LIMITATIONS OF THE ACCELERATED BCG REACTION AS A TEST FOR PREVIOUS INFECTION WITH THE TUBERCLE BACILLUS

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For obvious reasons, a mass BCG vaccination campaign without previous tuberculin testing has tremendous advantages in emerging countries where long distances ensure that a disappointing proportion of subjects who are tuberculin tested will present for reading and vaccination. A wealth of experience has accumulated in this country and elsewhere to show that vaccination of tuberculin reactors can be safely performed. Furthermore, much work has been done on the accelerated vaccination reaction as an index of pre-existing tuberculin sensitivity. Various studies in Durban schools during 1963, using multiple-puncture technique with the Heaf apparatus Mk III and freeze-dried percutaneous BCG vaccine, demonstrated an approximate correlation between accelerated BCG reactors at 48 hours and positive tuberculin reactors detected by the Heaf multiple-puncture test read after 7 days.

A previous investigation in 2 Johannesburg schools (one White and one Bantu) demonstrated that 48 hours is the optimum time for interpretation of the accelerated vaccination reaction (Fig. 1). In this study the children were given 10 TU of PPD Weybridge by intradermal injection into the anterior surface of the left forearm, and the transverse diameters of the reactions were recorded in millimetres after 72 hours, when all pupils received percutaneous BCG. The vaccination sites were examined daily on the following 4 days by 3 observers who recorded a majority vote of 'positive' or 'negative' on each occasion. A positive BCG reaction was defined as one which developed palpable induration at the site of the punctures. Erythema alone was ignored. Tuberculin reactions with transverse induration of less than 6 mm. were regarded as 'negative', and 6 mm. and more was 'positive'. A total of 459 children of both races attended on every occasion.

Five children with 'positive' tuberculin reactions showed no BCG reaction at any stage during the observation period. Of greater significance was the fact that 90 children with 'negative' tuberculin reactions showed a definite accelerated BCG reaction at some stage during the 4 days following vaccination.

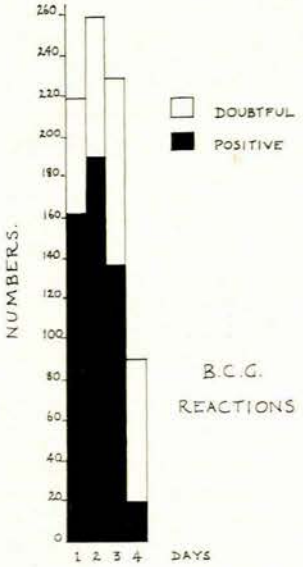

Fig. 1. Interpretation of 'positive' and 'doubtful' BCG reactions on the first 4 days following percutaneous vaccination.

This finding led me to conduct further trials in Durban in an attempt to explain the anomaly. Previous work by Kuper[1] in the Johannesburg area had demonstrated a type of tuberculin sensitivity which was more readily elicited by avian than human tuberculin. He suggested that avian sensitivity is acquired earlier in childhood than the human type. There is much literature which shows that atypical or non-tuberculous acid-fast bacilli occur fairly generally throughout the world. The World Health Organization has stated that the assessment of BCG-induced allergy in some parts of the world is made difficult by the existence in the population

of a widespread low-grade sensitivity to tuberculin, of presumably non-specific origin.[2] Its Expert Committee on Tuberculosis, reporting on the practicability of direct BCG vaccination in Mauritania,[3] stated that the findings confirmed that the induration which develops at the site of the injection 3 - 4 days after (intradermal) vaccination is correlated with the size of pre-vaccination tuberculin reactions in the vaccinated individuals, but that it was not possible to define any size of vaccination lesions which would efficiently demarcate the limit between 'reactors' and 'non-reactors' in the vaccinated group. In Dahomey[4] the WHO team found an almost complete lack of correlation between size of pre-vaccination tuberculin reactions and post-vaccination induration, at any time after vaccination, and considered that it would be impossible to estimate the pre-vaccination level of tuberculin allergy on the basis of the size of vaccination reactions. The preliminary findings of Egsmose[5] in Kenya seemed to indicate that early vaccination indurations might prove useful for judging the level of pre-vaccination tuberculin sensitivity, but in the area of Kenya where this study was carried out, non-specific tuberculin sensitivity was found to be virtually non-existent by Roelsgaard and Nyboe in 1961,[6] whereas it is highly prevalent in Dahomey.

Durban Observations

Most of my experience in Durban has been with the multiple-puncture tuberculin test, and in studies involving many hundreds of school children who each received human PPD Weybridge in a strength of 2 mg./ml. on the left forearm and simultaneous avian PPD Weybridge of the same strength on the right forearm, it was frequently observed that the reaction to avian PPD was stronger than that produced by human PPD. It has been stated by Van Zwanenberg[7] that in the epidemiology of tuberculosis large reactions to human PPD administered by multiple puncture appear to show significant evidence of infection by *M. tuberculosis*, while small reactions might be caused by infection with other mycobacteria ; or that the size of the reaction may depend on the dose of the infecting organism or on the number of times infection occurs. Stewart and Embleton[8] considered it likely that in man, as in animals, greater skin sensitivity is elicited by the homologous tuberculin than by heterologous tuberculins, and that when the identity of the infecting mycobacterium is not known and testing is carried out with two or more PPDs prepared from different types of bacilli, the one which is antigenically more closely related to the infecting organisms will produce the larger reactions.

It appears that in Durban and Johannesburg,[1] and possibly throughout the Republic, infection with some organism which produces greater sensitivity to avian tuberculin than to human tuberculin is widespread, and that this may be a factor in producing 'false-positive' reactions when the 'BCG test' is used to estimate the pre-vaccination level of tuberculin sensitivity in mass vaccination campaigns. One of many local studies which tend to show that this is so was carried out on the pupils of an Indian school. Of 714 accelerated BCG reactors, only 416 had positive human tuberculin Heaf tests at 7 days, while 120 further positive human tuberculin reactors produced no BCG reaction at 48 hours. In the same school, a group of primary school age was given simultaneous human and avian multiple-puncture tuberculin tests, and of 47 accelerated BCG reactors, all were negative to human tuberculin, and 44 were positive to avian tuberculin (Fig. 2). A group of 361 accelerated BCG reactors in another Indian school had 267 positive human PPD reactions and 335 positive avian PPD reactions (263 were positive to both).

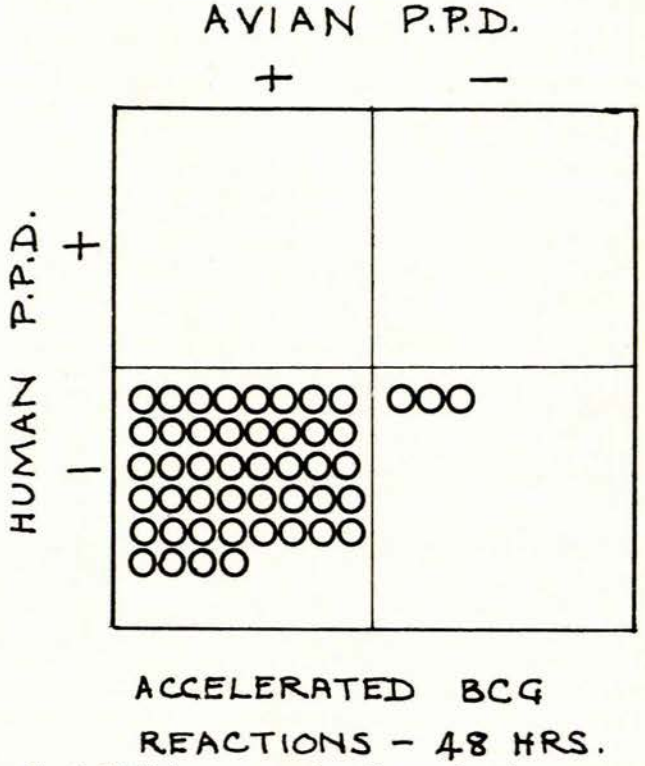

Fig. 2. Multiple-puncture tuberculin reactions in a group of 47 children who showed an accelerated BCG reaction at 48 hours.

In an earlier study in a White high school when an attempt was made to grade the BCG reactions at 48 hours in a similar way to the usual grading of the Heaf tuberculin reactions, with the addition of 'doubtful' BCG reactions to correspond with weak or doubtful Heaf reactions, Hartston[9] demonstrated that the avian results approximated the BCG grades more nearly than human PPD (Fig. 3).

Reactions

It is of interest to note that while large numbers of 'false-positive' reactions are encountered when using the BCG reaction at 48 hours to determine pre-vaccination human tuberculin sensitivity, there is also a smaller number of cases in which 'false-negative' reactions occur. Probably different mycobacteria are responsible for the confusion in different areas, and perhaps the optimum time for interpretation of the 'BCG test' varies with the severity of the infection and the lapse of time following infection.

Hartston[10] has described the *usual* 'normal' local reaction to multiple-puncture BCG vaccination in previously uninfected persons as a group of 2 mm. papules which appear in a week, remain about the same size, discrete and pink, and heal in 2 or 3 months with scarcely perceptible

pinhead scars. He also states that the intensity and duration of the local BCG reaction depends on the potency and dose of the vaccine, whether clumps of organisms are injected, the depth of injection into the skin and the individual peculiarities of the patient's tissue reactions;

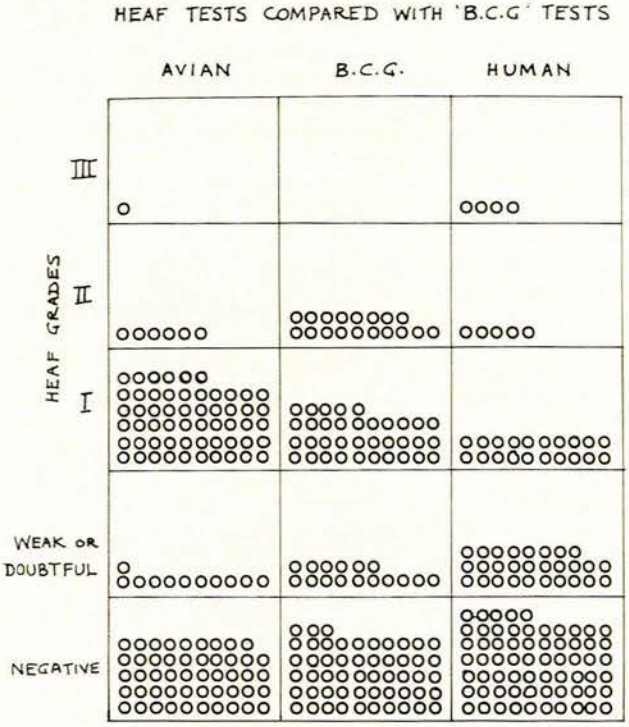

Fig. 3. BCG reactions at 48 hours compared with avian and human multiple-puncture tuberculin reactions (after Hartston).

and that the bacilli remain longer and multiply more at the site of injection in subjects previously infected. Proximity to a recent previous BCG vaccination or tuberculin injection gives a quicker and more intense reaction.

BCG has also been shown to be more sensitive than tuberculin in demonstrating pre-allergic and hypo-allergic states. Furthermore, the fact that it contains all fractions of the bacillus makes it reasonable to assume that sensitivity reactions are more likely to occur in the presence of infections with other acid-fast organisms than with a purified protein derivative of the human *M. tuberculosis*.

In my experience a typical accelerated BCG reaction occurring in a subject with marked tuberculin sensitivity consists of uniform induration of the skin beneath the puncture site, in addition to papule formation at the point of entry of each needle, together with a variable amount of erythema (the depth of penetration of the needles being 2 mm.). The lesion is sometimes present as early as 12 hours after vaccination, and persists for a variable period, usually months. In some children known to have marked avian sensitivity, healing was often not complete 6 months after vaccination, and in two cases a periodic flare-up involving increased erythema and induration was reported to occur in association with respiratory symptoms described by the parents as 'tightness of the chest'.

It has already been shown that in 2 Johannesburg schools in which 10 TU Mantoux tests were compared with BCG reactions on the 4 days following vaccination, the second day appeared to be the optimum time for reading the BCG test. However, in the mass BCG inoculation and diagnostic campaign of the Johannesburg City Health Department reported in this *Journal*,[11] the local reaction was generally read after 24 hours, although it was stated that observation in a group of 'positive' reactors 48 hours after inoculation showed the changes to be more marked than at 24 hours. The control programme of the Johannesburg campaign called for the treatment with isoniazid for 2 years of all 'positive' reactors under the age of 5 years, but the number of cases in this group was not stated.

Differences in Comparison

In a more recent campaign on a smaller scale conducted by the State Health Department in the Eshowe area, percutaneous BCG vaccination was given to 54,268 persons, of whom 12,604 were 5 years of age or less. Simultaneous vaccination with calf lymph was performed on all non-Whites (the vast majority) and in addition all non-Whites up to the age of 6 years received oral poliomyelitis vaccine. Three days after the immunization procedure, the BCG reactions were recorded, and 70 mm. chest X-ray films were taken of all accelerated reactors 6 years of age and above. Doubtful cases were regarded as 'positive', with the result that 3,448 children of 5 years and under were classed as 'positive' reactors and thus eligible for treatment with Neotizide. This figure is out of all proportion to the 109 cases of active pulmonary tuberculosis reported (in addition to known cases in hospitals), in the X-ray screening of 31,964 'positive' reactors in the age group 6 years and over. Obviously, gross error occurred through giving the benefit of the doubt in favour of 'positive' reactors, and no comparison can be made with the more carefully controlled Johannesburg campaign. Nevertheless, the mere fact that the element of doubt did result in such obvious over-reading in the Eshowe programme does raise the question whether the accelerated vaccination lesion can be used as a reliable guide to the detection of tuberculosis-infected individuals in the conditions generally applicable to mass immunization campaigns in the Republic. In this particular campaign the interpretation of reactions was done by lay personnel with little knowledge of tuberculin reactions and sensitivity phenomena, but I was present at 2 of the sessions when vaccination lesions were interpreted, and was able to confirm the difficulty of a clear-cut division into 'positive' and 'negative' reactors in many instances.

In an attempt to reduce the number of children who required treatment to reasonable proportions, subsequent multiple-puncture tuberculin tests using both avian and human PPD were carried out approximately 2 months after vaccination on a group of 163 Bantu children, bearing in mind that the usual conversion reaction following percutaneous vaccination is not greater than a Heaf grade 1 reaction, and that active tuberculous disease, in the absence of anergy-producing conditions, is generally associated with a more fierce tuberculin reaction. This rough and ready method disclosed that only about 20% of this group, who were designated as 'positive' BCG reactors, originally had Heaf reactions of grade II or more to human PPD; that the majority of children had

a grade I or weak (non-specific type) human reaction ; and that in many instances the avian reaction was appreciably stronger than the human reaction.

Results in the USA

A recent American report[12] claims that between 20% and 70% of the adult population in various parts of the United States demonstrate skin reactivity to antigens derived from one or more unclassified mycobacteria, and the incidence of these reactions increases rapidly after infancy and is most prevalent in warm climates at low altitudes and in populations which have close contact with the soil. It was further stated that a significant proportion of tuberculin reactions represent cross-reactions consequent to unclassified mycobacterial sensitivity.

SCHEME FOR MASS IMMUNIZATION

Our experience in Durban confirms the presence of widespread non-specific sensitivity occurring at an early age, readily elicited by avian tuberculin in many cases, and producing weak cross-sensitivity reactions to human tuberculin, so that no importance is attached to weak human tuberculin reactions in the absence of other evidence of tuberculous disease (Fig. 4). Testing with both avian and human tuberculin has become a routine in some cases,

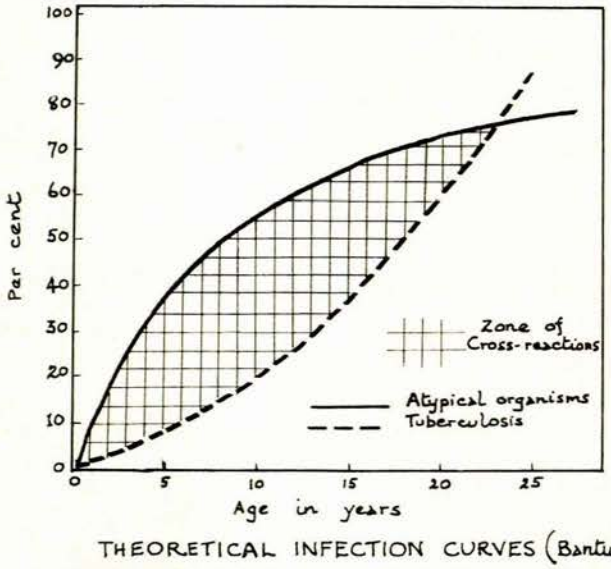

Fig. 4. Theoretical infection curves in the Bantu, showing a zone in which confusing reactions to human tuberculin might be expected to occur because of cross-sensitivity to an atypical organism; and in the older age groups, human tuberculous infection overshadows the atypical infections.

and research with other 'atypical' mycobacterial antigens is being undertaken in an attempt to establish diagnostic tuberculin profiles for local conditions. It is apparent that tuberculin testing with a single antigen can no longer be regarded as a satisfactory diagnostic measure in those cases which produce mild reactions.

A Practical Scheme for Indiscriminate BCG Vaccination Combined with a Diagnostic Procedure

Since the accelerated BCG reaction is unreliable as a diagnostic measure where confusing factors such as atypical mycobacterial infections are present, and because considerable numbers of persons fail to keep the second appointment in any selective vaccination campaign in this country, the following programme is suggested in order to derive the greatest benefit from any mass immunization campaign :

1. *Five years of age and under.* Simultaneous percutaneous BCG vaccination in the area of the right deltoid insertion and Heaf tuberculin test with human PPD on the left forearm at the initial visit. All significant positive tuberculin reactors to receive isoniazid, and chest X-ray examination reserved for those with clinical evidence of disease.

2. *All children of school-going age.* Simultaneous percutaneous BCG vaccination and Heaf tuberculin test as above, but

   (*a*) all positive tuberculin reactors to have a chest X-ray examination, and all those with radiological abnormality to receive isoniazid. Where possible, follow-up X-ray examination of all in this group should be carried out over a period of at least 3 years.

   (*b*) All fierce reactors (Heaf grade II or more) should receive isoniazid irrespective of radiological findings.

3. *All persons of post-school age.* Percutaneous BCG is given only on first visit. 'BCG test' should be read after 72 hours.

The reason for suggesting 72 hours instead of 48 hours is that the Heaf test can be read with reasonable accuracy on the third day, since any good reaction at 7 days will be unmistakably positive at 3 days, and thus a complete programme including all three groups can be carried out with only two visits to each centre. In adults, particularly in the Bantu, sensitivity due to natural tuberculous infection can reasonably be expected to overshadow that arising from unclassified mycobacterial infections (Fig. 4).

SUMMARY

Accelerated BCG reactions, in addition to signalling the 'Koch phenomenon' in the presence of tuberculous infection, also occur in the presence of various atypical or non-specific mycobacterial infections, which are widespread in the Durban area. The BCG test is thus unreliable as a diagnostic measure in areas where atypical mycobacterial infections occur, as demonstrated in Durban by skin sensitivity to an antigen prepared from the avian bacillus.

Cross-sensitivity phenomena may lead to confusion in the interpretation of tuberculin tests with human PPD in the presence of atypical mycobacterial infections, and weak reactions cannot be regarded as proof of infection with the human tubercle bacillus unless atypical infections have been excluded.

A practical scheme for indiscriminate BCG vaccination combined with a diagnostic procedure is suggested.

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