PREVENTION OF TUBERCULOSIS

BCG IN DIAGNOSIS AND PROPHYLAXIS

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Heaf,[1] writing in the introduction to his monumental symposium on tuberculosis, states that 'in all preventive work it is important to realize that the herd can be classified into 4 groups, namely the susceptibles, the non-susceptibles, the infectious and the potentially infectious'.

'Preventive measures,' he goes on to say, 'must be framed to do 5 things:

'1. Discover all infectious cases.
'2. Prevent the susceptibles becoming infected by breaking the contact between them and the infectious.
'3. Prevent the potentially infectious from becoming infectious by maintaining and increasing their resistance to the disease.
'4. Similarly prevent the non-susceptibles from becoming susceptible by maintaining their high resistance.
'5. Prevent the susceptibles developing disease when they may become infected. This can be done to some extent by vaccination.'

These 5 measures, succinctly set out, constitute the fundamentals of all antituberculosis campaigns.

In order to discover all infectious cases, tuberculin testing must be carried out, while to confer and build up resistance or acquired immunity to the disease, the value of BCG vaccination has now been so firmly substantiated as to require no further advocacy.

It is now firmly established that in tuberculosis the infected individual becomes allergic or hypersensitive to tuberculin, a protein constituent of the bacterial cell. This is the basis of the tuberculin reaction.

Of great diagnostic and epidemiological importance, however, is Koch's observation that whereas large quantities of tuberculin injected into healthy guinea-pigs produced no significant effect, much smaller amounts injected into tuberculous animals produced toxic symptoms and fever leading, in some cases, to the death of the animal.

If minute amounts were injected into the skin of such tuberculous animals, a marked local inflammatory reaction developed rapidly at the site—the so-called 'Koch phenomenon'.[2]

It has long been known that in a subject with tuberculous infection, vaccination with BCG will likewise produce a 'Koch phenomenon'. This is characterized by an accelerated local reaction at the vaccination site which appears within 12 - 72 hours and is usually well marked and definitely demonstrable within 48 hours. The severity of the reaction varies considerably and ranges from an erythema to induration and occasionally pustulation and ulceration; very rarely the local lymphatic glands are involved.

For this reason, among others, various authorities have advocated that only individuals free from tuberculous infection and who are negative tuberculin reactors, should be vaccinated.[1-3]

On the other hand, if the accelerated reaction can be shown to be invariable in positive tuberculin reactors, it could by this very token be employed to detect positive reactors in a population which has not been previously tuberculin tested; in other words BCG vaccination could serve the double purpose of a diagnostic test and of an immunizing agent.

It could, in the same way as tuberculin testing, act as a screen to separate positive from negative reactors and at the same time confer on the vaccinated subjects the benefit of the now universally accepted role which the vaccine plays in the prevention of tuberculosis, namely the artificial production of a greater or lesser degree of immunity and increased resistance to the disease.

Ustvedt and Aaronsen[4, 5] of Oslo (1949) were among the first to use BCG as a diagnostic test by an intradermal procedure. These investigators noticed 3 types of reactions:

1. A non-specific type which appeared after only 1 day, disappears usually on the 2nd or 3rd day, and always before the 6th day.
2. A positive early reaction beginning on the 2nd or 3rd day, reaching its maximum on the 6th or 7th day. When severe, it is regarded as a sign of active tuberculous infection.

3. A late reaction on the 10th to the 14th day.

We agree with Ustvedt's opinion,[6] that the second type of reaction is of special significance, since it provides a more sensitive and specific index than the Mantoux test. He also considered that in cases with a high sensitivity the early reaction may already be strong on the first day and reach its maximum on the 2nd or 3rd day. Our own findings have fully confirmed this observation.

THE VALIDITY OF THE KOCH PHENOMENON AS A DIAGNOSTIC TEST

In order to evaluate the reliability of the 'Koch phenomenon' as a diagnostic test, the following survey was undertaken:

Four groups of subjects were selected as follows—

1. A group of children in an orphanage (age group 8 - 13 yrs.)
2. A group of high-school children (age groups 13 - 17 yrs.)
3. A group of adult students (Indian) at a teachers' training college.
4. A group of known cases of active tuberculosis under treatment at the King George V Hospital.

All subjects in these groups were first tuberculin tested and subsequently vaccinated with BCG.

For simplicity and uniformity all tuberculin testing and vaccination was done with the Heaf multipuncture gun; 6 needles and 2 mm. penetration with 'Weybridge' tuberculin PPD (A. & H.) equivalent to 100,000 units of OT/ml. for tuberculin testing; 20 needles and 2 mm. penetration with freeze-dried BCG vaccine (percutaneous), A. & H.—Glaxo or Danish, for vaccination.

Heaf tests were done on the left forearm and BCG vaccination over the right deltoid.

Reading and classification of the tuberculin reactions were based on the criteria laid down by Heaf as follows:

Negative : Grade 0. Six faint marks on the skin without induration.

Positive : Grade I. Four or more palpable indurated papules each measuring at least 1 mm. in diameter. No reaction is positive unless definite induration is present. Three papules even if coalesced to form an arc are recorded as Grade 0.

Positive : Grade II. The papules have formed a ring of induration with normal skin in the middle. A broken ring is Grade I.

Positive : Grade III. A plaque or plateau of induration of any diameter.

Positive : Grade IV. An area of induration with blistering or ulceration.

BCG vaccination reactions were read after 24 hours and again after 48 hours. Any reaction appearing within 24 to 48 hours was regarded as an accelerated reaction (Koch phenomenon) and recorded as positive. Where no reaction was demonstrated within 48 hours it was recorded as negative.

Following criteria laid down by Griffiths[7] a reaction was recorded as *negative* if the majority of the puncture points produced no lesions (Grade A); and *positive* if the majority of the puncture points produced either macules or papules (Grade B) or pustules (Grade C).

All readings were done and recorded independently by the authors and subsequently compared and correlated.

Group 1: Orphanage

128 Coloured children, age group 9 - 13 years, were tuberculin tested and then vaccinated *en masse* 7 days later, after Heaf tests had been read and recorded.

Findings are set out in Table I.

TABLE I. RESULTS OF TUBERCULIN TESTS AND BCG VACCINATION ON 128 COLOURED CHILDREN

	Total	*%*
Heaf tested and vaccinated	128	100
Heaf-positive reactors	67	52·3
Heaf-negative reactors	58	45·3
Heaf-positive reactors with accelerated BCG reaction	57	85
Heaf-positive reactors with negative BCG reaction	11	16·4
Heaf-negative reactors with negative BCG reaction	40	70
Heaf-negative reactors with accelerated BCG reaction	8	12
% of doubtful BCG reactions in all reactors		2·4

Group 2

321 White children aged 13 - 17 years, attending high school were all Heaf tested, and vaccinated with BCG 7 days later, i.e. on same day that Heaf tests were read. Vaccination reactions were read after 24, 48 and 96 hours.

A positive reaction varying in intensity from Grade B to Grade C appearing within 24 - 48 hours after vaccination was regarded as an accelerated reaction or 'Koch phenomenon', and recorded as positive. Where no reaction was found within this period, it was recorded as negative or doubtful.

Observations are recorded in Table II.

TABLE II. RESULTS OF TUBERCULIN TESTS AND BCG VACCINATION ON 321 WHITE CHILDREN

	Total	*%*
Heaf tested and vaccinated	321	100
Heaf-positive reactors	157	48·9
Heaf-negative reactors	164	51·1
Heaf-positive reactors producing accelerated BCG reaction	115	73·2
Heaf-positive reactors with negative BCG reaction	37	23·6
Heaf-negative reactors producing negative BCG reaction	114	70
Heaf-negative reactors producing accelerated BCG reaction	23	14
% of doubtful BCG reactors in all reactors		9·3

Group 3

36 Adult Indian students at a teachers' training college were all Heaf tested.

18 subjects who were Heaf-negative reactors were vaccinated with BCG and the reaction read after 24, 48, 72 and 96 hours, and again after 7 and 11 days.

The results are tabulated in Table III.

TABLE III. RESULTS OF TUBERCULIN TESTS AND BCG VACCINATION ON 18 ADULT INDIANS

Total cases	*Heaf-positive reactors*	*Heaf-negative reactors*	*Heaf-negative reactors BCG-negative after 24 hrs.*	*48 hrs.*	*72 hrs.*	*96 hrs.*	*7 days*	*11 days*
36	18	18	16	13	9	5	8	8
			90%	72·7%	50%	27·7%	44·5%	44·5%

It will be seen that after 24 hours, 90% of these negative reactors showed no evidence of a BCG reaction. After 48 hours 72% were still BCG negative and 28% showed the Koch phenomenon.

On the 4th day after vaccination only 27·7% were BCG negative and 72·3% were showing a positive BCG reaction.

On the 7th day, and still later on the 11th day, 44·5% had no BCG reaction and 55·5% had a marked reaction.

Included in the negative findings on days 7 and 11 was 1 case which was positive after 24 hours and whose reaction had faded by day 7; 2 cases positive on 3rd day and negative on day 7; 5 cases were negative throughout observation period and 1 case with marked accelerated reaction after 24 hours was positive throughout.

Conclusion. The evidence in this small group suggests that in proven negative reactors BCG vaccination may produce an accelerated reaction evident within 48 hours (which was arbitrarily adopted as the crucial period), in 28% of the subjects and that 72% show no reaction. In a general BCG vaccination campaign therefore, in previously untested individuals, the absence of an accelerated reaction within 48 hours could justify the assumption that such individual was a negative reactor.

Group 4

Patients known to be suffering from active pulmonary tuberculosis and under treatment at King George V Hospital were all given BCG as a routine procedure after sputum conversion. Since June 1962, 2,200 patients in this category have been vaccinated. Personal observation of 500 of these cases has provided evidence that the Koch phenomenon appears without exception in these patients including children with primary tuberculosis and positive Heaf tests.

The reaction is visible within 24 hours in most cases and within 48 hours in all cases. It varies in intensity from grade B to grade C going on to ulceration in several instances. In no cases have there been any serious complications and regional glandular involvement is rare.

In this group the Koch phenomenon was invariably found in all the cases observed, and it can be confidently stated that in cases of active pulmonary tuberculosis an accelerated reaction will occur on the administration of BCG.

Conversely, if an accelerated reaction occurs in any subject who has been vaccinated with BCG, further investigation will be required to exclude active pulmonary tuberculosis. There is undoubtedly a very close correlation between the positive Heaf test, the Koch phenomenon and active tuberculous disease (Tables IV and V).

TABLE V. SUMMARY OF DATA FROM PREVIOUS TABLES

Institution	*Heaf-positive reactors*	*Heaf-negative reactors*	*Heaf-positive/ BCG positive*		*Heaf negative/ BCG negative*	
			Total	*%*	*Total*	*%*
Orphanage	67	58	57	85	40	70
High school ..	157	164	115	73·2	114	70
Teacher's training college..		18			16	88·8
King George V Hospital	500	0	500	100	0	0
					0	0
Total	724	240	672	92·8	170	71

DISCUSSION

Several important features emerge from an examination of the statistical analysis of 982 cases included in this survey and tabulated in Tables IV and V:

1. Of 985 cases that were Heaf tested, 742 were positive reactors and 240 negative. Included in the positive reactors were 500 cases of active pulmonary tuberculosis under treatment in this hospital.

2. Of 962 cases vaccinated with BCG, 719 gave an accelerated reaction (Koch's phenomenon) clearly demonstrable within 48 hrs.; 209 showed no reaction and in 33 the reaction was doubtful and for the purposes of the survey could be classed as negative.

The reactions varied in intensity from grade B to grade C and were usually of maximum intensity in the group of tuberculous hospital patients where the Koch phenomenon appeared without exception. With the exception of the hospital group all readings were done without previous knowledge of the tuberculin sensitivity of the groups concerned, although all cases had previously been tuberculin tested and findings recorded.

3. In a subsequent analysis it was found that of the 719 accelerated BCG reactions, 672 or 93% had occurred in proven Heaf-positive reactors and 48 or 6·6% in Heaf-negative reactors. There was thus a very close correlation between Heaf positivity and the Koch phenomenon. The correlation is sufficiently close to justify the assertion that, in a mass BCG vaccination campaign in a population of unknown tuberculin sensitivity or which had not been previously tuberculin tested, the appearance of an accelerated BCG reaction would, in more than 9 cases out of 10, indicate a positive PPD reactor.

To this extent therefore, BCG vaccination, *inter alia,* serves the same purpose as Heaf testing. It is at least as reliable as a screening measure and has the advantage of providing a rapid reading within 48 hours.

4. In 209 cases there was a negative BCG reaction and in 33 cases the reaction was doubtful and could be classed as negative. Of 240 Heaf-negative reactors, 209 or 70·8% were BCG negative. If doubtful BCG reactions are included, we find a 100% correlation between Heaf negativity, and BCG negativity.

Therefore by the same argument as above the non-appearance of the Koch phenomenon in a vaccinated subject would justify the assumption that the case was tuberculin negative and not suffering from active tuberculous disease.

5. In 33 cases which were Heaf negative an accelerated BCG reaction was noted. The reasons for this paradoxical result are at the moment obscure and will require further

TABLE IV. ANALYSIS OF ALL CASES HEAF TESTED AND VACCINATED WITH BCG

Institution	*Total Heaf Tested*	*Total Heaf +ve reactors*	*Total Heaf −ve reactors*	*Total Heaf doubtful reaction*	*Total vaccinated BCG*	*Total BCG +ve accelerated reaction*	*Total BCG −ve negative reaction*	*Total BCG doubtful reaction*	*Total BCG +ve ileaf +ve*	*Total Heaf −ve BCG −ve*	*Total Heaf +ve BCG −ve*	*Total Heaf −ve BCG +ve*	*% BCG +ve in Heaf +ve reactors*	*% BCG −ve in Heaf −ve reactors*
Orphanage Age group 9–13	128	67	58	5	123	65	55	3	57	40	11	8	85	70
High school Age group 13–17 ..	321	157	164	0	321	152	138	30	115	114	37	23	73·2	70
Teacher's training college Age group 18–25	36	18	18	0	18 only −ve reactors	2	16	0	0	16	0	2	0	88·9
King George V Hospital. Patients with active tuberculosis under treatment..	500	500	0	0	500	500	0	0	500	0	0	0	100	0
Totals	985	742	240	5	962	719	209	33	672	170	48	33	90·5	70·8

investigation. It may be due to the possibility that diagnostically BCG vaccination is a more sensitive test than PPD to cross-sensitivity and other factors.

In any event, in such cases, the appearance of the Koch phenomenon in itself would require further investigation to exclude active tuberculous disease and would still serve a valuable diagnostic purpose.

6. In a small percentage of cases (48 out of 962—5%) there was no Koch phenomenon obtained in known Heaf-positive reactors. This result will require further elucidation.

Frappier and Guy[8] and other authors have strongly advocated the use of BCG for diagnostic purposes and their scarification test is now extensively employed in Quebec, Newfoundland and the Indian Health Service where it has replaced PPD for elimination testing before vaccination. They and other authorities believe that the test is more sensitive than the standard PPD tests and that it detects total allergy, i.e. both tuberculin and so called 'infra tuberculin' or bacterial allergy.

South Africa has a large Bantu population scattered over a vast countryside, in areas of varying population densities and living under primitive conditions. Distances, inadequate roads and poor means of communication, make access to these communities difficult and public health measures, which are simple in an urban community, present a formidable problem in these rural areas.

Therefore procedures aimed at large-scale diagnosis and prevention under such conditions must be as simple and time-saving as possible. They should not require the employment of highly trained personnel, nor should they require too many visits to be made.

It would appear from this survey that BCG vaccination ideally fulfils this purpose, since the single inoculation serves a dual function. It confers a degree of immunity and provides also a sensitive diagnostic test in some respects superior to tuberculin.

It should be practicable to employ this single procedure to vaccinate the community and to detect within 24 - 48 hours by the appearance of the accelerated reaction, the incidence of tuberculin sensitivity in the vaccinated community and thereby active, latent or past disease requiring further investigations and appropriate treatment.

SUMMARY

1. A survey is described to determine the value of BCG vaccination as a diagnostic test and its practical application.

2. A very close correlation between the accelerated reaction after BCG vaccination and tuberculin sensitivity is clearly demonstrated.

3. No significant serious side-reactions have been encountered even in cases of active tuberculosis under treatment.

4. As a diagnostic test, BCG vaccination appears to be more sensitive than tuberculin.

5. It would be eminently suitable for employment in rural areas for epidemiological surveys and as an economical substitute for tuberculin for the following reasons:

(*a*) Procedure is simple.
(*b*) Reactions are clearly demonstrable within 48 hours.
(*c*) Highly trained personnel not necessary.
(*d*) Only 2 visits would be necessary at an interval of 48 hours.

6. A single inoculation serves the dual purpose of protection and diagnosis.

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