REVIEW ARTICLE

PRESENT STATUS OF IMMUNISATION AGAINST TUBERCULOSIS

G.V.J. BAILY*

The discovery of the tubercle bacillus by Robert Koch in 1882 and his classical demonstration, in 1891, of the effect of a second infection with tubercle bacilli in an already tuberculous guinea pig, which later came to be known as the ‘Koch phenomenon’, heralded scores of attempts to develop a specific immunising agent against tuberculosis, derived from the tubercle bacillus. The attempts were indeed inspired by the observations of Edward Jenner who about a hundred years earlier, in 1798, had also noticed the increased reactivity to vaccinia virus occurring in persons who had been previously vaccinated or who had had smallpox.

In animal experiments conducted over the years, the immunising capacity of four distinct types of ‘vaccines’ were studied: preparations consisting of small numbers of living tubercle bacilli; preparations containing mycobacteria that are non-pathogenic to man but pathogenic to certain animals or birds; products of tubercle bacilli or tubercle bacilli themselves, killed by a variety of physical and chemical methods and finally, preparations containing attenuated variants of originally virulent strains of tubercle bacilli pathogenic to man (Weiss 1959, a b, c).

The first was never widely tested and discarded as too hazardous. The second i.e. several mycobacteria that are non-pathogenic to man, were shown to be ineffective until the discovery of the effect of the Vole bacillus (M. microti) which causes naturally occurring disease among field rats (Wells, 1937) and is also pathogenic to certain other species of animals including the guinea pig. Vaccine prepared from the vole bacilli was shown to offer significant and measurable degree of protection in man (Medical Research Council, Great Britain, 1972). The first attempts to induce immunity with killed tubercle bacilli or their products were initiated soon after the discovery of the tubercle bacillus. For instance, Daremberg in 1889 reported that several rabbits which had been inoculated with cultures of tubercle bacilli sterilised by heating for 15 minutes at 115°C or for six hours at 70°C survived longer after virulent challenge infection. Later his claim was not substantiated by others. Since then scores of animal experiments using non-living vaccines have been reported (Weiss 1959, a b, c) with conflicting results. One of the possible reasons for these conflicting results could be the fact that the test-systems used for testing the vaccines in animal models varied from experimenter to experimenter, as is seen in the varying results in the potency assay of the same BCG vaccines in different BCG laboratories (Smith, et al 1971). Thus, non-viable vaccines have never been employed though interest in these vaccines has not ceased even to-day. Although Vole vaccine has been shown to confer a significant degree of protection, vaccination with Vole vaccine causes some unpleasant reactions at the site of vaccination and as such has never been practised on any large scale. Thus, the only vaccine that has been used, and used extensively through out the world, is the BCG (bacille Calmette Guerin) which is an attenuated variant of M.bovis. BCG vaccine does not cause progressive disease in man except in the extremely few recorded cases and under exceptional circumstances. It is also avirulent in experimental animals except the Syrian golden hamster.

Virtual since BCG vaccine was introduced by Calmette and Guerin in 1921, it has been a subject of controversy. It was introduced in Europe at a time when Europe was just recovering from the ravages of a war and tuberculosis was quite common, and interest in BCG, considerable. With greater ‘experience’ which was not uniform, interest in many countries including United States and Britain waned. Scandinavian countries however have always been very enthusiastic about BCG vaccination. In the post second world-war years, massive BCG vaccination campaigns were organised in Europe through the International Tuberculosis Campaign with Headquarters in Copenhagen. Tuberculosis at that time was still relatively common and the privations of war had aggravated the situation in many countries. Soon after, BCG was introduced in many developing countries of the world and in India, it was first tried out in 1948 and vaccination programme started on a large scale, as a mass campaign, in 1951.

By 1950, even though BCG vaccination was in use for nearly 30 years and several BCG campaigns had already started, the opinion about BCG in many developed countries, especially Britain and United States could only be considered as lukewarm. This was best stated by D’Arcy

*Tuberculosis Specialist, National Tuberculosis Institute, 8. Bellary Road, Bangalore-560 003.

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Hart et al as “….moderate opinion on BCG in Britain and in the USA in 1949 might have been summarised as follows: (1) it gave some protection in those specifically exposed to tuberculous infection in their homes or at work; (2) it could be expected, at least in general populations with low standards of living and high tuberculosis rates, to reduce the incidence of tuberculous disease appearing within a few years of a natural first infection with tubercle bacillus ….” (Hart, Pollock and Sutherland, 1957).

Opinions on the efficacy of BCG Vaccine were formed, in addition to the demonstration of its effects in animal models, in several ways: Observations based on ‘experiences’ with the use of BCG, early uncontrolled observations and studies on the protective effect of BCG and, the results of controlled trials. While the first two could be considered to be easily influenced by several factors, more recent observations indicate that conflicting results obtained even in well controlled trials could have been due to one or more factors as yet un-identified.

Protective Effect of BCG Vaccine

Though all BCG vaccine produced in the world in dozens of BCG laboratories to-day, comes from the original BCG culture produced by Calmette and Guerin, characteristics of the vaccines produced in different laboratories vary. This is because with repeated subculturing, the genetic characteristics of BCG (or, for that matter, several micro-organisms) undergo change. As a result of repeated sub-culturing, the changes in the BCG produced in one laboratory may not be the same as the changes obtained in another. In one instance, only the morphological characteristics of the bacilli may have changed with no changes in the protective effect. In another, while the morphological characteristics are not affected, the protective effect may have changed considerably. It is therefore, common practice to refer to BCG produced in different laboratories as ‘strains’ of BCG. Thus, BCG produced in Madras is referred to as ‘BCG-Madras’ (strain 1331) and BCG produced in Paris as ‘BCG-Paris’ (strain 1173) etc. In animal experiments, most strains of BCG show a higher or a lower protective effect measured as the survival time of the animals (guinea pig, mice etc) which have been vaccinated and later challenged, i.e. infected, with virulent tubercle bacilli, as compared to those that are not vaccinated but are only challenged. (Ladefoged, Bunch-Christensen and Guld, 1970).

In man, however, evidence of the protective effect of BCG vaccination can be obtained through clinical observation, or better still, through controlled trials. Literature is replete with reports on observations and controlled trials but most of these cannot be considered as statistically valid.

The first controlled trial which can be considered as statistically valid was started by Aronson and others (1958) in 1935. Prior to this study, most of the evidence in favour of a protective effect of BCG in man came from clinical observations. Some of these observations were more solid than the evidence available for several other prophylactic measures and are discussed below.

The earlier observations and studies

Heimbeck’s studies:

One of the earliest observations and studies on BCG were those by Heimbeck in Norway. In 1924, Heimbeck (Heimbeck, 1948), started tuberculin testing the staff of the Oslo municipal hospital in Norway. The hospital then had about 2,000 beds and about 300 of those were occupied by patients suffering from tuberculosis. He had observed that many nurses developed tuberculosis within a few years after joining nursing. Table 1 presents the fate of the nurses joining in 1924, 1925 and 1926. Of the 109 nurses joining in 1924, 58 were tuberculin positive and 51, tuberculin negative. By the end of three years, only one of the 51 nurses who was tuberculin negative continued to be tuberculin negative and all the others had converted to the tuberculin positive state. Over the next few years whereas only 1 case of tuberculosis developed among the initially tuberculin positive, among the 51 initially tuberculin negative nurses, 18 cases developed with 7 deaths. The fate of the cohorts admitted in 1925 and 1926 was also similar except for deaths in the tuberculin negatives.

Observing this striking fate among those initially tuberculin negative nurses, Heimbeck offered, from 1927 onwards, BCG vaccination to all tuberculin negative new entrants. He, however, did not compel them too much to get vaccinated with the result that of the 899 nurses (Table 2) admitted between 1927 and 1934, 436 were tuberculin positive, 95 were tuberculin negative but refused vaccination, and 368 were tuberculin negative and BCG vaccinated. Whereas 42 cases of tuberculosis developed among the 95 unvaccinated tuberculin negatives, 37 cases developed among the 368 vaccinated tuberculin negatives during the following few years after vaccination - a reduction of about 76 percent.
Table 1

Heimbeck’s observation among student nurses in Oslo

<table>
<thead>
<tr>
<th>Year of admission</th>
<th>Tuberculin Positive</th>
<th>Tuberculin Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Cases of TB</td>
<td>Deaths</td>
</tr>
<tr>
<td>1924</td>
<td>58</td>
<td>1</td>
</tr>
<tr>
<td>1925</td>
<td>42</td>
<td>1</td>
</tr>
<tr>
<td>1926</td>
<td>52</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2

Heimbeck’s BCG study among student nurses in Oslo: 1927-1934

<table>
<thead>
<tr>
<th>Tuberculin and BCG status on entry</th>
<th>Nos.</th>
<th>Cases of Tuberculosis</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tub. Positive</td>
<td>436</td>
<td>27</td>
<td>6.2</td>
</tr>
<tr>
<td>Tub. Negative, Not vaccinated</td>
<td>95</td>
<td>42</td>
<td>44.2</td>
</tr>
<tr>
<td>Tub. Negative, BCG vaccinated</td>
<td>368</td>
<td>37</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Table 3

Hyge’s study: An Epidemic of Tuberculosis among School girls during the second World War

<table>
<thead>
<tr>
<th>Status before Epidemic</th>
<th>Students exposed</th>
<th>Cases of tuberculosis (Primary)</th>
<th>Progressive Pulmonary T.B. over 12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tub. Negative</td>
<td>94</td>
<td>41</td>
<td>20</td>
</tr>
<tr>
<td>Tub. Negative, BCG vaccinated</td>
<td>106</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Tub. Positive, Not vaccinated</td>
<td>105</td>
<td>1</td>
<td>14</td>
</tr>
</tbody>
</table>

The fate of the pupils is shown in a summarised form in Table 3. While of the 94 who were tuberculin negative and were not vaccinated, 41 cases of primary tuberculosis occurred, among the 106 tuberculin negatives vaccinated with BCG, no case of primary tuberculosis occurred. The development of progressive primary disease is also presented. Though this is a retrospective study, and again, not statistically fully valid, the complete absence of primary disease among the vaccinated is striking and can scarcely be explained as being entirely due to bias. Indeed the above two studies gave strong indications of the protective effect of BCG in man and provided an impetus for planning statistically valid studies to obtain irrefutable proof of the protective effect of BCG.

Hyge’s study:

An epidemic of tuberculosis in school girls aged 12-18 years, has been described by Hyge (Guld, 1980). The epidemic occurred in a blacked out air-raid shelter where all the pupils were exposed to infection by chance. This occurred 1-3 months after routine tuberculin testing (Mantoux 100 units) and X-ray examination of all pupils and one year after BCG vaccination of the majority of tuberculin negatives.

among vaccinated. This early observation of Heimbeck cannot be considered as absolute proof of the protective effect of BCG mainly because the 95 ‘controls’ were self-selected and thus the allocation was far from blind. Even so, since the study population was all uniform i.e. all women aged about 20 and all belonging to urban middle class families, of similar socio-economic status and exposed to similar risk of infection, the study can be considered as of interest and provided one of the first evidences of the protective effect of BCG in humans.
The controlled trials

Controlled trials have come to be recognised as the most reliable methods of establishing the efficacy of therapeutic or prophylactic measures in man and confirm what has been studied in animal models as also from ‘experiences’ from application in humans. The trials are meant to establish not only that a curative or a prophylactic measure is effective, but the actual degree of efficacy. In these trials, after the safety of the measures is assured and ethics of the study examined, the hypotheses are clearly laid down, subjects (persons) among whom the studies will be conducted are carefully identified, the appropriate design selected and meticulous care is exercised in the follow-up of all subjects for the same period of time. Possibly, the most important characteristic of these trials is that, neither the person who administers a measure nor the subject to whom it is administered decides which measure is applied to whom. Subjects are allocated to the measures through a double-blind randomised scheme.

In the BCG trials, following an appropriate randomisation scheme, subjects are allocated either to ‘BCG vaccination’ or to ‘no BCG vaccination’ (controls) blindly. All the subjects are followed-up for a specified and the same duration of time, to identify the new cases of tuberculosis arising from among them. (It will be obvious that preliminary investigations are carried out to exclude from analysis of the protective effect persons who at the time of allocation are either infected or are actually suffering from tuberculosis). The protective effect of BCG is expressed as the proportion by which the incidence of new cases is reduced among the vaccinated as compared to the controls.

A very large number of BCG trials have been reported in the literature. Most of these trials, for one reason or another do not satisfy the criteria mentioned above and are thus statistically not valid. As up to the time that the Chengleput study of the protective effect of BCG vaccination was started, the studies indicated in Table 4 can be considered as some of the studies that are statistically valid and conducted in the general population.

Table 4

<table>
<thead>
<tr>
<th>Trial and age of subjects</th>
<th>Intake period</th>
<th>Duration of follow-up yrs</th>
<th>Vaccination group</th>
<th>No. of subjects</th>
<th>Cases of tuberculosis</th>
<th>Protective effective %</th>
</tr>
</thead>
<tbody>
<tr>
<td>North Amer.* Indians (9) 1-13 yrs.</td>
<td>1935-38</td>
<td>9-11</td>
<td>Control BCG</td>
<td>1457</td>
<td>238</td>
<td>64</td>
</tr>
<tr>
<td>Georgia (14) 6-17 yrs.</td>
<td>1947</td>
<td>12-23</td>
<td>Control BCG</td>
<td>2341</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Puerto Rico (13)</td>
<td>1949-51</td>
<td>5½-7½</td>
<td>Control BCG</td>
<td>27338</td>
<td>73</td>
<td>93</td>
</tr>
<tr>
<td>Georgia, Alabama(21) 5+years</td>
<td>1950</td>
<td>14</td>
<td>Control BCG</td>
<td>17854</td>
<td>32</td>
<td>26</td>
</tr>
<tr>
<td>Great Britan (5) 14-15 ½ yrs.</td>
<td>1950-52</td>
<td>15</td>
<td>Control BCG</td>
<td>12699</td>
<td>240</td>
<td>56</td>
</tr>
<tr>
<td>Madanapalle (15) All ages</td>
<td>1950-55</td>
<td>9-14</td>
<td>Control BCG</td>
<td>5808</td>
<td>46</td>
<td>28</td>
</tr>
</tbody>
</table>

*Figures in brackets indicated the reference nos. of the reports on these studies.
The first of these studies was conducted among the North American Indians (Aronson, Aronson and Taylor, 1958). The study population was characterised by low socio-economic conditions and a high risk of tuberculous disease. At about the 10th year of follow-up the incidence of tuberculosis cases among the vaccinated was 80% less than the incidence among controls. At the time of the final follow-up i.e. at about the 18th year, the protective effect was still of the order of 72% since there were 42 cases of tuberculosis among the BCG vaccinated compared to 185 cases among the controls. In this study not only the emergence of new cases was evaluated but also, the deaths were carefully assessed. As at the and of follow-up, there were 13 tuberculous deaths among the BCG vaccinated compared to 68 tuberculous deaths among the controls giving a protection of 82%. Acid fast bacilli could be demonstrated among 5 deaths vaccinated and among 27 deaths that were not vaccinated again giving a protection rate of 82%. On the whole, this early but well conducted study indicated a protective effect of about 80%.

Similarly, three other studies were started in different parts of United States of America during the late forties. In the study in Puerto Rico, started in 1949, the protective effect of BCG has been assessed in 27,338 controls and 50,634 vaccinates. As at about 6 years the protective effect was 31% (Palmner, Shaw, and Comstock, 1958) while at the 18th year of follow-up it still was the same i.e. 28.7% (Comstock, Livesay and Woolpert, 1974). The effect was similar in different age groups. In another study in Georgia in a population of about 5,000 children aged 6-17 years, no protective effect of was observed. In the third American study in Georgia and Alabama a very modest protective effect of was observed. In the third American study in Georgia and Alabama a very modest protective effect of about 14% was observed. (Comstock and Webster 1969).

The Medical Research Council (MRC), Great Britain carried out a study among British school leavers (all aged 14-15 ½ years) wherein 12,699 were unvaccinated and 13,598 were offered BCG vaccination. The protective effect was assessed at various intervals for 15 years and it was found that it was almost constant at about 80%. This was also true when the effect was assessed against different manifestations of tuberculosis. In the same trial, another section of the study subjects had been vaccinated with Vole vaccine and in them also the protective effect of Vole vaccine was similar to that of BCG, i.e., about 80%. In a small study in a general population of about 10,000 persons in Madanapalle in South India, the protective effect as at about 9-14 years after vaccination was assessed to be about 30% (Frimodt-Moller, Acharyulu and Parthasarathy, 1968).

It will thus be observed that while animal models almost always showed a measurable degree of protection by BCG, experience in humans varied considerably. In the words of Ian Sutherland, who was always associated with the MRC trial in Britain, “…the instinctive reaction of any scientific worker, when he finds that his results differ from those of another scientific worker, is to mistrust the other man’s results, and so it was not surprising that there was a good deal of coming and going across the Atlantic between the MRC workers and the U.S. Public Health Service Workers, each group prepared to be very critical about the other’s investigations. The results of this exercise have, however, been entirely beneficial in that our mistrust has been dispelled …” (Sutherland, 1971). After considerable deliberations, they agreed that, of the many reasons that can be associated for the lack of protective effect in American studies, two reasons might be the most relevant; firstly, the vaccine used in some of the American studies could have been prepared from poor strains of BCG and secondly, that infection with atypical mycobacteria prevalent in the United States may have offered some degree of protection which masked the protection offered by BCG. When the Chingleput study was planned and started in 1968, this was the state of knowledge regarding the protective effect of BCG vaccination.

The Chingleput BCG trial

In 1963, the Government of India took up the question of conducting a BCG trial in India. There was still some controversy in the country about the use of BCG and it was felt that the problem had to be settled by a controlled field study under Indian conditions. The study (Tuberculosis Prevention Trial, Madras, 1980) was planned in collaboration with the World Health Organisation and the Center for Disease Control, United States Public Health Service and conducted by the Indian Council of Medical Research as a separate project.

The study was undertaken in Trivellore taluk of Chingleput district in Tamil Nadu. The intake (i.e. admission of population to the study) was started in July, 1968 and completed in March, 1971. During this period, a total population of about 3,60,000 persons in 209 contiguous villages and one town were registered on individual cards. All persons aged one month and above were offered one of two doses of BCG vaccination (0.01 mg or 0.1 mg) or a placebo on a random
basis. Two strains of BCG, the Copenhagen and BCG, the Copenhagen and the Paris strains were used. At the same time, all persons aged 1 year and above were tested with Tuberculin (PPD-S) and an antigen prepared from an atypical mycobacteria (PPD-B), the former, to elicit the status of infection with *M. tuberculosis* and the latter to elicit infection with atypical mycobacteria. All persons aged 10 years and above were also X-rayed and for those in whom X-rays showed any abnormality sputum examination by direct smear and culture was done.

The study population was systematically and intensively followed up by X-ray and sputum examinations in an effort to diagnose all new cases of pulmonary tuberculosis occurring in the community. In addition, representative samples of population were tuberculin tested using PPD-S in order to elicit the status of tuberculin sensitivity after BCG vaccination.

The population was characterised by high prevalence and incidence of tuberculous infection as well as high prevalence of non-specific sensitivity. The overall prevalence of tuberculous disease (pulmonary) was also high being very much higher in males than in females.

Table 5 presents, in brief, the main results regarding the protective effect of BCG vaccination in the prevention of pulmonary tuberculosis as observed in the study.

Table 5
*The Chingleput BCG trial: Results* (7 ½ Years)

<table>
<thead>
<tr>
<th>Tuberculin reaction at intake</th>
<th>Given standard Dose BCG (0.1mg.)</th>
<th>Given standard Dose BCG (0.01mg)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7mm</td>
<td>37</td>
<td>37</td>
<td>28</td>
</tr>
<tr>
<td>8-11mm</td>
<td>14</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>

(i) Distribution of definite bacillary cases of pulmonary tuberculosis only.
(ii) Results similar for less definite bacillary cases (culture negative on one specimen only) and cases positive on X-ray only.
(iii) Nos. vaccinated are similar in all three groups.

The table shows the distribution of new cases of pulmonary tuberculosis that were positive on culture of at least two specimens of sputum i.e. in all probability, these were definite cases of tuberculosis. The protective effect is studied among those who were initially tuberculin negative i.e. reacting with 0-11 mm to PPD-S. These are again divided into two groups, one reacting with 0-7 mm i.e. definitely not infected at intake and the other reacting with an induration of 8-11 mm. Some of the latter could be considered to have been infected with *M. tuberculosis*. Because of the large size of the study population the denominators can be taken as similar. The difference observed between the three groups do not attain statistical significance. Thus, BCG gave no protection against the development of bacillary pulmonary tuberculosis in this study. The results were similar when analysis was done for less definite bacillary cases as well as X-ray positive but abacillary cases.

Current Status of Immunisation Against Tuberculosis in India Based on the Results of Well Conducted BCG Trials

The Chingleput study was conducted on the hypothesis that BCG offers protection against tuberculosis and one of the objectives was to measure the exact degree of protection offered by BCG. With the present result in hand it is scientifically appropriate to examine the possible reasons for this result.

The study was meticulously conducted and the procedures followed were constantly monitored in order to obtain accurate results. Even so, a committee of experts was appointed to scrutinise the methodology and it, concluded that no errors could have been introduced. In further discussing the possible reasons for this result in the Trial in India, one major assumption is made. That all trials listed in Table 4 and the percent one are scientifically valid. Only those hypotheses that are amenable to testing are presented.

One of the reasons put forward by the American workers was that the low protective effects observed in the trials conducted in the U.S. were due to the masking of the protective effect of BCG by the protection afforded by previous infection with atypical mycobacteria. Examining the problem in animal studies, Palmer and Long (1966) found that atypical mycobacteria do give some protection against tuberculosis in animals. While BCG confers about 80% protection, photochromogens confer 68%, Scotochromogens and non-chromogens 50% and rapid growers 15%. Further, if animals which have been previously infected with photochromogens, are injected with BCG the protection is not additive but goes up to 80% as in the case of BCG. Thus—in an animal study, if animals are first infected with photochromogens and then vaccinated with BCG...
the protection that will be attributable to BCG would be only 12% (= 80%-68%). If what is observed in animals is true of man, then in areas with high prevalence of non-specific mycobacteria in the environment, only the residual protection would be observed in the BCG trials. As has been said earlier, the prevalence of nonspecific sensitivity was very high in the study area indicating a high prevalence of environmental atypical mycobacteria.

A rough estimate of the type (photochromogens, scotochromogens, etc) of environmental mycobacteria prevalent in the area of the study can be obtained from cultures of sputum samples collected from study subjects, usually in a survey such as this, at their homes. From the sputum samples collected under field conditions, such environmental mycobacteria would be grown as contaminants. In the over 2,00,000 sputum samples collected and cultured during the study, in nearly 6% such contaminants were grown indicating the very high prevalence of environmental atypical mycobacteria. However, it was observed that most of the mycobacteria were those that gave only a low degree of protection. In effect, only 1% of all the atypical mycobacteria isolated were typed as photochromogens which were shown by Palmer and Long to confer a protection close to that of BCG. If BCG were to confer a high degree of protection of the order of 80%, one should have observed some residual protection in the study population since most infections with atypical mycobacteria would probably be caused by organisms that confer low degree of protection. Thus infections with atypical mycobacteria may not, at least fully, explain the zero protection observed in the study.

Disease occurring as a direct extension of the first infection (primary) itself is most common in children and the forms of disease can be termed as childhood forms of tuberculosis. These include, besides the primary complex, complications such as miliary, meningitis, bone and joint tuberculosis etc. In contrast, adult forms of tuberculosis represented mainly by cavitary pulmonary tuberculosis is considered to be mainly a result of later endogenous reactivation of a healed primary complex, and not as a result of another exogenous reinfection with tubercle bacilli. Since Koch demonstrated that a second infection with tubercle bacilli in a guinea pig is far more difficult than the first, it has occurred to most workers that much of adult forms of tuberculosis occur as a result of endogenous reactivation. The role of BCG was based on this hypothesis as it will be obvious that if exogenous reinfection is the main cause of adult type of tuberculosis, BCG obviously cannot help.

In Chingleput area, infection with tuberculosis is very high and the virulence of M. tuberculosis isolated in the area is probably low. If the high incidence of tuberculous infection results in exogenous reinfection being the prime cause of adult forms of tuberculosis, BCG may not be expected to protect against such disease. This hypothesis appears promising in explaining the complete lack of protective effect in Chingleput study. Attempts are being made to investigate this hypothesis. This is relevant not only for the explanation of the failure of BCG to protect in this study but also for the Tuberculosis Programme in general.

Several other hypotheses can be put forward. Two of these are: the differences in immunological responses in different population groups; the effect of nutrition on immunological responses in the body. While the former could be investigated, the latter appears to be not relevant because one cannot classify the entire population of the study area as undernourished or malnourished. Further, tuberculin sensitivity, which is and immunological response to antigens derived from the tubercle bacilli, is not influenced by the state of nutrition in the population. In a study by Ganapati and Chakraborty (1981) where the state of under-nutrition was classified into 4 grades depending on the severity of under-nutrition, tuberculin sensitivity status was similar in children on all the four grades of undernutrition as also in children classified as normal.

The present status of BCG vaccination stems from the knowledge as it stands to-day, BCG offered no protection against pulmonary tuberculosis. At the same time, one cannot assume that BCG may not protect against childhood forms of tuberculosis, which were not investigated in the trial. It is however quite likely that BCG would protect against such disease for the following reasons: disease forms in animal studies, where BCG almost always conferred a measurable degree of protection, resemble more closely childhood forms of tuberculosis rather than adult forms. Secondly, several controlled trials wherein protection against other forms of tuberculosis has been investigated (Medical Research Council, 1972; Rosenthal et al 1961) have shown that BCG offers protection against childhood forms of tuberculosis. It is thus appropriate that BCG vaccination, at present in India, is limited to the prevention of tuberculosis in childhood.
In all studies, except the small study in Madanapalle, where BCG was shown to be protective, it was demonstrated that the protection was durable i.e. it lasted as long as the follow-up of the population was continued. This is true irrespective of the degree of protection as evidenced in the British trial where the protection was high, and Puerto Rico where the protection was low. On this basis, if a good vaccination is offered at an young age, revaccination may not be indicated as, in those studies, protection lasted from 15 to 20 years. Primary infection is most frequent in the younger ages and so is primary disease. Thus if BCG vaccination has to be given to prevent primary disease, it should be given before primary infection occurs i.e. in India well before the age of 5 years. After 20 years of age, primary infection is less frequent in India and risk of primary disease even less frequent. Revaccination is indicated only when the first vaccination has not been satisfactory i.e. given either with a poor vaccine with a poor technique. It may however be remembered that post vaccination allergy tends to wane with time (Tuberculosis Prevention Trial, 1980) and deciding on revaccination on the basis of waned post-vaccination allergy may not be quite appropriate. In animal experiments it has been shown that BCG induced allergy wanes very fast but can be restored by repeated tuberculin testing. With the waning of allergy, the acquired resistance does not wane nor, at the same time, with restoration of allergy by repeat ‘tuberculin test’ is the acquired resistance enhanced (Magnus, 1957). In a study in children it was shown that BCG induced allergy wanes with time but can be restored by repeated tuberculin testing. Thus, revaccination may be practised only if a group of children vaccinated very early in life show poor post-vaccination allergy shortly after vaccination say between 2 to 6 months. For all practical purposes, revaccination is not indicated if the first vaccination has been good. Discussed above is the status of immunisation against tuberculosis in India to-day. In developed countries, with the sharp decline of tuberculosis, interest in immunisation has also declined. However, developing countries like India, which have missed those winds of change, may have to continue their interest in immunisation. The story of immunisation against tuberculosis is not yet over.

REFERENCES


