BCG Vaccination Against Leprosy[1]

The importance and value of a protective vaccine against leprosy are obvious. Unfortunately a specific vaccine prepared from killed or attenuated bacteria is not available for testing because the causative organism of leprosy, *M. leprae*, has not been cultured *in vitro*. However, the original observation of Fernández in 1939 ([7]) that conversion to lepromin positivity occurred in a large proportion of lepromin-negative children following BCG vaccination, an observation subsequently confirmed by many workers, led him to suggest that BCG vaccination might confer some protection against leprosy. The later work and writings of Fernández ([8]) and Chaussinand ([3]) drew attention particularly to the possible similarities between tuberculin and lepromin sensitivity as a measure of protective immunity against tuberculosis and leprosy respectively. Because BCG vaccination could induce positivity to both skin tests in negative subjects, and because there was already evidence that BCG vaccination gave protection against experimental tuberculosis, there was a strong case for using BCG vaccination against leprosy in man. Their views dominated the field of leprosy, and several small trials of BCG vaccination against leprosy followed, in particular those by de Souza Campos ([15]), Fernández ([9]) and Convit ([4]). Although there was some suggestion of protection in the vaccinated group, especially against the development of lepromatous type leprosy, none of the trials was carried out on a large enough scale or with adequate control or special care to establish the vaccinated and unvaccinated groups by random allocation, so as to withstand critical analysis.

This was no particular criticism of the leprosy workers, because, in fact, exactly the same criticism and uncertainty existed at that same time regarding the value of BCG vaccination against tuberculosis. In fact, it was not until 1956, with the first publication of the definitive trials undertaken by the British Medical Research Council ([1]) that the value of BCG against tuberculosis in man was finally established to the satisfaction of all the critics. For several years recommendations had been made to establish large-scale trials of BCG vaccination against leprosy which would yield scientifically acceptable results, and these had been urged by successive WHO Expert Committees on Leprosy ([18, 19]) and International Congresses of Leprology. Therefore the first progress report by Kinnear Brown and Stone on a large-scale trial of BCG vaccination of children against leprosy ([2]) is a most important contribution to this difficult and controversial subject. The report is of an investigation into the prophylactic effect of BCG vaccine planned by the Uganda Government with continuing scientific and technical guidance by the Leprosy Committee of the British Medical Research Council. The controlled trial was initiated in September 1960 in the Teso District of Eastern Uganda, and, by September 1962, 19,079 children, more than 80 per cent of whom were aged under 10 years, had been included. All were relatives or contacts of known leprosy patients. All the children were examined and those with leprosy or with suspected leprosy lesions were recorded; all were tuberculin-tested also, by the Heaf multiple puncture method, but the majority of the trial children were not lepromin-tested. The children with negative reactions (Grade 0) or with weak positive reac-

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tions (Grade I or II) were assigned at random to an unvaccinated group (8,152 children) and to a BCG-vaccinated group (8,149 children). The BCG preparation used was freeze-dried; tuberculin retests in a sample of children given each batch of BCG vaccine showed satisfactory potency of the vaccine. Those with positive Grade III or Grade IV reactions (1,096) were all left unvaccinated, as were children (390) who already had skin lesions due to leprosy. The efficiency of the first follow-up between May 1963 and May 1964 was remarkable. By one means or another the investigators reexamined 94 per cent of the children within one to three years of entry in the trial. The present report is of a preliminary nature, and the periodic examinations are continuing.

The main basis of the comparison in the report is the incidence of new cases of leprosy detected in the unvaccinated and vaccinated groups (16,301 children) within the first three years after entry into the trial. The most stringent precautions were taken to avoid any bias at the time of the follow-up examination. In particular, no BCG vaccination records were available to the examiners and a piece of adhesive paper was placed on *every child* at the site where vaccination would have been made, whether they were vaccinated or unvaccinated, in order to conceal the presence of a vaccination scar from the examiner. In the vaccinated and unvaccinated groups there were 107 cases of leprosy, 89 among the 8,071 unvaccinated children and 18 among the 8,091 BCG-vaccinated children. Thus the incidence in the unvaccinated children was 11.0 per thousand and in the vaccinated children 2.2 per thousand. The probability of this difference arising by chance is less than one in a million. Thus, under the conditions of this trial, BCG vaccination reduced the incidence of leprosy by 80 per cent.

Brown and Stone are to be congratulated in undertaking a trial of BCG in leprosy, incorporating, for the first time, all the control procedures and statistical methods considered necessary for assessing the value of a protective vaccine in man. Their present study was based on an effectively random allocation of children with negative or weakly positive tuberculin reactions (up to Grade II) to the vaccinated and unvaccinated groups. These two groups can, therefore, be regarded as alike on entry to the investigation, apart from their vaccination status, and as exposed to the same risks of contracting leprosy subsequently. Furthermore, the two groups have been followed similarly, and no bias has been allowed to enter into the assessment of the cases of leprosy developing among them. Therefore the difference in the incidence of the disease in the vaccinated and unvaccinated groups can be attributed directly to the vaccine, and at the present stage of the follow-up it can be concluded that BCG vaccination of children in Eastern Uganda has conferred substantial protection against early forms of leprosy for a period of one to three years (average two years).

These points are stressed because the authors, also very wisely, emphasized that these preliminary significant results apply to a period of only three years and apply only to protection against early forms of tuberculoid type leprosy. Such caution is especially relevant in a very chronic infection with a long incubation period in which, in children, it is well known that self-healing of early tuberculoid lesions is a common feature ([12]). The latter point is brought out in the Uganda trial, where the 1-3 year follow-up of the children with leprosy detected at intake showed that 8 per cent had resolved completely and that a further 21 per cent appeared to be resolving at that time. It is thus possible that the early types of leprosy skin lesions in children represent a natural immunologic response to infection with *M. leprae*, and vaccination may have done no more than modify this response to a first infection. It is therefore of particular importance to follow up the children in the trial for some years (the trial is planned for a minimum of 5 years) in order to see how these lesions evolve in the unvaccinated, and whether or not later more fully developed tuberculoid type leprosy appears in the vaccinated group. In Uganda, as in most of Africa, some 90 per cent of leprosy is of the tuberculoid type; the more severe

and highly infectious lepromatous type affects some 8 per cent of patients in the Teso area and in the first follow-up period no lepromatous cases were found in the trial children. Again, it is hoped that this trial will be continued in order to see if BCG vaccination protects against lepromatous type leprosy also. In this respect the large-scale trial of BCG started in 1964 by WHO ([20]) in Burma will be of particular importance, and complementary to the Uganda trial, because in Burma the lepromatous rate is between 40 and 70 per cent.

One surprising finding was that BCG vaccination gave the same order of protection (80 per cent) against leprosy as was obtained by the British Medical Research Council in their trials against tuberculosis ([1]). However, such cross immunization is not unique in the field of vaccination, as exemplified by the classic use of cowpox vaccine in prophylaxis against smallpox in man. Moreover, within the family of mycobacteria experimental studies have shown that BCG vaccination gives protection against *M. ulcerans*, *M. avium* and *M. balnei* ([6]) and against *M. lepraemurium* ([11]). Even more relevant to this phenomenon are the results obtained by Shepard ([13]), who showed that BCG vaccination significantly diminished the multiplication of *M. leprae* in experimental leprosy in the mouse foot pad. All these results are particularly encouraging because there is still no immediate prospect of being able to prepare a specific vaccine from *in vitro*-grown *M. leprae*.

An even more surprising observation was that the percentage reduction in leprosy incidence is apparently independent of the age of the child when vaccinated. A proportion of the older children will already have been infected with leprosy bacilli at the time of vaccination, and in such circumstances vaccination might have been expected to be less effective. However, in a subsidiary part of the investigation, a small group of children with suspected lesions initially were included in the random allocation process and for them vaccination did not reduce the incidence of leprosy. There must, therefore, be some stage in the development of clinical leprosy, following infection with leprosy bacilli, after which vaccination is no longer able to modify or arrest the process, and it can be anticipated that more detailed analyses of the data from the Uganda trial will help to answer more precisely this important question. Moreover, there is recent evidence from the experimental side to anticipate that BCG vaccination given even during the stage of incubation may prevent the development of overt leprosy; this view is based on Shepard's observation that the multiplication of *M. leprae* in the mouse foot pad is suppressed efficiently whether the animals were vaccinated before or during the active phase of the infection when the bacilli were multiplying in the log phase ([14]).

For the main part of the Uganda trial it was decided to omit lepromin testing of the children in the vaccinated and the unvaccinated groups. To determine the lepromin conversion by BCG two lepromin tests, pre- and postvaccination, would have been required. Because lepromin itself, unlike tuberculin, is capable of inducing lepromin positivity, particularly on repetition ([16]), it was considered that lepromin might also produce some measure of protection against leprosy, and, if so, that this effect might be enhanced by the addition of BCG vaccination. Because of these possibilities it seemed essential in an assessment of the protective effect of BCG vaccination to exclude the use of lepromin, particularly since lepromin testing could not be included in mass BCG vaccination programs. However, BCG vaccination does not induce 100 per cent conversion to lepromin positivity and it has been suggested, particularly by Hanks ([10]), that the "poor converters" include those subjects most susceptible to leprosy. It is hoped that the subsidiary group of children in the Uganda trial who were also lepromin-tested will eventually be analyzed and will be large enough to elucidate this problem.

Although it will be essential to continue the follow-up in this Uganda trial for at least a further five years, the observed significant prophylactic effect of BCG against the development of early cases of tuberculoid leprosy in children already suggests that BCG vaccination should be incorporated now into leprosy control programs.

Because one peak incidence in leprosy is reached at the age of 15 years, there is a good case for vaccinating within the first year of life, and certainly all children up to the age of 15 years should be vaccinated in order to protect as many children as possible before they become infected. To facilitate the introduction of BCG vaccination for protection against leprosy in endemic areas it will be essential for the national and international leprosy control schemes to collaborate and plan their programs in association with the tuberculosis organizations concerned with BCG vaccination. The recent recommendations by the WHO Expert Committee on Tuberculosis ([21]), based on the view that BCG vaccination can be given safely without prior tuberculin testing, provide a practical means of carrying out BCG vaccination in leprosy control schemes without employing specially trained personnel for the tuberculin testing. However, if such widespread schemes are undertaken, it would be wise at this stage to screen the older children and to withhold vaccination from those with incipient leprosy lesions as well as those with obvious disease. This point is stressed because Brown and Stone believed there was a suggestion from the Uganda trial that in some individuals vaccination may even have stimulated the development of the disease, and two of the 18 vaccinated participants who developed leprosy dated the first signs of their disease to the weeks immediately following vaccination. Furthermore, BCG vaccination, like other inoculations, may precipitate reactions in leprosy patients ([17]). Finally, the results of the Uganda BCG trial, coming, as they do, within a few weeks of the preliminary results from a continuing, long-term study in India, at the Central Leprosy Teaching and Research Institute, Chingleput, Madras ([5]), indicating that dapsone may have a prophylactic effect in children exposed to leprosy, may, with the results of that study, provide, for the first time, preventive measures that will contribute significantly to the final successful control of this historic infection.

—R. J. W. Rees

REFERENCES

1. [British Medical Research Council.] BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescents. First progress report. Brit. Med. J. **1** (1956) 413-427.
2. Brown, J. A. K. and Stone, M. M. BCG vaccination of children against leprosy: first results of a trial in Uganda. Brit. Med. J. **1** (1966) 7-14.
3. Chaussinand, R. Prémunition relative antilépreuse par la vaccination au BCG. Rev. colon. Méd. Chir. **21** (1949) 170.
4. Convit, J. Studies of leprosy in the German ethnic group of Colonia Tovar, Venezuela, V. The morbidity rates in BCG-vaccinated and unvaccinated groups during five years. Internat. J. Leprosy **24** (1956) 269-274.
5. Dharmendra, Mohamed Ali, P., Noordeen, S. K. and Ramanujam, K. Prophylactic value of DDS against leprosy—an interim report. Leprosy in India **37** (1965) 1-20.
6. Fenner, F. Homologous and heterologous immunity in infections of mice with Mycobacterium ulcerans and Mycobacterium balnei. American Rev. Tuberc. **76** (1957) 76-89.
7. Fernandez, J. M. M. Estudio comparativo de la reacción de Mitsuda con las reacciones tuberculínicas. Rev. argentina Dermatosif. **23** (1939) 425-453.
8. Fernandez, J. M. M. Relaciones inmunoalergicas entre tuberculosis y lepra. Proc. 3rd Argentine Congr. Tuberc., Rosario. **3** (1951) 1-28.
9. Fernandez, J. M. M. Influence of the tuberculosis factor on the clinical and immunological evolution of child contacts with leprosy patients. Internat. J. Leprosy **23** (1955) 243-258.
10. Hanks, J. H. Immunological and physiological basis of immunization in tuberculosis and leprosy. *In:* Ciba Foundation Symposium on Experimental Tuberculosis. London, J. & A. Churchill (1955) pp. 364-387.
11. Hanks, J. H. The magnitude of the immune response incited by killed and attenuated mycobacteria. J. Immunol. **81** (1958) 297-301.
12. Lara, C. B. and Nolasco, S. G. Self-healing, or abortive, and residual forms of childhood leprosy and their probable significance. Internat. J. Leprosy **24** (1956) 245-263.

13. SHEPARD, C. C. Vaccination against experimental infection with Mycobacterium leprae. American J. Epidemiol. **81** (1965) 150-163.
14. SHEPARD, C. C. Vaccination against human leprosy bacillus infections in mice: protection by BCG given during incubation. J. Immunol. **96** (1966) 279-283.
15. DE SOUZA CAMPOS, N. BCG in the prophylaxis of leprosy. A preliminary report. Internat. J. Leprosy **21** (1953) 307-312.
16. WADE, H. W. Induction of lepromin reactivity by repeated lepromin testing. Internat. J. Leprosy **23** (1955) 310-315.
17. WADE, H. W. BCG-induced activations. Internat. J. Leprosy **28** (1960) 179-181.
18. [WORLD HEALTH ORGANIZATION.] WHO expert committee on leprosy. First report. WHO Tech. Rep. Ser., No. 71 (1953).
19. [WORLD HEALTH ORGANIZATION.] WHO expert committee on leprosy. Second report. WHO Tech. Rep. Ser., No. 189 (1960).
20. [WORLD HEALTH ORGANIZATION.] Cyclostyled report MHO/PA/131.64. Geneva (1964).
21. [WORLD HEALTH ORGANIZATION.] WHO expert committee on tuberculosis. Eighth report. WHO Tech. Rep. Serv. No. 290 (1964).