LOOKING AT B.C.G. VACCINATION
It's value and limitations in light of recent evidence

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It has been stated by many, familiar with the tuberculosis problem "in high prevalence areas," that "Immunity is the master word in tuberculosis." It is more to be desired than freedom from infection for the latter is an unobtainable ideal. There are still others who hold the opinion that immunity to tuberculosis, either naturally acquired by previous infection, or artificially acquired by BCG vaccination, is of questionable or of no practical value for the individual or for the community. The purpose of this paper is to present some pertinent clinical and statistical data and to try to draw a few practical conclusions which may be of some help to others who are working in this field.

Method and Administration of BCG

B.C.G. is a viable attenuated bovine strain of tubercle bacilli, isolated in 1922 by Calmette and Guerin. The purpose of vaccination with BCG is to produce an artificially acquired immunity to tuberculosis, in contrast to a naturally acquired immunity which follows healing of the primary tuberculous infection.

In 1922 it was shown that BCG vaccination was able to protect cattle against virulent bovine tuberculous infection and its resultant complication. BCG vaccination of newborn infants was first tried at this same time (1922) by Weill, Halle, and Calmette using the oral route. Wallgreen later showed the superiority of the intradermal route and more recently Rosenthal has shown the efficacy of the multiple puncture method of vaccination.

Since 1921, over 100 million BCG vaccinations have been done throughout the world without a single proven incidence of progressive tuberculosis due to BCG. At the present time, there seems to be no question of its safety. There are still current conflicting views and reports as to its efficacy and its usefulness. Is BCG vaccination protective against TB and to what extent and for how long a time? Where does its value lie as an immunological tool and as a practical means of tuberculosis control?

Who may Safely by Given B.C.G. Vaccination?

These are the criteria we find best adapted to

our circumstances here in Korea and they may not be exactly applicable to other localities of low prevalence tuberculosis.

1. Any healthy person with a negative skin test to tuberculin within at least 2 weeks before vaccination.

2. New-born infants within three weeks of delivery without any tuberculin test, if there is no known contact with active tuberculosis in the home. If there is known active tuberculosis in the home, it would be ideal to isolate the newborn for a period of 4-6 weeks prior to vaccination, and then for a period of 4-6 weeks after vaccination, until a "post vaccination-take" can be demonstrated by conversion of the tuberculin skin test. However, since this procedure here is impossible, and since the danger of infection is great, the following policy has proven safe and effective. Where there is a known case in the home, the infant is vaccinated as soon as possible after birth preferably within the first 48-72 hours. If this has been impossible, then the infant is not vaccinated until 6 weeks of age, at which time the tuberculin test should be reliable. Since we have seen cases of full blown clinical tuberculous meningitis and bone TB at as young as 3 weeks of age, we cannot over emphasize the need of vaccination at the earliest possible date following delivery.

3. Poorly nourished infants and malnourished children (at any age) should have a pre vaccination chest X-ray and clinical evaluation. (Even with a negative skin test to second strength O.T.) Active disease with a negative tuberculin in a person in
the pre-allergic stage, or interval period between infection and the production of a positive tuberculin skin reaction, must be ruled out. This period may be as short as 6 weeks or as long and variable as months in debilitated persons, or in overwhelming recent active infection. We are impressed by the high incidence of negative tuberculin skin tests even in well nourished infants and children with clinical and/or X-ray evidence of active tuberculosis. Children with/and clinical symptoms under heavy exposure, even in the face of a negative tuberculin, should have X-rays and physical examination before BCG vaccination.

4. BCG vaccination should not be done in any person while receiving corticosteroid therapy since these drugs can block the allergic skin reaction to tuberculin.

5. Premature or full term infants under 5 lbs. should not be vaccinated.

6. Any person with extensive acute or chronic dermatitis should not be vaccinated.

7. In the presence of fever, or during any acute infectious disease, BCG is contra-indicated.

8. During chronic illness, debility and convalescence, especially from typhoid fever, hepatitis, or nephritis, BCG vaccination is contra-indicated. In such patients not only is the tuberculin skin test unreliable, but because clinically the BCG vaccination like any other immunization may be expected to produce very little immunity in terms of post vaccination conversion of the tuberculin test.

9. BCG vaccination given, even in the presence of active tuberculosis, of itself is not harmful. Except for local ulceration and pain at the site of vaccination. Nor has it been shown to cause a spread or exaggeation of existent tuberculous pathology which was present at the time of vaccination.

BCG Vaccination—nature and duration of immunity

If a successful BCG vaccination can be expected to produce some immunity against tuberculosis, than how do we go about measuring this immunity? The tuberculin skin test is a measure of the body's allergic response to the protein tuberculin. Granted that the tuberculin test, which measures the allergic response, is not a direct or equivalent measure of the immune response of a person to limit the disease process, nevertheless, since it is the only test we have at present, it becomes our "standard of reference."

A successful vaccination, as measured in terms of conversion of the previously negative tuberculin skin test to positive, can be expected to occur from the third to the eighth week after vaccination. Usually the post-vaccination tuberculin positive is slight but a definite 1 plus or 2 plus. If a 4 plus occurs, it probably indicates a superimposed virulent human infection. It must be remembered that it takes at least 6 to 8 weeks for immunity to develop, so that during the immediate post-vaccination period one is highly vulnerable to infection especially with close contacts and overwhelming exposures. The percentage of conversions of the tuberculin skin test following vaccination as reported by various workers is as low as 70% to as high as. To some extent the expected rate of tuberculin 100% conversion depends on the potency, storage and manufacture of the vaccine, as well as the technique and experience of those giving the vaccination. There seems to be little significant difference between the newer preparations of well standardized liquid as compared with the freeze-dried type of vaccine. Good conversions are obtained by either the multiple puncture, sacrifice or intra-dermal route of administration.

Variations in the age groups does not seem to give any significant differences in the percent conversions of the tuberculin skin test. Rosenthal has obtained 99% -100% conversion in the newborn, childhood, adolescent and adult groups. However, the duration of immunity, or the duration of the positive skin test after successful vaccination seems to vary with the different age groups. Persistence of the positive tuberculin can be expected from one to ten-years the average being for approximately three years following BCG vaccination. In the newborn series, 90% of those converted still had their positive tuberculin at the end of 4 years. Whereas in the adolescent group the average duration of immunity following BCG vaccination, as measured by the persistent Positive tuberculin, was
2 years). Repeat re-vaccination may be done whenever, or as often as indicated.

**Post vaccination immunity protective value**

In considering protective value, let us begin with the assumption that immunity by BCG vaccination can be expected to prevent only the majority of ordinary exogeneous Primary Tuberculous infections. The degree of immunity is limited by individual response, by the duration of time in which protective immunity lasts, by the degree of massive or repeated exposures to the disease, as well as the presence of intercurrent disease or malnutrition. With these qualifications in mind, let us review some of the clinical and statistical data from recent well controlled studies.

BCG vaccination when employed as part of a tuberculosis control program, can reduce the mortality and morbidity of primary tuberculosis in infants and children. Case incidence can be reduced from 68 to 100% in the vaccinated group as compared to a tuberculin negative unvaccinated group of the same age. In the Chicago study, it is was shown that BCG can prevent primary tuberculosis is 100% successfully in vaccinated newborns for a one and a half year period where there has been no known exposure before the vaccination has had a chance to “take”. Following this group further for a period of 15 years post-vaccination, it was found that the case incidence of tuberculosis infection in the BCG vaccinated group as compared to the unvaccinated, unprotected control group, was reduced in ratio of 4:1. At the end of 15 years, there were four times as many cases of primary TB infection in a group of 4,128 unvaccinated newborn infants, as there were in a group of 5,737 vaccinated newborns. Tuberculosis, when it did occur in the vaccinated host, produced less extensive lesions than in the non-vaccinated control. The mortality rate from tuberculosis (chiefly from TB meningitis) was 5 times as great in the unvaccinated infected infants as compared to the vaccinated infants who were infected.

In a series of 56,000 adolescent students in Great Britain, it was found that the case incidence of Primary Tuberculosis could be reduced in a ratio 5:1 of BCG (vaccinated as compared to unvaccinated control group. Furthermore-approximately 22% of the infected cases in the unvaccinated tuberculin negative control groups, showed serious complications of a progressive primary type disease, as evidenced by pleural effusions. In the BCG vaccinated tuberculin negative group, there were no complications of progressive type disease. This represents a reduction of 82% in the incidence of primary first infection type tuberculosis in a tuberculin negative BCG adolescent group and no serious complication in a group where danger is ordinarily high. (4) In this same study in Great Britain, a separate group of 13,000 adolescent students, whose positive skin test to tuberculin represented a naturally acquired immunity from a previous primary TB infection, showed an annual case incidence of reinfection TB, less than tuberculin negative unvaccinated group, but greater than the incidence of primary TB in the tuberculin negative BCG vaccinated group.

It would seem therefore, at least in this study, that during a four year period of adolescence, where there is great danger or serious complications from either primary tuberculosis, or reinfection type tuberculosis, that the BCG vaccinated group seemed to carry the greatest protection when faced with exposure or re-exposure to tuberculosis. The same type of conclusions have been drawn by other groups watching the case incidence of tuberculosis in adolescents and young adults under conditions of heavy exposure - i.e. medical students, doctors, nurses, laboratory and hospital personnel.

From our personal clinical observations here in Korea, we feel that the use of BCG vaccination can successfully decrease mortality, case incidence, and the serious complications of primary tuberculous infection. Our experience has been limited to a group of healthy infants from the newborn period to 12(twelve) months of age-the total number successfully vaccinated being 2,236 by Japanese manufactured freeze-type vaccine. Our aim in using BCG vaccination was to protect healthy infants under known or presumed "heavy exposure" to tuberculosis both at home and at our clinic. Since our aim was not to study the efficacy of BCG
vaccination, we have no comparable control group of tuberculin negative unvaccinated Korean children under 1 year of age. Also due to economic conditions, no attempt could be made to isolate these infants from known contacts either before or after vaccination.

Of the children whom we have been able to follow for a two year period after vaccination, 2% became infected with primary tuberculosis as evidenced by hilar enlargement and ormedial widening on x-rays of the chest. There have been no cases of serious progressive complications of primary disease, such as meningitis, pleural effusions, renal or bone tuberculosis, in the vaccinated group, despite known heavy repeated exposure from an open-infected case in the home.

Let us turn briefly from the results of more selected smaller groups, to the conclusions which can be drawn from data on mass-population BCG vaccination programs. These data may vary as we might expect according to geographic location, nutrition, the prevalence of tuberculosis in the general population, housing, etc., all of which have been found to be important factors in determining the rate of tuberculosis in both the vaccinated and the unvaccinated groups. There was variation as to whether this was composed of tuberculin negative and tuberculin positive reactors (in the unvaccinated) or only tuberculin negative unvaccinated controls. The age incidence as well as the number of years for case follow up was a variable. The results in terms of ratio of new cases of tuberculosis among the vaccinated group, as compared to the unvaccinated group, vary anywhere from as low as 1:7-100 in East Germany to as high as 69:100 in Puerto Rico. It must be remembered that in high prevalence areas where it is impossible to isolate the vaccinated from heavy contact exposures, there would necessarily be a higher rate of infection in the 6-8 week period before vaccination “take”. German observers made the following conclusions on their mass vaccination data. BCG vaccination achieves a striking reduction in the incidence of post primary complications especially TB meningitis. The rate of disease incidence between vaccinated and non-vaccinated groups varied from 1:10 to 1:5 in different sections of Germany. Previously tuberculin negative non-vaccinated control groups showed an incidence of tuberculosis seven times that of the vaccinated group. They concluded that they could expect a 51-66% reduction in the incidence of tuberculosis in the age group of the newborn to 25 years, within two years after successful vaccination.

<table>
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<th>Rate of Infection</th>
<th>Tuberculin Neg. Unvaccinated</th>
<th>Tuberculin Neg. BCG vaccinated</th>
<th>Tuberculin Positive</th>
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<td>0.5</td>
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<td>ADOLESCENT S-Britain end of 2½ yrs. normal exposure</td>
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<td>Chicago end of 2½ yrs. heavy exposure</td>
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Vaccination Who Should Receive It?

It becomes apparent that from the vast population of tuberculin negative individuals who theoretically could safely be vaccinated, local conditions will determine where and how we can best concetrate our time and efforts in the use of BCG vaccination.

I. Low Prevalence Areas

1. On the basis of studies in the literature, an appreciable reduction in the incidence of clinical tuberculosis may be anticipated when certain groups of people who are likely to develop tuberculosis because of unusual exposure or inferior resistance, or both, are vaccinated. 

2. In low prevalence areas, where infection rate is falling, most people question the justification for mass BCG vaccination. Under these conditions, its use should be confined to those “living or working at risk”.

II. High Prevalence Areas

1. The need becomes proportionately more
urgent to vaccinate any individual of any age group “living or working at a risk”.

a) Personelle working in hospitals, clinics, laboratories and

b) Individual contacts unavoidably exposed to infectious tuberculosis in the home.

2. Most Vulnerable Age Groups—whether they are under heavy exposure (Direct contact) or normal exposure (from the population)

Natural susceptibility, inferior resistance, increased incidence of serious complications and higher mortality from tuberulous infection occurs in certain age groups. These vulnerable or danger periods are from newborn to 4 years of age, and then again during adolescence and young adult life. If the probable risk of infection is high, as it will be in countries or communities where the over all prevalence of tuberculosis is high, then routine large scale vaccinations of these two groups would be most advantageous and practical. The serious type progressive primary tuberculosis, with the danger of meningeal, renal and bone complications, occurs in approximately 30% of children infected under 3 years of age. Serious complications such as pleural effusions, were found to occur in as high as 22% of an adolescent tuberculin negative group undergoing their primary infection.

In a country such as Korea, where by the end of 4 years, 29% of the children have already been infected, and the end of 19 years, 62.2% have had their primary infection as evidenced by a positive tuberculin, advantages of BCG vaccination become apparent.

In Korea we are faced with the medical problem that financial resources are insufficient to meet the need for adequate chemotherapy in cases urgently demanding it. If we are able, through artificial immunizations to eliminate a 30% group of complicated primary tuberculosis infection, as well as decrease the total number of cases infected by 68 -100%, cannot we readily see the far reaching value of BCG in helping to decrease the potential cases needing chemotherapy among the childhood population? If this can be accomplished, what drugs we have available within our economic resources can be used to best advantage in completely rehabilitating the cases of adult reinfection type of tuberculosis which cannot be prevented by BCG vaccination.

“The ultimate goal in treatment of tuberculosis is full and permanent rehabilitation of the patient. This depends first on prevention of death, next on arrest of the disease and finally on prevention of relapse. In prechemotherapy days, failure too often occurred at the first step, the disease progressed to fatal termination and the death rate was high. Modern antituberculous drugs are truly “miracle drugs” in preventing early fatality, but their very success has created new problems in control of the disease. Many now saved from death cannot be cured from tuberculosis, but become chronic invalids alive but not rehabilitated, constantly threatened with relapse, a burden to the community and a source of infection to their associates.” (8) This has become one of the major tuberculosis problems, especially in countries of high prevalence like Korea, where the total number of cases needing drugs far exceeds the financial resources for adequate long term chemotherapy. The extremely high rate of relapse from inadequately treated cases, both of primary extra pulmonary complications as well as reinfection a dult type pulmonary tuberculosis, is at present a major unresolved medical problem, as well as a constant community threat. Thus mass BCG vaccination of the vulnerable age groups in high prevalence areas, seems to take on new and important value in terms of future tuberculosis control.

BCG in Tuberculosis Control

In a country of low prevalence tuberculosis such as the United States, it has been stated that the greatest public health hazard or problem is in the group of tuberculin positive population facing the dangers of reinfection tuberculosis%. BCG vaccination is of no value in this group. Following from this, very few people will be infected with primary tuberculosis during the danger age when extra pulmonary complication are high. When less than 5% of the population will be infected under 19 years of age as estimated by the positive tuberculin test, certainly the complications of primary tuber-
tuberculosis, will never become an overwhelming therapeutic or public health hazard. In such low prevalence areas, prophylactic chemotherapy seems to have practical value, since it has been found to be 80% effective in preventing extrapulmonary complications of asymptomatic active primary tuberculosis in children under 3 years of age. This also tends to de-emphasize the importance of 'BCG vaccination in tuberculosis control.

In contrast with this, in countries of high prevalence, the public health hazard is equally great as a result of infectious cases complicating primary disease, i.e., renal, bone, glandular lesions, as the hazard resulting from open cases of reinfection type adult pulmonary tuberculosis. In a country, where one out of every 3 children faces the danger of ending up with a life-crippling complication, primary tuberculosis is not only a danger to the individual but a threat to the community large. As we have pointed out before, any attempt to decrease complications by using prophylactic chemotherapy on all asymptomatic primaries under 3 years of age in high prevalence areas, would be a financial impossibility, or at least an unrealistic appraoch. In Korea, BCG vaccination becomes a more effective and less expensive tool, since it can be expected to reduce the incidence of complications in primary tuberculosis by 98-100%.

Summary and conclusions

1. BCG seems to find its value by permitting the safe substitution of a non-virulent organism which does not risk progressive clinical disease for the virulent organism of primary tuberculosis infection in an age group where the risk is high, or where exposure is heavy.

2. An attempt has been made to show what benefits are derived by immunity thus acquired as well as financial saving for necessary and adequate chemotherapy in high prevalence areas with limited economic resources.

3. That a positive tuberculin test from naturally acquired infection is of any protective value to a person faced with the dangers of reinfection tuberculosis, is still open to controversy and contradicting statistics. Whether this be a fact or not, one can conclude that a positive tuberculin from artificial immunity acquired through BCG vaccination is of definite advantage to an individual when facing his first or primary infection from tuberculosis.

4. The advantages of letting a child in a high prevalence area face his primary infection without any immunity, relying on chemotherapy to prevent complications or to treat them should they occur, seems open to serious question.

5. Both mass population BCG vaccination as well as smaller well controlled studies in various countries have shown that BCG vaccination can reduce the incidence of infection from tuberculosis anywhere from 50-100% depending on the age group vaccinated, the number of revaccinations, the follow up period and the period of isolation or direct exposure following vaccination. BCG vaccination in all studies has shown the ability to reduce serious complication of primary tuberculosis by 98-100%.

6. Reduction in total case incidence and their complications by BCG, automatically assures more adequate chemotherapy, fewer recurrences, fewer relapses and better rehabilitation for a greater number of cases.

7. In Korea, future tuberculosis control needs emphasis on the side of immunity, for prevention of infection is as yet an unobtainable ideal, prophylactic chemotherapy a financial impossibility and therapeutic drug rehabilitation cannot be effective until total case incidence and complications are partially reduced.

8. Although the value of BCG vaccination in a tuberculosis control program is widely recognized, it must be remembered that it is a supplement to, and not a substitute for, any of the other recognized control measures. As relative values and limitations of other control measures become apparent in a given area, BCG assures an important role in protecting the individual as well as the Community.

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