B. C. G. Vaccination

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Tuberculosis is still one of the greatest scourges of mankind. As physicians, present-day medical students will in the future have to take part in the fight against this disease, both in prophylactic work in the homes, and by treating this disease in hospitals.

The B.C.G. vaccine was produced for the first time by Professor Calmette and his pupil Guérin in 1921, from a bovine-type of the tubercle bacillus, after this had been cultured for thirteen years in a special medium. During these years the bacillus had lost entirely the power to produce tuberculous disease, but without losing the usual ability of a tubercle bacillus to develop a relative immunity or power of resistance against the tuberculous contagion.

The vaccine, having been tried for many years on animals, was in 1921 given to new-born babies by oral administration. (Weill Hallé 1921, (1)). However, it was proved in a statistical way, that only 30% of the babies, vaccinated with this oral administration, were sensitive against tuberculin, and therefore this form of administration lost much of its epidemical value. (Wallgren (2), Greenwood (3), Rosenfeld (4)). Besides, the Lubeck tragedy made the oral methods unpopular, in spite of the fact that this tragedy was not due to the B.C.G. vaccine, which fact was definitely proved by the German Law Courts (Lange (5)).

It was the Scandinavian physicians Heimbech (6) and Wallgren (7) who were the first to use the parenteral administration — Heimbech by subcutaneous and Wallgren by intradermal injections.

The intradermal method proved to be the best one and it is now the standard method in use everywhere. Some other methods (Rosenthal's multi-puncture (8) and the scarification method of Negre and Bretey (9)) have been used to a certain extent.

By vaccinating non-reactors to tuberculin, we can convert them into reactors to tuberculin in a very high percentage of cases (98% to 99%). That means that we can give the non-reactors the same protection against tuberculosis, as the reactors to tuberculin have obtained through a natural (but often dangerous) infection.

Many experiments have been carried out to determine the degree of protection given by the B.C.G. vaccine. The difficulty in these experiments has always been to get really good control groups. In order to prove the effect of the vaccine, we should have a relatively large group of non-reactors to tuberculin, of which every second person — chosen absolutely at random — should be given B.C.G. vaccine and the others left as controls. The whole group (B.C.G. vaccinated and controls) should live under exactly the same conditions and be controlled in the same way. If the B.C.G. vaccine gives protection, fewer cases of tuberculosis will occur among the vaccinated than among the controls.

In practice, it is almost impossible to carry out a study where these strict conditions for control are fulfilled to such a degree that all statisticians will be satisfied.

Of the controlled studies which come closest to the theoretical conditions, the following can be quoted:—

1. Heimbech (6) in the years 1924-

1926 on probationers entering the nursing school of the Ullevaal Hospital in Oslo, had seen that while many of those who did react to tuberculin became ill with tuberculosis at an early stages of their training, only few cases developed among those found to be reactors to tuberculin on admission. Prompted by this experience, Heimbech began B.C.G. vaccination of the non-reactors among his nurses in 1926 and today he is still following up most of them. Among the probationers entering the school in the period 1924-1936 for a three-year training course, 668 were found to be reactors to tuberculin on admittance, 501 were non-reactors and B.C.G. vaccinated, while a further 284 non-reactors were not vaccinated. The following rates of morbidity and mortality were calculated for the three groups per 1,000 observation years: for the reactor group the rates were 12.4 morbidity, 0 mortality (22 cases of tuberculosis, including such forms as: erythema nodosum, pleurisy, etc., and no deaths), for the vaccinated 24.1 and 2.1 (35 cases, all forms included, and 3 deaths) and for the non-reactor group 141.2 and 14.6 (97 cases and 10 deaths). Both morbidity and mortality appear very high in the latter group; and Heimbech stresses the fact that among the nurses who were vaccinated, the incidence of tuberculosis has been reduced to one sixth.

2. Wallgren (7), a pediatrician, was the first to show the importance of B.C.G. in the control of tuberculosis in a community. Injecting all the children of tuberculous families and those exposed to infectious sources in the town of Gothenburg in Sweden, he obtained a sudden drop in the mortality rates from tuberculosis in the younger age groups. Whenever possible, the children were isolated from the source of infection for six weeks before and after vaccination until allergy had developed. Thus a total of 1,069 persons were given B.C.G. intradermally in the period 1927-37 in Gothenburg alone. Anderson and Belfrage in 1939 made a study of this material, and were able to examine 905 vaccinated persons. They found that tuberculous disease had developed in two cases only, and in a benign form. Furthermore, a small child had died from a specific primary infection, with generalisation, which had developed three weeks after vaccination. This child had not been isolated prior to the vaccination, and it must be presumed that B.C.G. had been inoculated in the incubation period.

3. R. G. Ferguson's (10) observations on vaccination of general hospital nurses and of sanatoria nurses showed that the protection given by B.C.G. would apply as well to the groups with a high annual in-

B.C.G. Vaccination in Hospitals and Sanatoria of Saskatchewan (R. G. Ferguson).

(1934-1943)	Number of persons	Tuberculosis cases	% with Tuberc.	Aver. years observed.
Nurses in general hospitals (Yearly infection rate of 11.8%)				
Positive on entrance	478	5	1.05	2.43
Negative, not vaccinated	1,368	55	4.02	2.43
Negative, vaccinated	1,005	9	0.89	2.42
Nurses in Sanatoria (Yearly infection rate of 71.8%)				
Positive on entrance	293	11	3.75	1.25
Negative, not vaccinated	113	18	15.9	1.06
Negative, vaccinated	203	5	2.46	1.07

fection rate (sanatoria nurses: 71.8%) as to the groups with a much lower annual infection rate (general hospital nurses: 11.8%).

Comparison of the percentage of cases developing a tuberculous disease in the vaccinated and non-vaccinated groups shows a ratio of 1:6.5 for the more exposed nurses, and of 1:4.5 for the less exposed nurses who had received B.C.G. Such a marked reduction can hardly be attributed to mere chance or to the annual decline of the death and case rate in Canada.

4. In the years 1935-1938, Aronson (11) in the United States started in 13 different Indian reservations, scattered from Arizona to Alaska, what was to become one of the most accurate studies on B.C.G. 1,551 North American Indians were vaccinated with B.C.G. and 1,457 were kept as controls. All the subjects chosen for the experiment were in the age-group 1-20, and the division between those to be vaccinated and those to be followed up as controls was made quite at random. All the subjects were re-examined annually by tuberculin tests and radiography. The specialist reading the X-ray films did not know to which group a given subject belonged. The two groups were found to be similar in age distribution, amount of exposure to tuberculous infection and completeness of the follow-up.

When the results of the Indian study were first published after 6 years of observation, there were 28 deaths due to tuberculosis among the controls as compared with only 4 such deaths among the B.C.G. vaccinated. This is a rate of 3.4 against 0.4 per 1,000 person years, with a ratio of 1:7.7 in favour of the vaccinated. The total incidence of tuberculosis, that is, the sum of all the cases and all the deaths due to the disease, was 185 in the control group and 40 in the vaccinated group; a rate of 24.3 as against 4.7 per 1,000 person years, or 1:5.2 in favour of the vaccinated.

5. Quite exceptional are the observations by Hyge (12) in a Danish school for girls, and his findings have been compared to those of a controlled laboratory experiment on human beings. Following the discovery of an open case of tuberculosis among the pupils, the whole school population of the Aurehoj State School was X-rayed and tuberculin tested in November 1941 and again in February 1942. At this date 144 girls out of 200 non-reactors to tuberculin volunteered for vaccination and were subsequently found to be reactors to a control tuberculin test. A new examination took place in December 1942 and of the 368 pupils examined 105 were found to be non-reactors to tuberculin, 130 reactors after natural infection, and 133 reactors after B.C.G. vaccination. About two months later, in January and February 1943, an influenza-like epidemic broke out among the school girls, beginning with several cases of erythema nodosum. After a renewed, thorough examination, the source of infection was found to be a teacher of science who held classes in a damp, permanently blacked-out cellar. Some of the classes had not been in contact with the teacher in question, so that out of the total 105 non-reactors, 94 had been exposed and 70 of them had become reactors (74.5%). Of these inverters, 41 showed X-ray changes of the thoracic organs and 37 had a positive gastric lavage. In 11 cases, that is 11.7% of the exposed subjects, a progressive pulmonary tuberculosis developed, followed by death in one case. Among the 133 vaccinated, 102 had been in contact with the infectious source, and only two cases of tuberculosis developed (1.9%). The only girl who had lost allergy after vaccination also suffered from a mild form of the disease. No other cases were found in 5 years of observation in this group. In the group of 130 who were originally reactors to tuberculin, 105 had been exposed, and four cases with positive gastric lavage were found.

Thus we find that most of the experiments on human beings which can be subjected to statistical analysis give a percentage varying between 70-100 of protection to those who are vaccinated (Irvine (15). This evidence has now been accepted universally, and the use of vaccination in the fight against tuberculosis is no more a matter of faith as it was in Calmette's day.

After many years of study and trials, B.C.G. vaccination passed from the experimental phase to practical application in the field of tuberculosis control.

In the spring of 1947, a tuberculosis relief action was started from Denmark through the Danish Red Cross in several European countries. We thought it our duty to make available to the countries where the B.C.G. vaccination was so badly needed, our experience in the practical execution of B.C.G. mass-vaccination programmes, as well as the vaccine and tuberculin necessary. In 1947 more than one million people in six different European ccuntries were tuberculin tested by Danish personnel, and more than 29,000 non-reactors to tuberculin were B.C.G. vaccinated.

In the spring of 1948, the relief organisations in the other Scandinavian countries (Swedish Red Cross and Norwegian Help for Europe) joined the action initiated by the Danish Red Cross, and it then became a joint Scandinavian programme.

In the beginning of 1948, the United Nations International Children's Emergency Fund (U.N.I.C.E.F.) became interested in the B.C.G. vaccination programme, and on 12th March, the Executive Board of U.N.I.C.E.F. allocated the sum of 4 million Dollars for a B.C.G. vaccination programme; 2 million Dollars for the B.C. G. programme in Europe, and 2 million Dollars for the work outside Europe. The actual execution of the B.C.G. programme was left to the Danish Red Cross, acting also on behalf of its other Scandinavian associates. This complicated undertaking was called "The Joint Enterprise". The World Health Organization has, of course, shown great interest in this international programme and is giving technical advice through its Tuberculosis Expert Committee, and especially through the "Sub-Committee on Tuberculin Testing and B.C.G. Vaccination".

Therefore it will be understood that this is a real international fight against tuberculosis which rightly deserves the name "International Tuberculosis Campaign".

For a mass-vaccination programme with B.C.G., it is necessary not only to have experience in the organization of the programme, in the technique of tuberculin testing and application of the vaccine, but also to have a vaccine that has been carefully tried out. Production of a good and well-controlled vaccine is a speciality in which considerable experience is needed. The vaccine must not be so strong that it causes complications, but on the other hand it must be strong enough to be effective in inverting at least 98% to 99% non-reactors to tuberculin into reactors. Only with such a strong vaccine can the allergy and protection produced, last for a considerable period of time. Such a vaccine is available from Denmark, Norway and Sweden in practically unlimited amounts. For the tuberculin testing prior to the vaccination, well-standardised tuberculin must be used, and this is alsc available in practically unlimited quantities.

Only persons showing no reaction to a tuberculin test — the so-called "non-reactors to tuberculin" — shculd be given B.C.G. vaccination. These non-reactors have either never been infected with tubercle bacilli, or the tuberculous infection which they might have had has taken place so long ago that they have either no antibodies against tubercle bacilli at all, or too small a quantity of anti-bodies to give any protection worth mentioning against tubercle bacilli. The B.C.G. vaccine can invert the non-reactors to tuberculin into reactors.

The B.C.G. vaccination will be of no use to persons giving a positive reaction to tuberculin (reactors to tuberculin). Such persons have already obtained, by a natural infection, sufficient antibodies to give them a certain protection (immunity). B.C.G. vaccine is not harmful to such persons, but it might cause some inconvenient complication—(Koch phenomena). Great experience has shown that there is no danger in giving B.C.G. vaccine, even to a person with a case of tuberculosis.

The tuberculin test before the vaccination is made for three reasons:—

1. To eliminate from the vaccination cases of tuberculosis. That means the tuberculin test should be such that practically all the cases of tuberculosis will be reactors.

2. To avoid "Koch phenomena".

3. To divide the population into two groups:—

(a) the persons having immunity enough from natural infection.

(b) the persons needing to have their allergy and immunity increased by vaccination.

The tuberculin test before the vaccination is made in order to protect the reputation of the B.C.G. vaccine. If B.C.G. is given to reactors to tuberculin, we can never be sure that cases of tuberculosis will not be vaccinated also. If that happened, and the case of tuberculosis was diagnosed shortly after the vaccination, the vaccination might be accused of having caused the disease.

If B.C.G. vaccination is made on tuberculin-sensitive persons,some of them will develop the so-called "Koch phenomena", a red, sore infiltration around the site of the vaccination. appearing one or two days after the vaccination has been made and looking very much like an infection with such germs as streptococci. These Koch phenomena are not dangerous, but they are most inconvenient, and will often be erroneously interpreted to mean that the vaccine has been contaminated with ordinary pyogenic germs.

We know that reactors to tuberculin would not benefit from B.C.G. vaccination, that there will be cases of tuberculosis among the reactors, and the Koch phenomena will occur among the reactors. There is therefore no sense in giving B.C.G. to reactors to tuberculin; to do so would soon make the vaccination unpopular.

In the Campaign in Malta we are using **Adrenalin-Pirquet-Test.**

Standardised tuberculin (1.7x International Standard), to which Adrenalin has been added (1 drop 1% Adrenalin solution to 1 cc. tuberculin), is used for this test. By adding Adrenalin, the test is made more sensitive, which means that a greater number of specific reactions are obtained, and that positive reactions are larger and therefore easier to read. The Adrenalin will lose its effect after some time, and, therefore, the mixture cannot be used more than one week after its preparation.

The test is made on the middle third of the volar side of the left forearm. With a vaccination needle (which should not be too sharp), a scratch half to one cm. long is made through the epidermis, but not so deep that any bleeding results. A little bleeding after the tuberculin has been applied seems to be of minor significance. The most common failure is to make the scratch too superficially. A drop of Tuberculin-Adrenalin is rubbed into the scratch with a glass stick. The drop of tuberculin is allowed to dry for at least five minutes before the arm is covered.

The reading of the test is made on the third day. The infiltration and redness are measured where the reaction at the site of the scratch is largest. Positive reactions must show infiltration of at least 4 mm. Reactions with a diameter of 2-3 mm. are regarded as doubtful and infiltration of less than 2 mm. as negative.

The technique of testing and vaccina-

tion is not difficult, but the work has to be done very accurately, and the personnel have to be instructed in detail. The little complications which may arise are mostly due to some carelessness and a little rough technique.

In a very few cases, the local lymph node, usually located in the axillary or subclavicular areas, will enlarge, be a little sore and — in rare instances — even form an abscess. These lymph node abscesses usually develop 2 to 3 months after the vaccination.

If the examination of a vaccinated person reveals that a definite lymph node abscess has developed, a single puncture with aspiration of the abscess should be made. After such an aspiration (in some few cases repeated a month later), this abscess will heal by itself without bursting. It sometimes happens, however, that the vaccinated person does not report to the doctor until the abscess has burst. In this case, no special treatment should be given and especially incision of these lesions should be avoided. It must be remembered that these lesions heal by themselves and should not be considered and treated as ordinary tuberculous abscess.

As mentioned before, complications resulting from the intradermal vaccination are extremley rare. In Denmark we have found only one case in each two thousand persons vaccinated. Nevertheless, people who are to be vaccinated should be warned that such complications may occur, otherwise they will be frightened if a complication does occur.

In the Scandinavian Countries we have great faith in the B.C.G. vaccination, and as you may perhaps know we have compulsory vaccination for several groups of the population.

We have seen the best results among adults between 15 and 25 years old among students, nurses, soldiers and young labourers, living close together in schools, camps and factories. We are sure that the B.C.G. vaccination has saved many of these young people from the "white plague".

The B.C.G. vaccination is of special importance to medical students, who during their hospital training have to work among the tuberculous patients, at an age, when the natural infection produces 10 times more cases of tuberculosis than in early childhood.

It is my wish that medical students in Malta will use a little of their valuable time to obtain a sound knowledge about B.C.G. Vaccination, so that they may be in a position to tackle successfully any difficulty with which they may be confronted on the matter.

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