized agency[24]. A tuberculosis control program is a prerequisite for approval of distribution to organizations. Orders should be received in Chicago at least one week in advance of desired delivery date. As of March 1962, one fourteen dose vial of vaccine was priced at $5.00. The vaccine has an approximate expiration date of six months.

(3) Methods of vaccination

Three methods of applying BCG vaccine to the skin appear in the current literature[18]. Irvine describes the intracutaneous injection of 0.1 ml. of vaccine over the insertion of the deltoid, the angle of the scapula or the anteriolateral surface of the thigh. One half that dose is used for infants under one year of age. Using this technique, the resulting lesion appears in two weeks as a painless papule. It increases in size, up to 20 mm., until the sixth week. One half of the reactions will form a superficial ulcer, as large as 10 cm. in diameter, which persists for up to three months. The other half remain in the papule stage for up to one year. This method is also described by the Public

Health Service.[25] The superficial ulceration provides an opportunity for secondary infection and leaves a scar. To avoid these complications, Rosenthal[38] introduced a superficial scarification method, utilizing 30 transcutaneous needle punctures into the skin through a drop of vaccine. A further modification of this has introduced the quite popular multiple-puncture-disc method. The innoculating instrument, developed by Rosenthal and available from the Research Foundation at a nominal cost, consists of a stainless steel, flat, disc one inch in diameter. On one side, there are thirty-six small protruding prongs. The opposite surface is smooth and is designed to cling to the surface of a small, hand-held magnet which offers a means of controlling the disc. After the vaccine has been spread over the skin, the multi-puncture is accomplished in one simple pressure movement. Rosenthal notes that this method results in the formation of small discrete papules, without ulcerations, or abscesses. Obviously, this method has manipulatory advantages over the intracutaneous method especially when dealing with small children.

Griffiths[15] has published an excellent study an the reliability of several forms of multi-puncture apparatus, including automatic firing "guns" with standard penetration-depth and force. In most techniques, the vaccination site is allowed to dry, before covering with clothing, and is kept dry for 24 hours. Six to eight weeks after vaccination, the patient should be tuberculin tested to determine whether conversion has occurred. The following are contraindications to BCG vaccination: lack of being tuberculin tested within

the preceeding two weeks, tuberculin positivity, acute illness, suspected respiratory disease, skin disease, and yellow fever, polio or small pox vaccination within the past four weeks.[25][18]

V. DISCUSSION AND CONCLUSIONS

BCG vaccine has been in use for almost a half a century. In spite of the vaccination of millions, an abundance of proof supporting its efficacy is not available. In some areas of the world, tuberculosis has been successfully managed without widespread use of BCG. However, redent advancements have again raised its desirability in the campaign against tuberculosis.

Although BCG induced resistance to tuberculosis cannot be directly measured, many well controlled clinical trials have demonstrated that this resistance does occur. Aronson's studies have definitely shown that this is especially true in certain racial groups with an inheirent low resistance to the disease. The current British study strongly suggests that BCG also induces resistance to tuberculosis in a general population of teenagers and young adults. However, Palmer's report again reminds us of the variability that is found in tuberculosis immunity. What is true for one race, geographical area, or age group is not necessarily true for others.

On the basis of the record presented, there should be no doubt as to the safety of BCG vaccine. This is especially true with the advent of the new freeze-dried or lyophilized form. The stability of this vaccine allows ample time for testing and standardization before distribution. Side effects or complications exist for most

immunizing agents. Those due to BCG vaccination are uncommon and usually respond well to therapy.

The prime question to be answered is whether or not a need exists, in the United States, for this vaccine. A change in the status of tubercular disease has been noted in our country. By far, the majority of tuberculosis prevalence exists in the older age groups. Although the mortality has decreased in an accelerated fashion, the morbidity remains relatively high. Statisticly, the greatest risk of acquiring tuberculosis no longer exists in those who are tuberculin negative. It is the tuberculin positive, particularly those who, with the Intermediate Mantoux, respond with over ten millimeters of induration and these people are not eligible for BCG vaccination. Judging from the above, one might easily deduce that, with continued application of standard public health measures against tuberculosis, the problem would gradually die out as new generations evolve. This, in my opinion, is not completely true, for several disturbing facts remain. Blomquist's 1956 report indicated that nearly half of the far advanced, active cases of tuberculosis in the United States remain at home, independent and frequently without adequate medical treatment or supervision. This provides a large source of tuberculosis contact. Certain individuals, because of their field of employment or living conditions face an increased exposure to this source. In some locales, this risk is fully appreciated and stringent public health, anti-tuberculosis regimens are enforced. However, today and even more so in

the near future, as the tuberculosis problem gains less and less attention, one can fully anticipate a gradual relaxation of control programs. It would therefore seem more than reasonable to urge BCG vaccination in all individuals that are tuberculin negative and facing an increased exposure risk. This includes physicians and paramedical personnel whose work brings them into daily contact with clinic or general hospital patients, particularly the elderly and the indigent. Their risk is even greater since, to some degree, familiarity with the disease breeds contempt. Exposed infants and children and those who are recent tuberculin converters may be treated with isoniazid only if a reasonable degree of patient co-operation is assured. Those persons, unavoidably exposed to tuberculosis in their home, are definite candidates for vaccination, not only for their own protection, but also because they serve as the primary contagious link to the general population. At the risk of repeating, it can be again stressed that standard, public health, anti-tuberculosis regimens have been responsible primarily for the decline of the problem in the United States. Any degree of abandonment of these measures, with or without BCG vaccination, invites disaster.

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VII. SUMMARY

The history of the development of BCG vaccine, and its early use in humans, are briefly reviewed. Divergent opinions on the efficacy of the vaccine, along with a description of outstanding literature reports on recent clinical trials, are presented. The question of the need of BCG vaccination in the United States is considered. Supporting arguments for the safety of the vaccine are noted. The methods of BCG vaccination, tuberculin testing and related information are outlined. Finally, suggestions are made as to indications for use of BCG vaccine.

BIBLIOGRAPHY

1. Abruzzi, W. A., Tuberculosis: Incidence Among American Medical Students; Prevention and Control and the Use of BCG, New Eng. J. Med. 248:722, 1953.

2. Anderson, A. S., The Case Against BCG, Brit. Med. J. 5135:1423 (June 6), 1959.

3. Aronson, J. D. and Aronson, A. F., Appraisal of the Protective Value of BCG Vaccine, J.A.M.A. 149:334, 1952.

4. Aronson, J. D. et al, A Twenty Year Appraisal of BCG Vaccination in the Control of Tuberculosis, Arch. Intern. Med. 101: 881, 1958.

5. Badger, T. L., Tuberculosis, New Eng. J. Med. 261:30, 1959.

6. Barclay, W. R., BCG Vaccination, Pediat. 24:3, 1959.

7. Blomquist, E. T., Nonhospitalized Tuberculosis Patient, Am. J. Pub. Health 46:149, 1956.

8. Burrows, William, Textbook of Microbiology, 17th ed., W. B. Saunders, Phila., 1959, p. 640.

9. Childress, W. G., Tuberculosis Case Findings by General Hospitals, J.A.M.A. 22:1063, 1943.

10. Daniels, M. et al, Tuberculosis in Young Adults: Report of the Prophit Tuberculosis Survey-1935-1944, W. K. Lewis, London, 1948. Cited by: Abruzzi, W. A., Tuberculosis: Incidence Among American Medical Students; Prevention and Control and the Use of BCG, New Eng. J. Med. 248:722, 1953.

11. Davison, W. C., Advantages of BCG Vaccination in Preventing Tuberculosis, Quart. Rev. of Pediat. 13:131, 1958.

12. DeFriez, A. I., Tuberculosis in BCG Vaccinated Nurses; a Five Year Study at the Boston City Hospital, New Eng. J. Med. 257:161, 1957.

13. Editorial, For and Against BCG, Brit. Med. J. 5135:1460, 1959.

14. Finland, M., Tuberculosis Mortality and Morbidity and the Problem of BCG Vaccination in the United States, New Eng. J. Med. 261:699, 1959.

15. Griffiths, M. I., Multiple Puncture Vaccination in the Newborn with Freeze-dried BCG Vaccine, Brit. Med. J. 5206:1116, 1960.

16. Ikezaki, F. M., BCG After 35 Years; A Disaster or Triumph?, J. Kan. Med. Soc. 59:460, 1958.

17. Irvine, K. N., et al, Discussion on the Modern Outlook in the Management of Pulmonary Tuberculosis, Proc. Royal Soc. Med. 50:485, 1957. Cited by: Ikezaki, F. M., BCG After 35 Years; A Disaster or Triumph?, J. Kan. Med. Soc. 59:460, 1958.

18. Irvine, K. N., The Present Status of BCG, Practitioner 183:289, 1959.

19. Lichtenstein, M. R., Prophylaxis of Tuberculosis in Children, Ill. Med. J. 120:83, 1960.

20. Lorber, John, Long Term Effectiveness of BCG Vaccination of Infants in Close Contact with Infectious Tuberculosis, Brit. Med. J. 5135:1430, 1959.

21. Myers, J. A., BCG Vaccination, Am. Rev. Tubere. 57:107, 1948

22. Oatway, W. H., Current Status of Routine Chest X-Raying in General Hospitals, Ariz. Med. 6:23, 1949. Cited by: Abruzzi, W. A., Tuberculosis: Incidence Among American Medical Students; Prevention and Control and the Use of BCG, New Eng. J. Med. 248:722, 1953.

23. Palmer, C. E., Community Trials of BCG Vaccination, Am. Rev. Tubere. 77:877, 1958.

24. Permantier, A., personal communication, Research Foundation.

25. Public Health Service, Technique of Tuberculin Testing and BCG Vaccination, U. S. Government Printing Office, Washington, D. C., 1953.

26. Raffel, Sidney, Vaccination with BCG, Bull. Nat. Tubere. Assoc. Oct., 1957.

27. Report of Ad Hoc Advisory Committee on BCG to the Surgeon General of the United States Public Health Service, Am. Rev. Tubere. 76:726, 1957.

28. Report of the Medical Advisory Committee of the Research Foundation, Why Have We Not Accepted BCG Vaccination, J.A.M.A. 164: 951, 1957.

29. Report (first) to the Medical Research Council by Their Tuberculosis Clinical Vaccine Trials Committee, BCG and Vole Bacillus Vaccines in the Prevention of Tuberculosis in Adolescents, Brit. Med. J. 4964:413, 1956.

30. Report (second)to the Medical Research Council by Their Tuberculosis Clinical Vaccine Trials Committee, BCG and Vole Bacillus Vaccines in the Prevention of Tuberculosis in Adolescents, Brit. Med. J. 5149:379, 1959.

31. Research Foundation, BCG Vaccination, Chicago, Ill., 1956.

32. Rich, R. R., The Pathogenisis of Tuberculosis, Charles C. Thomas, Springfield, Ill., 1951. Cited by: Ikesaki, F. M., BCG After 35 Years; A Disaster or Triumph?, J. Kan. Med. Soc. 59:460, 1958.

33. Rosenthal, S. R., Immunological Aspects of BCG Vaccination, J. Pediat. 36:3, 1950.

34. _____, Standardization and Efficacy of BCG Vaccination Against Tuberculosis, J.A.M.A. 157:801, 1955.

35. _____, BCG Vaccine, Am. J. Med. Tech., 23:354, 1957.

36. Sams, C. F., Medical Care Aspects of Public Health and Welfare in Japan, J.A.M.A. 141:527, 1949.

37. Skin Testing Committee of the American Trudeau Society and the National Tuberculosis Association, unpublished data. Cited by: Badger, T. L., Tuberculosis, New Eng. J. Med. 261:30, 1959

38. Smith, Theobald, Studies in Mammalian Tubercle Bacilli, J. Med. Research 13:253, 1904-05. Cited by: Rosenthal, S. R., Immunological Aspects of BCG Vaccination, J. Pediat. 36:3, 1950.

39. Statement of the Commission of Therapy of the American Trudeau Society, Role of BCG in the Prevention of Clinical Tuberculosis, Am. Rev. Tuberc. 78:145, 1958.

40. Vorwald, A. H., BCG Vaccination in Silicosis, Am. Rev. Tuberc. 62:455, 1950.

41. Waegele, V. C., Simultaneous Mantoux and Vollmer Patch Tests in 855 School Children, Dis. Chest 31:636, 1957.

42. Wallgreen, A. J., BCG, Past, Present and Future, Am. Rev. Tuberc. 76:715, 1957.

43. Wells, A. Q., Vaccination with Murine Type Bacillus (Vole Bacillus), Lancet 2:53, 1949.