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THE CASE AGAINST B.C.G.

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Since 1882 numerous attempts have been made to produce immunity artificially in tuberculosis. A large number of preparations have been produced and tried. Some have consisted of living bacilli of various degrees of virulence and types, while others have been composed of fractions of or whole organisms killed by different methods, including heat, electricity, chemicals, etc. None of these preparations has passed the controversial stage. This is probably because an attack of tuberculosis does not result in dependable immunity, so the disease is notoriously a relapsing one.

There are about half a dozen preparations referred to as vaccines now being recommended as immunizing agents in various parts of the world. The one at present in the ascendancy is bacillus Calmette–Guérin (B.C.G.).

As good or better results in tuberculosis control have been reported in parts of the world where only fundamental methods have been employed as in other places where B.C.G. has been added.

The main purpose of this paper is to call attention to various items in the natural history of tuberculosis, and the factors which seem to have been most important in the relatively rapid-changing tuberculosis scene.

It was recently stated that there were approximately 100,000 newly reported cases of tuberculosis in the United States in 1930 and in 1954, inferring that nothing was accomplished in the interim (Medical Advisory Committee of Research Foundation, 1957). The actual figures were 124,940 in 1930, 100,540 in 1954, and 68,866 in 1956—a decrease of 44.9%. In 1930 most of the reported cases were found because they were ill. Presymptomatic lesions in a large number of persons that year were not sought. In 1954 and 1956 the number of cases examined because of symptoms had decreased. To those cases, however, were added many persons whose disease was detected in the pre-symptom stage by periodical examinations, mass surveys, and the like.

More precipitous decreases occurred in mortality. In 1930, 86,142 persons died from tuberculosis—a death rate of 70.2 per 100,000 population; but in 1954 there were only 17,074 deaths and in 1956 14,061 deaths—rates of 10.2 and 8.4 per 100,000. Children and young adults profited most, as they were born after the fundamental protective measures such as sanatoria and control of disease in animals were instituted. Among persons from birth to 24 years, between 1942 and 1946 the annual number of deaths was over 9,000; whereas in 1956, 600 died. In 1942, 2,702 children from birth to 14 years died from tuberculosis, whereas in 1956 there were 290 deaths. The mortality rate decreased more than the case rate because of new methods of treatment, which at least postponed death for many tuberculous persons.

There is an estimated backlog of approximately 56,000,000 persons harbouring tubercle bacilli. These individuals and those whom they may infect provide the new clinical cases. Under present conditions the case rate cannot decrease very fast. In fact, it will depend upon the dwindling of the backlog of infected persons which is taking place by preventing tubercle bacilli from invading the young and by exodus of the older generations, where most of the tubercle bacilli lurk.

Marked decrease has occurred in the tuberculous infection attack rate. Indeed, tuberculous infection in infancy has become relatively rare in most places. Among children of grade-school age, usually not more than 2 to 3% in rural areas react to tuberculin. Even

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in one city of half a million people, infection decreased from 47% among grade-school children in 1926 to less than 4% in 1954 (Myers, Gunlaugson, *et al.*, 1955). In Syracuse, testing of junior high-school students in 1934 revealed 34.7% reactors, but in the school year 1957–8, only 3.7%.

From 1949 to 1951 Palmer *et al.* (1956) tested more than 120,000 white men and women, 17 to 21 years of age, with an intermediate dose of tuberculin. They included Navy recruits from all parts of the United States and students, mostly freshmen, attending colleges and universities in 17 states. Only 8.8% reacted.

On the basis of actual tuberculin-testing in a few counties, it has been estimated that about one-third of the people of the United States are harbouring foci of tubercle bacilli. Most of these persons are 40 years or older. In a county-wide tuberculin-testing survey in Minnesota, Jordan and Jordan (1954) found 50.8% of women and 59.3% of men between 60 and 69 years old reacted to tuberculin. As children they were provided little or no protection against tubercle bacilli. It is they who are now contributing the bulk of morbidity and mortality from tuberculosis. In the entire state in 1957, the tuberculosis mortality rate was 3.1 per 100,000. However, 85% of the deaths were in persons 40 years or older and 52% were 60 or older. From birth to 24 years only four (4.8%) deaths occurred. There were corresponding morbidity percentages in the various age groups.

Inasmuch as most B.C.G. proponents recommend it only for those uninfected, it would not be applicable to the approximately 56,000,000 citizens in the United States who already are tuberculin reactors. Moreover, among the remainder the tuberculous infection attack rate has reached such a low ebb that relatively few would be expected to become infected—and it is still decreasing. Furthermore, treatment now available is effective for recently developed clinical lesions.

Veterinarians of Canada and the United States put B.C.G. to most rigid tests among the cattle herds in the late 1920s and early 1930s, but they found it neither practical nor efficacious. In some other areas of the world B.C.G. has been abandoned as a part of the tuberculosis eradication programme. International organizations dealing with livestock diseases in Europe, including the International Office of Epizootics, the World Health Organization, and the Organization for European Economic Co-operation, recognize the incompatibility of B.C.G. vaccination with proved methods of control based upon use of the tuberculin test. These bodies are on record as recommending that such products as B.C.G. and vole bacillus be omitted from control programmes designed for eventual eradication of bovine tuberculosis (O.E.E.C., 1952).

Specificity of the Tuberculin Reaction

From 1908 to 1912 Anton Ghon (1916) did careful necropsies on the bodies of 184 children who during life showed no evidence of tuberculosis except reactions to the epidermal tuberculin test (Pirquet). Tuberculous lesions were found in 183 (one was not completely examined). He said: "From the standpoint of the pathological anatomist, my researches, which in regard to the question is not limited to the cases described here, justify me in concurring entirely with those who advocate the specific value of the tuberculin reaction." The millions of necropsies on tuberculin reactor animals have also supported the specificity of the tuberculin reaction (Steele and Ranney, 1958).

Of the various phases of examination, only the tuberculin reaction and the recovery of tubercle bacilli are specific for tuberculosis.

Other Values of the Tuberculin Reaction to be Preserved

The tuberculin test is exceedingly important in differential diagnosis. It determines earlier than any other procedure when tubercle bacilli have invaded the body. It is the best epidemiological agent. It determines the effectiveness of tuberculosis control measures far earlier and more accurately than other criteria. It determines responsibility in tuberculous cases that come to litigation. There is the hope that anti-tuberculosis drugs will be found to cure tuberculosis in the sense of destroying all tubercle bacilli if they are administered with reasonable promptness after the invasion occurs. At that time, lesions are microscopic and vascular, so drugs in the blood stream may reach all tubercle bacilli. If time lapses so that the characteristic loss of blood supply to lesions has occurred, the hope of reaching all tubercle bacilli with drugs in the blood stream is forfeited.

These and other uses of the test are lost to persons whose tissues are sensitized to B.C.G. tuberculoprotein. Concerning the possibility of differentiating between reactions caused by B.C.G. and those by natural infection, Quaiser (1954) said: "It is impossible to distinguish between the tuberculin sensitivity produced by natural infection and that produced by B.C.G. vaccination by means of the intracutaneous tuberculin test with old tuberculin or even with B.C.G. tuberculin."

Veterinarians of Canada and the United States reported that B.C.G. destroyed the use of the tuberculin test, which is their best diagnostic agent. They continued with this test to screen infected animals to be removed from herds. From 1917 to 1958, in the United States, they administered the test to cattle 396,687,286 times and did necropsies on 4.077,995 reactors (U.S. Department of Agriculture, 1959). This programme cost approximately $326,000,000, but on the basis of current prices it has saved more than $150,000,000 annually. Thus, every two years nearly as much is saved as the entire 40-year programme cost (Steele and Ranney, 1958).

Many more millions of tests have been administered in other parts of the world, indicating the confidence veterinarians have in the specificity and accuracy of the tuberculin reaction.

Initial Invasions with Tubercle Bacilli

Krause (1928), Vorwald (1932), and Lemon and Montgomery (1934) demonstrated that when tubercle bacilli are introduced subcutaneously direct into the pleural space, and into the blood stream of animals, they soon appear in other parts of the body, including those remote from the site of administration. Nearly always some of these bacilli become deposited in the lungs, while others are focalized in various extrathoracic locations. In fact, Ravenel and Reichel (1908) and Calmette (1923) found that when tubercle bacilli are introduced direct into the gastro-intestinal tract of animals, some soon appear in the lungs.

Establishment of Primary Tuberculosis Complexes

Vorwald (1932) has shown that lesions start to form within an hour after tubercle bacilli are introduced into

the bodies of animals. Wallgren (1955) found that when tubercle bacilli invade the bodies of infants it requires about three to seven weeks before sensitivity to tuberculoprotein is demonstrable. In people, primary tuberculosis complexes are well established by the time sensitivity to tuberculoprotein can be elicited by the tuberculin reaction.

When allergy can first be elicited by the tuberculin reaction the primary pulmonary infiltrate cannot be located by any phase of an examination in approximately 95% of the cases. This is because the infiltrates do not have consistency or are not large enough to cast visible shadows on *x*-ray films, or they are located in the 25% of the lungs not visualized on the usual postero-anterior *x*-ray film or are extrathoracicly located. In the remaining 5% of cases primary pulmonary infiltrates have size, consistency, and location to cast shadows on *x*-ray films of the chest.

When B.C.G. is effectively introduced into the layers of the skin it sets up lesions at the site of administration and in the regional lymph nodes. When allergy can first be elicited many lesions in the skin are too deep or too small to appear significant and the involved lymph nodes are not palpable. In others the skin lesions are larger, and the regional lymph nodes are palpable. In some, much larger lesions appear in the skin which break down and discharge pus, while regional lymph nodes become markedly enlarged and may rupture.

It was formerly believed that B.C.G. has a fleeting existence in animal and human bodies, but Gernez-Rieux *et al.* (1950) administered it to guinea-pigs by the scarification method and regularly recovered organisms from the skin lesions on the 41st and occasionally on the 79th day. Regional lymph nodes revealed bacilli on the 175th day. Vorwald *et al.* (1954) found living bacilli for at least 18 months in silicotic guinea-pigs. B.C.G. is also carried from the site of administration to lymph nodes and internal organs a short time after administration. Ström (1950) observed that some bacilli administered intracutaneously reached the nearest lymph node 18 cm. distant in three minutes, and about half had arrived at this point in 10 minutes. Gernez-Rieux *et al.* (1950) found organisms in the spleen on the 11th day.

It appears, therefore, that tubercle bacilli of the initial invasion, whether they are from natural infection or from introduced B.C.G., take essentially the same course with reference to distribution and with the formation of primary lesions. All who develop sensitivity to tuberculoprotein, whether from natural or B.C.G. infection, have primary tuberculosis complexes. Apparently the only significant difference in the two groups is that the one is produced artificially in the skin and the other appears naturally, especially in the lungs. It does not seem reasonable to give those in the lungs a different classification from those produced in the skin and regional lymph nodes. Demonstrable primary infiltrates in the lungs usually come under control spontaneously, as do corresponding B.C.G. lesions in the skin.

Demonstrable primary pulmonary infiltrates from natural infections vary in size from those scarcely large enough to be visualized on *x*-ray film to large dense homogeneous areas. Indeed, the shadows they cast may suggest extremely serious and extensive clinical disease. In some cases acid-fast bacilli may be recovered from gastric washings for a brief time, and occasionally they result in haemoptysis. Before there had been opportunity to conduct longitudinal studies on such lesions, drastic treatment was nearly always recommended. However, when an opportunity came to observe a group of children with such lesions under varying conditions they were found to be benign, and they resolved over the course of a year or more, leaving only evidence of Ghon tubercle formation at the former site of the pulmonary infiltrate and/or evidence of calcific deposits in the regional lymph nodes.

In fact, Myers *et al.* (1935) strongly recommended institutional care for all children who had demonstrable primary pulmonary infiltrates. Some families permitted their children to be admitted; others refused, but allowed their children to attend a special day school; while other families refused both institutions, and their children remained at home. When traced later, all the primary pulmonary infiltrates had resolved in the same manner regardless of how much or how little treatment was administered.

The report (Myers *et al.*, 1935) contained the following statement: "Therefore, the immediate prognosis of tuberculosis of the first infection type among children and young adults is excellent either in the absence or presence of treatment."

When in 1920 one of us began longitudinal observations on persons infected with tubercle bacilli (Myers, 1927, 1933), there was a widespread belief that if the initial infection were postponed to young adulthood it would result in much more serious and rapidly progressive disease than when acquired in childhood. There were those who expressed great fear of this situation, believing that infections postponed to the teenage period or later would be exceedingly hazardous.

However, no report was found of a longitudinal study of a group of individuals to determine just when their infections had occurred and the sequence of subsequent events. There was no doubt about the destructiveness of pulmonary tuberculosis in girls and boys in the teenage period. In fact, in the state of Minnesota 200 or more died from tuberculosis annually. As late as 1942–6 more than 3,000 girls and boys from 10 to 19 years old died annually in the United States. Longitudinal observations which began in 1920 offered some promise of determining whether the destruction in the teenage period occurred among those recently infected. Sizable numbers of children, tuberculin reactors and non-reactors, were observed as they entered and passed through the teenage period along with groups of students of nursing and medicine whose tuberculin sensitivity status was determined on admission to school, and the non-sensitive individuals were tested periodically to determine if and when infections with tubercle bacilli were acquired.

By 1937 enough young adults had become infected under our observation and were observed, so that a report containing the following seemed justified (Myers *et al.*, 1937):

"In a small percentage of those who in adult life become contaminated for the first time, the focus of the disease when located in the pulmonary parenchyma attains sufficient size to cast a shadow on the *x*-ray film which can be visualized by the naked eye. Such shadows usually become visible during the first three or four months after the infection has occurred. When these shadows reach their maximum size, they may show the same general appearance over a period of many months, after which they gradually

recede. In some cases, the shadows remain, revealing evidence of fibrous and calcium deposits, while in others they completely disappear.

"The first infection type of tuberculosis as observed in our group of adults has resulted in no significant symptom or abnormal physical sign throughout the entire course of development. Indeed, the lesions in the majority of our cases would not have been known to exist had it not been for periodic tuberculin-testing and the making of roentgenograms of the positive reactors.

"In our experience, adults in whom the first infection type of tuberculosis develops, even with considerable involvement of the pulmonary parenchyma and regional lymph nodes, do not require treatment in any form."

Twenty years later (Myers, 1957), 2,315 persons were reported who were observed to convert from non-reactors to reactors to tuberculin in adulthood, of whom 15 had died from non-tuberculous conditions, and 34 had not recently been traced. The remaining 2,266 had 27,099 person-years of follow-up.

Of the 2,266, there were 2,080 with 24,431 person-years of follow-up who had no demonstrable tuberculous lesion.

Among the remainder, 54 presented demonstrable primary pulmonary infiltrates about the time they were found to be sensitized to tuberculin. They had been observed from 2 to 25 years since the primary infiltrates were first seen and had a total of 749 person-years of follow-up. Five (9.3%) subsequently developed clinical tuberculosis from 1 to 10 years after the primary infiltrates were first in evidence. In the entire 54, the demonstrable primary pulmonary infiltrates gradually resolved over a period of one year or more, with no evidence of clinical disease in the areas they had occupied.

Among the 2,266 traced, another group of 67 developed pleurisy with effusion of whom 14 had coexisting demonstrable primary infiltrates. There was a follow-up of 932 person-years. Of the nine who had pleurisy with effusion but later developed clinical lesions, only two had presented demonstrable primary pulmonary infiltrates. These resolved in the usual way.

Thus no case in this entire group of 2,266 persons who acquired primary tuberculous infection in adulthood developed rapidly progressive fatal disease.

Differentiation Between Primary Infiltrates and Clinical Lesions Imperative

Inasmuch as primary pulmonary infiltrates (both demonstrable and non-demonstrable) are so benign, it is imperative that the demonstrable ones be differentiated from chronic reinfection (clinical) type of tuberculous lesions which cause so much illness and death. Primary pulmonary infiltrates resulting from natural infections are the initial inflammatory stage of Ghon tubercle formation.

X-ray shadows are not pathognomonic, and even when they are cast by tuberculous lesions one cannot differentiate between primary infiltrates and those due to reinfection (clinical) types of lesions. It is only when a series of tuberculin tests have been administered and recent conversion has occurred that the primary infiltrate can immediately be differentiated from the reinfection type of clinical lesion. If such tuberculin testing has not been done before a primary infiltrate is discovered, it can be identified only by a period of observation with serial *x*-ray films. This usually requires a year or more.

Although primary pulmonary infiltrates have hilum lymph-node components, McPhedran's (1927) careful studies revealed that it is not possible to detect lymph-node enlargements on *x*-ray films unless they extend towards the periphery and encroach upon the lung parenchyma. Many lymph-node components of primary tuberculosis complexes do not attain such size; therefore the absence of shadows in differentiating between primary infiltrates and clinical lesions is not helpful.

Immediate Danger of Natural Primary Infection Overemphasized

In pre-vaccination campaigns the impression has sometimes been left that most uninfected children and young adults are in great immediate danger if infection should occur. From May, 1921, to November, 1941, 813 infected children ranging in age from birth to 5 years were observed (Torres *et al.*, 1944). Among them were 102 (12.54%) who presented demonstrable primary pulmonary infiltrates, all of which subsided in the usual manner. Of the 813, only 11 (1.35%) developed acute, fatal reinfection forms of disease and another 11 later developed chronic reinfection type of lesion in bones, joints, lymph nodes, etc. Over a 20-year period beginning in 1921, 6,823 children from 6 to 14 years of age were examined (Harrington, 1944). Of the 2,979 who reacted to tuberculin, 137 (4.6%) had or subsequently developed tuberculosis of reinfection type. The majority had chronic extrathoracic lesions.

Thus, among 3,810 tuberculin reactor children from birth to 14 years, 3,651 developed no evidence of clinical disease. If B.C.G. had been administered before natural infection, it might have been given credit for preventing clinical disease in these 3,651 children.

From May, 1921, to November, 1941, among more than 19,000 children examined, 300 had demonstrable primary pulmonary tuberculous infiltrates (Myers, 1959). Among the 267 recently traced, 10 stated that they were in good health, but have not yet been re-examined. Twenty-six had died. Nine of the deaths were due to tuberculosis, of which seven were caused by meningitis, miliary disease, and pneumonia soon after the infections occurred, and the primary pulmonary lesions were in evidence. The remaining two died from chronic pulmonary tuberculosis 8 and 13 years after the primary pulmonary infiltrates were first found. Among the 241 traced survivors (10 not recently examined), nine had developed chronic clinical types of tuberculosis. One appeared five years after the primary pulmonary infiltrate was seen, one 7 years, one 9 years, two 11 years, one 15 years, one 25 years, and two 27 years. Seven of these cases had pulmonary lesions, one bronchial, and one renal. All were treated successfully.

The surviving traced and examined 231 have had 6,009 person-years of follow-up. No evidence of clinical tuberculosis had developed in 222.

Most of the morbidity and mortality reported in the above studies occurred approximately two decades ago. By fundamental protective measures in the same city, case and mortality rates decreased so that in 1956 only 17 cases were reported among persons under the age of 20 years (of which only five were clinically significant), and no one under the age of 35 years died from tuberculosis (Myers, 1959). If B.C.G. had been administered it might erroneously have been given credit for this accomplishment.

Long-term Hazard of Primary Infection Emphasized

To avoid erroneous deductions with reference to efficacy of therapeutic and preventive measures, it is of extreme importance to recognize the demonstrable primary pulmonary infiltrate. However, its benignity affords no security regarding subsequent acute and chronic clinical forms of tuberculosis. While it has not been demonstrated that the 5% of persons with demonstrable primary infiltrates later develop clinical disease more frequently, percentage-wise, than the 95% with non-demonstrable primary infiltrates, it should be emphasized that all persons with primary tuberculosis as manifested by the tuberculin reaction should be examined periodically for possible evolving clinical lesions.

The individual who reacts to tuberculin is likely to have not only primary pulmonary infiltrates, but also focalization in other locations. Thus, the reactor may have clear *x*-ray films of the chest but develop tuberculous meningitis from lesions of short or long standing in or adjacent to the central nervous system, as demonstrated by Rich and McCordock (1933). Another individual with clear *x*-ray films may have several lesions appear or clinical pulmonary disease evolve at any time after allergy is established.

Levine (1950) made a follow-up study of 1,165 persons, of whom 601 had received B.C.G. during infancy and 564 had been followed from infancy as controls. Two who had received B.C.G. in infancy had developed reinfection type of pulmonary tuberculosis. This had occurred in none of the controls. He said: "There is no evidence to indicate that B.C.G. given in infancy is capable of preventing reinfection tuberculosis in adolescence."

Long ago it was demonstrated that chronic contagious clinical tuberculosis evolves only among those whose tissues are sensitized to tuberculin. More recently, in four areas where B.C.G. studies were in progress, Palmer and Shaw (1953) found that 286 of the total of 335 cases of demonstrable tuberculosis occurred among those who were reactors at the beginning of the study. Of the remaining 49, it apparently was not determined how many were only demonstrable primary pulmonary infiltrates which one may expect to observe in approximately 5% of recent tuberculin converters.

If tuberculosis eradication is the consideration, mass B.C.G. administration campaigns, as well as those for special groups, are puzzling, because time, effort, and funds are spent upon the non-reactors to tuberculin. Among them there is no present tuberculosis problem. The belief that uninfected persons develop rapidly progressive disease within one or two years after becoming infected and thus create the serious contagious clinical problem has not been verified on a long-term basis.

To spend time, effort, and funds on individuals who have not been infected and many of whom will not be, while the infected are allowed to produce a constant crop of clinical and contagious tuberculous persons disseminating tubercle bacilli among their associates, is bad economy.

Unavoidably Exposed Groups

Inasmuch as B.C.G. administration has been strongly recommended for "unavoidably exposed groups," including students of nursing and medicine attention must be called to results of protective measures without B.C.G. reported by Myers, Diehl *et al.* (1955). Prior to and during the 1920s, clinical tuberculosis was a serious problem among their professional students. A programme was developed which consisted of testing all entering students with tuberculin. Those who reacted were examined promptly and thereafter periodically, including inspection of the chest by *x*-ray films. This screened out those who had clinical pulmonary disease on admission and discovered those destined to develop such disease during their school years. Non-reactors on admission were retested with tuberculin periodically. For those who converted while in school the sources were immediately sought, and were often found in pathological and bacteriological laboratories, in post-mortem rooms, in affiliated hospitals and sanatoria, on various services in general hospitals, and among personnel members. In this manner it was learnt which hospitals and departments were permitting materials and patients to infect students, and this knowledge led to the correction of the situations or the abandonment of such teaching services. Rigid contagious-disease technique was introduced where, in line of duty, students came in contact with known cases of contagious tuberculosis. Patient-admission examinations for tuberculosis and pre-employment examinations of all personnel, with subsequent periodic examinations, were instituted.

Among the graduates in the classes from 1919 to 1932 in the School of Medicine, a survey reported in 1941 revealed that 92 had developed demonstrable tuberculosis and 11 had died while in school or after graduation; whereas, after the programme was well under way, among those who graduated from 1943 to 1957 only one presented a clinical lesion large enough to cast a visible shadow on an *x*-ray film. This occurred a decade ago in a student who was a tuberculin reactor on admission to school.

In a school of nursing where 12 to 19% of the students developed demonstrable tuberculous lesions before these protective measures were introduced, only four have since presented clinical pulmonary tuberculosis, each of whom reacted to tuberculin on admission to school (Myers, Boynton, and Diehl, 1955).

Had B.C.G. been employed in these schools, obviously it would not have been administered to the one student of medicine and the four students of nursing who developed clinical lesions, since they had been naturally infected before admission. Moreover, the large number of non-reactors would have received B.C.G. to no avail, but it could have been erroneously concluded that they were protected by this culture.

To speak of "unavoidable exposure" groups is a reflection on the administration and professional staff of any hospital or professional school. The precedent has been established for almost complete solution of the problem by a method based on sound principle and practice with unquestioned efficacy.

Importance of Accurate Diagnosis and Prolonged Control

Literally hundreds of papers have been published on B.C.G., many of which—in fact, the majority—contain favourable statements. However, a carefully controlled study has never been conducted comparable to what has always been demanded by way of control in other

fields. There has been failure to differentiate between primary tuberculosis infiltrates (Ghon tubercles in the inflammatory stage) and clinical tuberculosis. Other factors operating at the same time have been overlooked, and even with unsatisfactory control no study has been conducted long enough to justify favourable conclusions.

In a large number of reports the only evidence presented pertains to conversion to sensitivity to tuberculoprotein. From that alone it was assumed that the recipients were protected. In another but smaller group, efficacy was based largely on seeing more *x*-ray-shadow-casting lesions in the lungs of controls than in those infected with B.C.G., with no differentiation between primary infiltrates and clinical lesions.

The observations of Aronson *et al.* (1958) on American Indians which began about 1936 revealed more shadow-casting lesions and more deaths in the controls. In one of the reports the following statement appears: "Principally, the information for the analysis consists of annual observations on the tuberculin reaction and annual *x*-ray films of the chests with only limited clinical and laboratory data." Apparently, diagnoses were made largely from *x*-ray shadows. Presumptive diagnoses from shadows are temporarily allowable in practice but have no place in research reports, where diagnosis must depend upon bacteriological findings and where information must be factual for world-wide dissemination. The favourable effect of B.C.G. claimed by Aronson *et al.* becomes less impressive when it is known that better results have been achieved among American Indians in a state in which B.C.G. played no part. In that state the mortality rate among Indians decreased from 529 per 100,000 in 1937 to 0 in 1955.

The alleged efficacy of the numerous agents intended to protect against clinical tuberculosis, both past and present, has differed little. It has been reported that about four or five times more tuberculosis has developed among controls than among the vaccinated. The number of primary pulmonary infiltrates that attain *x*-ray-shadow-casting proportions soon after natural initial invasion occurs is sufficient to account for a considerable part of this difference.

The report of the Tuberculosis Vaccines Clinical Trials Committee of the Medical Research Council of Great Britain (1956) concerned 13,300 adolescents who were non-reactors to tuberculin and served as controls; 14,100 who were non-reactors and received B.C.G., and 6,700 non-reactors who were given vole bacillus. In selecting these groups there were 8,200 examined who already reacted to tuberculin and were observed for subsequent developments. At the time this report was completed the participants had been in the study for two and a half years.

The annual incidence of demonstrable thoracic and extrathoracic lesions in the controls was 1.94%, in the B.C.G. group 0.37%, and in the vole bacillus group 0.44%. The lower figures, which are statistically significant, in the last two groups were thought to indicate that B.C.G. and vole bacillus conferred a substantial degree of protection against tuberculosis. However, the pulmonary lesions were not less extensive or severe in those who had received B.C.G. or vole bacillus. How many of the pulmonary lesions in the control group were only primary infiltrates is not known. Among the 13,300 controls, 756 (5.7%) had become tuberculin reactors on the second test, three to five months after the initial one. This is the time in the natural history of tuberculosis when demonstrable pulmonary lesions are in evidence. Grouping of primary pulmonary infiltrates with clinical lesions provides a number large enough to appear statistically significant, whereas accurate differential diagnosis would probably reduce the number of clinical cases below this level.

The study of the Tuberculosis Vaccines Clinical Trials Committee is designed for a prolonged period. A fine opportunity exists to introduce accurate differential diagnosis and thus make a contribution previously unparalleled. If anti-tuberculosis drugs are administered to each person who presents an *x*-ray shadow, however, it may be impossible to obtain the desired information. Apparently these drugs have little or no effect on demonstrable primary pulmonary infiltrates. On the other hand, they usually significantly hasten resolution of clinical lesions and cause them to take the same course as primary infiltrates do naturally.

No group of B.C.G. recipients have been followed long enough to justify conclusions concerning efficacy. Such outstanding workers as the Oxford University investigators of the vole tubercle bacillus vaccine, Medlar, and others saw the impossibility of conducting a well-controlled follow-up study among people. In fact, the Oxford group, headed by A. Q. Wells, said: "To plan a controlled experiment in tuberculosis vaccination in man is a matter of so much difficulty as to be virtually impossible."

The Calmette-Guérin Organism

Ravenel (1902) said: "We are certain that the various types of tubercle bacilli known to us have sprung from a stock common to them all, and that they have acquired their racial peculiarities by residence in different animals through which they are subjected to a difference in food, temperature, and resistance. In other words, the struggle for life is carried on in the various species of animals under varying conditions, the results being that in each animal the tubercle bacillus acquires properties which best enable it to carry on life in that particular host."

Sweany (1956) says: "The other drawback to antimicrobial therapy is due to that fundamental law of nature, the ability of living species to adapt to changing environment by the survival of mutants when changing environment threatens to exterminate the parent species. Molecular rearrangement within the genes (genotypic changes) result in variations in the offspring that are better adapted to the new condition. . . . The end product of the tubercle bacillus (as well as all other species of living organisms) is therefore the end result of a rigid selection of mutants to fit environments in which they are obliged to grow. . . . In spite of the fact that the tubercle bacillus has appeared to be a rather stable parasite, many variations have been observed since its discovery involving among other changes, variations in morphology, virulence, chromogenesis, and gross colony formation."

The bacillus which Calmette studied and later designated bacillus Calmette-Guérin (B.C.G.) would not produce tubercles in animal tissue. Therefore he regarded it as safe when introduced into humans and referred to it as a *virus fixé*. As time passed, however, it was observed that, when introduced subcutaneously

and later intracutaneously, tuberculous abscesses and ulcers sometimes formed at the sites of administration and the regional lymph nodes enlarged, broke down, and discharged pus. These and lesser visible local lesions occurred often enough to be annoying, and constituted good evidence that changes had occurred in the culture.

Petroff *et al.* (1929) dissociated B.C.G. into two "R" and "S" colonies, with the "S" colony invariably producing progressive tuberculosis in guinea-pigs and occasionally in rabbits. Jensen (1946), of Copenhagen, pointed out that the cultures available in Scandinavia at the end of the second world war varied appreciably with reference to the severity of the skin lesions which they could elicit in guinea-pigs. Dubos (1949) said: "Similarly, it has been observed in our laboratory that three strains of B.C.G. obtained from American collections differ significantly in their ability to produce pulmonary lesions in mice following intravenous injections." Concerning the culture he said, "There is no doubt that it has undergone considerable variations in the course of its long career. Indeed, it would be very surprising if it had not." The cultures he and co-workers studied were mixtures of different bacterial forms and differed in properties such as extent of multiplication *in vivo* in experimental animals.

In cultures obtained from various laboratories, Suter *et al.* (1951) found that none consists of a single bacterial form such as Calmette and Guérin produced. Each culture was composed of multiple bacterial forms which differed in many of their properties. It was found that a culture introduced into mice on deficient diet resulted in progressive and sometimes killing pulmonary tuberculosis (Dubos, 1949). It was also observed that the culture maintained and highly recommended for humans by the Research Foundation of Chicago regularly caused progressive and highly fatal tuberculosis in silicotic guinea-pigs (Vorwald *et al.*, 1954). Hauduroy and Rosset then reported that the culture they employed regularly caused widely disseminated and killing disease in normal golden hamsters (1951) and ground squirrels (1953).

Reports began to appear of serious clinical tuberculosis developing in various organs of people remotely located from the sites of administration. In some groups, particularly infants, a higher percentage of cases developed lesions than others. For example, Hsing (1954) said, "The result of B.C.G. vaccination in newborn babies was alarming and is a matter causing great concern." In 23.3% of his cases lymph nodes ruptured. In other reported groups, such lesions have developed in much smaller numbers, down to 1% or less. Finally, Scandinavian physicians made careful necropsies and concluded that B.C.G. was responsible for fatal tuberculosis in humans (Hollström and Hård, 1953; Meyer, 1954; Thrap-Meyer, 1954; Falkmer *et al.*, 1955). Although only four of these cases have been reported it is not known whether others may have had the same experience, because, in areas where most B.C.G. has been administered, in 38 nations there has been no satisfactory follow-up.

It is stated that with the advent of a freeze-dried preparation of B.C.G. it is now possible to standardize completely the viability, potency, and sterility, as well as to determine its safety before distribution (Medical Advisory Committee of Research Foundation, 1957). This is what Calmette and Guérin believed when in 1924 they designated their culture a *virus fixé*. It is what producers and distributors have claimed for their cultures throughout the decades preceding the freeze-dried era. However, the numerous changes already described, varying from culture to culture, occurred. When Calmette and Guérin's culture was considered a *virus fixé*, it had been under observation longer than the freeze-dried preparation has been available.

The freeze-dried material is still composed of living tubercle bacilli, and it has yet to be proved that they will take a different course on prolonged growth in human or animal tissues than has been observed with cultures derived from the original Calmette-Guérin culture.

Calmette's advice to the effect that living tubercle bacilli which cause tubercle formation in animal tissue should never be introduced into the human body is as pertinent to-day as when it was offered.

Summary

Tuberculosis differs from smallpox in that an attack does not result in dependable immunity. Thus there is slim premise for attempting to produce immunity artificially. Allergy to tuberculoprotein is not an indication of immunity, but is prerequisite to the development of clinical tuberculosis. The human body defends itself better against first invasions with tubercle bacilli than it does against reinfections. Clinical disease develops only in persons who have been previously sensitized to tuberculoprotein.

Accurate differentiation between primary pulmonary infiltrates and reinfection type of clinical lesions is of the utmost importance. Without this, erroneous deductions are made with reference to efficacy of B.C.G. For example, it may be credited with beneficial effects when primary infiltrates are grouped with reinfection type of lesions, so it appears that more control subjects develop clinical disease than those who have primary lesions produced in the skin by B.C.G.

An adequately controlled study of B.C.G. among people living in their homes has never been accomplished. It has been found impossible. However, well-controlled studies were conducted among cattle in North America and elsewhere. B.C.G. failed and was abandoned. In the few places where it is still used with major dependence upon it, tuberculosis remains a serious problem among cattle.

Among people, the most phenomenal accomplishments in tuberculosis eradication have been achieved where little or no B.C.G. has been used, including Iceland, Hawaii, and the Netherlands. In countries which have employed B.C.G. extensively, including Denmark, Norway, and Sweden, marvellous results have been achieved, but along with B.C.G. they have employed the same fundamental methods which alone brought about the most phenomenal accomplishments in history. This also applies to special groups such as students of nursing and medicine.

The numerous values of the tuberculin test in diagnosis, epidemiology, etc., are lost to persons whose tissues have been sensitized to tuberculoprotein by B.C.G.

Bacteriological investigations have revealed that cultures designated B.C.G. were not composed of just one, but of multiple bacterial forms, some of which were definitely invasive for animal tissues. No two cultures were alike. Evidently different mutants and changes had occurred in each of the cultures studied.

Apparently mutants produced destructive disease in animals on deficient diet, those which were silicotic, and at least two species of normal animals. In people, they sometimes caused lesions at the site of administration and of regional lymph nodes, as well as other organs, and death in at least a few cases. Calmette repeatedly warned that no living organism capable of producing tubercles in animal tissues should be administered to people.

If methods of preventing mutation in cultures have been or can be devised, there is no assurance that it will not occur after the living organisms are introduced into human tissues.

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LONG-TERM EFFECTIVENESS OF B.C.G. VACCINATION OF INFANTS IN CLOSE CONTACT WITH INFECTIOUS TUBERCULOSIS

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It has been demonstrated many times that B.C.G. vaccination can prevent tuberculosis. For example, Aronson *et al.* (1958) vaccinated 1,557 American Indian children 20 years ago and left 1,457 as controls. The incidence of tuberculosis in that community was high at the time these vaccinations were done. Twenty years later they were able to account for over 99% of both groups, and found that 104 (6.7%) of the vaccinated subjects had died. Tuberculosis was responsible for 0.8% of the deaths. Of the controls, 150 (10.4%) died, including 4.7% from tuberculosis. The excess of deaths in the control group was entirely due to deaths from tuberculosis. Hyge (1947) observed an epidemic of tuberculosis in a school in Denmark. Of 94 tuberculin-negative children who were exposed to an infectious school teacher, 41 developed tuberculosis; whereas of 106 B.C.G.-vaccinated children who were exposed to the same infection, only two developed the disease. The Medical Research Council (1956) conducted a large-scale controlled trial on adolescent boys and girls. It was found that the annual incidence of tuberculosis in the initially tuberculin-negative unvaccinated group was 1.94 per 1,000, whereas in the B.C.G.-vaccinated group it was only 0.37 per 1,000.

Present Investigation

In this country there have been no reports so far about the long-term effectiveness of B.C.G. vaccination in contacts. We have therefore decided to review the results of B.C.G. vaccination in all the 267 children who attended our contact clinic, and who were under the age of 2 years when they were vaccinated with B.C.G. between October, 1949, and October, 1952. All of those who had been in contact with an active case of tuberculosis were segregated for six weeks after the initial negative tuberculin test. They were then retested and when a second negative result had been obtained were immediately vaccinated with 0.1 ml. of the liquid Danish B.C.G., given intradermally over the left deltoid. A further period of segregation followed for six weeks, or for a longer period if by then tuberculin conversion had not taken place. In the case of newborn infants in potential contact with a case of tuberculosis the initial tuberculin tests were omitted. These were vaccinated at birth with 0.2 ml. of B.C.G. and segregated until tuberculin conversion was demonstrated. After tuberculin conversion all were allowed to return home, irrespective of the condition of the index case.

The children were then seen at approximately annual intervals, or more often if required At the end of the third year and annually thereafter the tuberculin tests