The purpose of this presentation is to review very briefly some of the history of the controversial BCG vaccine. This is a living, attenuated, bovine strain of tubercle bacilli. This strain was first isolated in Paris as a very virulent organism for animals, and it was attenuated by serial passage in artificial media for a period of 13 years.

By 1921, Calmette and Guérin were satisfied in their own minds that they had produced an attenuated bacillus, but they delayed the announcement and the distribution of cultures to other laboratories until about 1924. From 1921 to 1928, large numbers of experiments were conducted to try and revert this attenuated bacillus to its original virulent characteristic. All experimental attempts in this direction failed.

In 1930 the vaccine received a setback from which it has never fully recovered, when 240 children received it as an orally administered vaccine at Lubec and 72 of them died. A full-scale investigation subsequently revealed that the BCG strain was not the cause of the disaster. A contaminating strain of bacilli in the culture administered was positively identified by growth and color-producing characteristics. I think it is improper to speak of "a BCG vaccine." Just as the original vaccine was able to mutate from a fully virulent strain of organisms to an attenuated form, mutations continue to go on producing relative degrees of infectivity or invasiveness. There is no such thing as absolute virulence and absolute avirulence. Rather, there is a continuous spectrum of invasiveness which an organism may exhibit, and an organism may change its characteristics of invasiveness from one culture to another.

Therefore, one may read in the literature that a BCG vaccine given in Scandinavia has produced a certain amount of immunity and a certain amount of hypersensitivity, but one cannot expect to exactly reduplicate the same result here; because you just cannot get the same Scandinavian vaccine here and reduplicate that experience. In this country there are several sources of BCG vaccine that a laboratory may acquire or a physician may use. The one most commonly used is manufactured in Chicago by the Tuberculosis Research Institute and is licensed for administration to humans. However, a strain is also produced in Philadelphia which is different from the Chicago strain, and in Canada two strains are available, one from the Connaught Laboratories in Toronto and one from the University of Montreal. Only in recent years has success been achieved in standardizing the product which you may get for administration to humans.

The strain that is sent out from Chicago now is probably as pure and reliable a strain as one can obtain anywhere. This depends on the fact that the cultures are not made by transferring from one culture medium to another. Rather, a mother strain has been prepared and then a large quantity of it freeze-dried and stored in a frozen state. Each new batch of BCG vaccine is cultured from this lyophilized, frozen strain and therefore, the vaccine that you receive from this source 10 years from now will be identically the same as the vaccine produced today.

The second great advance came in connection with the problem of viability of the vaccine. One can, of course, create a meas-
ure of immunity to tuberculosis by giving a fairly large dose of dead organisms. However, the immunity is not great and it is not lasting. A desirable degree of clinical immunity is secured only by the administration of living organisms which can undergo some multiplication and have some degree of invasiveness.

The vaccine as it is frozen and sent out in the dried state from the Chicago laboratories contains a high percentage of living organisms for a long period of time after the vaccine is made, and so a pharmacist or a physician may keep the vaccine for a fairly extended period of time and still be able to use it with complete confidence. This factor of viability is an extremely important one because, in essence, it is what determines the dose.

The administration of BCG organisms can be done in several ways, and I think I have used all of them. The method first recommended was as an oral vaccine. The first Indian babies to whom I gave BCG vaccine a number of years ago had it administered to them in milk in the nursery during the first week of life. I did not see any adverse effects from this. A high incidence of tuberculin-positivity was produced, and the vaccine seemed to confer a satisfactory level of immunity in that these children later in life were less susceptible to tuberculous infection.

I have also used the vaccine by intracutaneous injection, which gives a very reliable vaccination. One injects an exactly known quantity of a suspension of exactly known density, and therefore one can be absolutely certain that the vaccine is well given and that a high degree of tuberculin sensitivity will be produced. However, the disadvantage is that this technique may cause a draining ulcer, which may drain for as long as 8 or 9 months.

The scratch technique then became popular. The vaccine is placed usually on the back of the infant above the buttocks, and a scratch about 2 inches long is made through it. Actually I have used this more than any other method. I make two scratches on either side of the vertebral column through four drops of vaccine.

The method advocated in the literature with the vaccine sent out from Chicago is a multiple-puncture method. I have used this on medical students, infants and children, and it is a very satisfactory method. The results are quite reliable. A high conversion to tuberculin sensitivity is achieved. It is absolutely painless; a 4 or 5-year-old child can have the multiple-pronged disc pressed into the arm without a cry or fuss, and this is an important consideration in the administration of vaccine in office practice. Also, the local reaction is minimal. A few red spots remain over the deltoid area for a period of perhaps a month. I have not seen any regional lymph node involvement, although I am sure that if you vaccinated someone with a low degree of resistance to tuberculosis this could occur.

Is BCG vaccine safe? All physicians who give a vaccine want to be assured that they are not going to produce any morbidity or mortality. Actually, the mortality from BCG vaccine has been around 2 per 10,000,000 doses administered. The cases that have died following the administration of BCG vaccine have never been sufficiently documented to prove that it was the BCG vaccine that caused the fatality. There has always been another factor involved to make one suspicious that the youngster had tuberculosis even before BCG vaccine was given, or that he was exposed to the disease before BCG vaccination could become effective.

I think the exacting requirements for an effective vaccine, which will confer a high degree of tuberculin sensitivity and at the same time give significant immunity, as judged by large clinical trials, without unfortunate complications or regional adenitis, are well achieved in the vaccine which is available from the Tuberculosis Research Institute in Chicago.

How effective is BCG vaccination? The arguments about BCG vaccination have really hinged on whether or not it confers any significant degree of immunity. Unless
one does a great deal of work with tuberculosis, he is apt to be confused by reading the literature on this subject. Tuberculosis is a disease which shows a marked difference in manifestations depending upon the socioeconomic and racial group under consideration. If it is a group of individuals who have a good nutritional state, who have ideal housing conditions, who are not exposed to intercurrent infection, and who come from a racial stock that has a high incidence of tuberculin sensitivity—resulting in a high natural resistance from natural selection—then BCG vaccination offers relatively little. Such people can be vaccinated, along with adequate controls, without showing significant difference between the number of active cases among the vaccinated and the nonvaccinated. This is because the factors already enumerated lower the rate of clinical infections to a much greater degree than the single factor of administration of BCG vaccine. The few people who contract clinical tuberculosis under such conditions are probably individuals that no measure of vaccination might have protected. They may have had a severe intercurrent disease, they may have had a very heavy exposure, and no vaccine can protect against an extremely large infecting dose.

In 1950, the Medical Research Council of Great Britain selected adolescents between 14 and 15 years of age in North London, Manchester and Birmingham for vaccination; this was done because, having tuberculin-tested and x-ray-surveyed these youngsters, it could be predicted accurately what the incidence of tuberculosis would be. It was known that, because of housing, nutrition and other factors, this was a group that had a high incidence of tuberculosis. BCG vaccination of 14,100 such school children, keeping 13,200 unvaccinated children as controls in the same classrooms, showed a measure of protection of approximately 80%. This is really quite good, I think, for any vaccine. Ferguson of Saskatchewan, Canada, vaccinated about 1,000 nurses and observed 1,000 unvaccinated controls. He reported that the degree of clinical tuberculosis in the unvaccinated was about four times as high as that in the vaccinated.

From the point of view of pediatricians, what are the indications for recommending BCG vaccination to a family? Children in daily contact with a family member who has active, arrested or even healed tuberculosis (of the type to be described) may be legitimate candidates for vaccination, but the amount of exposure such children receive depends on many factors.

Of ever potential danger is a person who has had active pulmonary tuberculosis but is presently classified as "inactive." One should keep in mind that so-called "healed" tuberculosis may relapse, without overt symptoms, to active disease and considerable time elapse before the infectious status of the patient is recognized.

Sometimes a patient may not show any roentgenographic evidence of extension of disease and, under most circumstances, not excrete bacilli, but with upper respiratory tract infections will have an intermittently positive sputum; this reverts to negative when the active respiratory infection subsides.

After thoracoplasty, many patients fall into this category.

Of increasing importance are people who have persistent cavitation apparent in roentgenograms, but whose sputum is consistently negative for tubercle bacilli at the times it is examined. However, there is no assurance that such people do not intermittently excrete tubercle bacilli.

Finally, there is the good, elderly "chronic," who exhibits diffuse fibrosis by roentgenogram and intermittently excretes tubercle bacilli, but who is relatively asymptomatic. Many grandparents fall into this group.

Of special importance are children in a low socioeconomic group, particularly if the family is a transient type, constantly moving from one place to another. Such children escape vigilant medical observation and a single therapeutic procedure, such as vaccination, is the only effective protection one can offer them.
There are two alternatives to vaccination. The first is to maintain careful watchfulness for early tuberculosis in the child. This means frequent and repeated tuberculin tests. The second is to treat the child with isoniazid prophylactically. Both of these alternatives suffer serious disadvantages. Despite very frequent tuberculin testing, a child could still contract active infection and suffer serious progression of the disease before detection. From a practical standpoint, however, physicians and parents just do not co-operate sufficiently to do the tuberculin testing with regularity and frequency. As a matter of fact, most physicians don’t even take the trouble to perform tuberculin tests in their own immediate families. In my opinion, the prophylactic use of isoniazid cannot substitute for vaccination. Children cannot be depended upon to take prolonged protective therapy. In fact, most patients with tuberculosis receiving drug therapy abandon their program entirely or in part before the physician would readily sanction it. Those who continue to take prophylactic therapy often do so with irregularity.

The contraindications to vaccination are: a definitely reliable family, thoroughly known to the physician in practice; population groups with high economic and social status, where it is known that the incidence of positive tuberculin tests is extremely low; or in circumstances where those vaccinated might take the attitude that no further precautions would be necessary to prevent infection.

The incidence of new cases of tuberculosis has been reduced to the point where we do not need mass vaccination as practiced in some countries. On the other hand, we do need to use the tuberculin skin test as a means of following outbreaks of infection, for as we move away from the mass roentgenographic survey, we have to find some substitute for locating the open case; tuberculin sensitivity among children is one of the most valuable ways of doing this. Find a tuberculin-positive child, and with less effort than in any other situation, you can usually find an adult with open tuberculosis.

In summary, BCG vaccine is as useful a vaccine (in terms of protecting against infection) as a great many of the vaccines we now use. It is a safe vaccine, it is an easily-administered vaccine, but it has distinct advantages as well as disadvantages. I would urge you not to close your mind completely in respect to this agent. I think there are situations where you can fulfill your obligation as a physician better by using BCG vaccine than you can in any other way.

REFERENCES
PROCEEDINGS: BCG VACCINATION
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