INTERNATIONAL JOURNAL OF LEPROSY
and Other Mycobacterial Diseases

OFFICIAL ORGAN OF THE INTERNATIONAL LEPROSY ASSOCIATION

EDITORIAL AND PUBLICATION OFFICE
National Hansen's Disease Center
Carville, Louisiana 70721, USA

VOLUME 50, NUMBER 2 JUNE 1982

EDITORIALS

Editorial opinions expressed are those of the writers.

BCG Vaccination in Leprosy[1]

Leprosy, a chronic infectious disease caused by *Mycobacterium leprae*, has formed a part of man's natural disease pattern from as far back as Neolithic times. There are estimated to be about 15 million sufferers in the world today, mainly in tropical and subtropical areas, particularly associated with regions of overcrowding, poor hygiene, and poverty. Although the prevalence is not high compared with many other diseases, leprosy presents a serious problem in that 20%–30% of patients develop severe physical deformity.

Control is essential and a major breakthrough was made with the development of antileprosy drugs. Unfortunately, their effect has to a large extent been offset by the growth in population in endemic areas and the emergence of drug-resistant strains of *M. leprae*.

One of the major lines of attack in the control of any disease is primary prophylaxis by vaccination, sensitizing the host's immune system to subsequent challenge by the infecting organisms. Since man is thought to be the only important natural reservoir of *M. leprae*, sensitization will intercept the spread of bacilli, thus decreasing the incidence of disease and reducing the infective pool, ultimately resulting in its eradication.

Man normally responds to infection by *M. leprae* by mounting a cell-mediated immune response, and the changes observed in the tissues are all directed towards elimination of the foreign bacteria from the body. The level of cell-mediated immune response that is mounted will determine the efficiency with which this occurs, and in leprosy this varies greatly among individuals[2].

In the majority of individuals, exposure results in sub-clinical infection with a rapid stimulation of cell-mediated immunity (CMI) and healing. Some people develop indeterminate leprosy (IL) and remain immunologically virgin, mounting only a non-specific immune response. This progresses in about 30% of cases to a determinate form, more

[1] This review was written in 1980 by Janet E. Price, M.B.B.S., while she was a medical student at Sheffield Medical School, U.K. It was written in response to the annual competition set up by the British Leprosy Relief Association (LEPRA) for essays on various aspects of leprosy and was the first prize winner for 1980. We take great pleasure in publishing this review. Dr. Price's present address is 20 Borrowcap Lane, Lichfield, Staffs, WS16 9DF, U.K.

[2] Bullock, W. E. Leprosy—a model of immunological perturbation in chronic infection. J. Infec. Dis. **137** (1978) 341–354.

often towards the lepromatous end of the spectrum. A complete spectrum of immune responses is seen in the determinate forms. Those who develop multi-bacillary lepromatous leprosy (LL) have a complete absence of CMI and produce massive quantities of antibody; while maximal stimulation of CMI without antibody production results in tuberculoid leprosy (TT). A degree of instability exists in the borderline (intermediate or non-polar) forms, the disease progressing towards LL or TT depending on the conditions.

The variation in response to infection poses problems, since lack of ability to mount a simple cell-mediated immune response on challenge and thus resistance to *M. leprae* will greatly detract from the protective effect of a "normal" vaccine.

Primary prophylaxis thus has two aspects: a) the development of resistance in those individuals capable of mounting a cell-mediated immune response, and b) stimulation of the immune system, or removal of its suppression, in those who appear unable to respond to *M. leprae*.

The suggestion that Bacille Calmette Guérin (BCG) might have a protective effect against leprosy was first noted at the end of the 1930s. BCG is an attenuated vaccine developed by subculture of a strain of *Mycobacterium bovis* over a period of 13 years, during which time it gradually lost its pathogenicity. Its main use has been in protection against disease caused by *M. tuberculosis*.

Work by Fernandez in Argentina[3] had indicated that there was some correlation between an individual's responses to tuberculin and lepromin skin tests. Further studies demonstrated that BCG vaccination caused between 30% to 100% of non-responders to lepromin to give a positive result[4], in a manner similar to the positive conversion observed with tuberculin. Extrapolating a hypothesis of Bielings', Fernandez stated that BCG vaccination acted in a similar manner to natural tuberculosis infection[3], altering the course of infection by *M. leprae* by an "allergizing" effect. The concept of a close relationship between the two diseases was extended in the late 1940s by Chaussinand[5] when he suggested that the decline in leprosy throughout Europe was due to the rising incidence of tuberculosis. More recent work has suggested a number of ways in which BCG may affect immunity and provide some degree of protection against *M. leprae*[6].

Direct antigenic stimulation. *M. leprae*, like *M. tuberculosis*, has certain antigens in common with BCG. Seven cross-reacting mycobacterial components have been identified, and some or all of these may act as "keys" for the specific "locks" or receptors on certain T lymphocytes. BCG vaccination sensitizes specific T cell clones which may transform rapidly on subsequent exposure to *M. leprae*. This is the concept of activation of immune mechanisms by "cross-reacting" antigens.

Antigen adjuvant effect. Certain antigens carried by bacteria do not have a great capacity to react with and sensitize T cells. This low immunogenicity is modified by BCG in a number of ways:

a) It stimulates the incorporation of bacterial antigen into the macrophage membrane and this antigen-membrane complex, on presentation to the T cell, has a greatly enhanced immunogenic capacity.
b) It acts at the T lymphocyte membrane, possibly at adjacent receptor sites to the bacterial antigen, again resulting in increased T cell sensitization.
c) It induces certain mononuclear cells to produce an arming factor (SMAF) for T cells lacking specific discrimination. This increases antigenic recognition.

Thus BCG may lower the threshold of immunological recognition of *M. leprae*.

General immunopotentiation. This is exerted on:

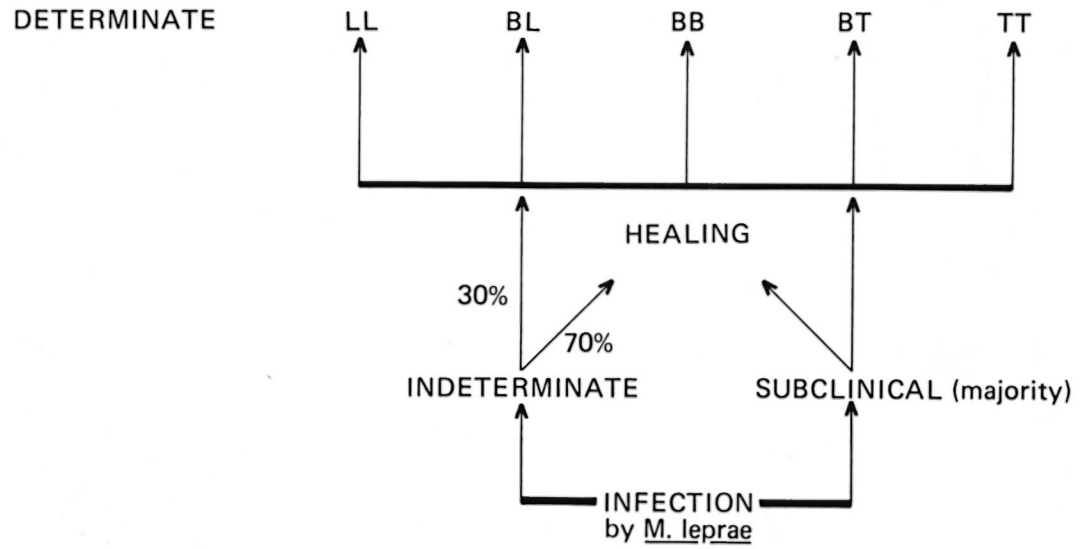
---

[3] Fernandez, J. M. M. Use of BCG in immunoprophylaxis of leprosy. Rev. Arg. Derm. **23** (1939) 425.

[4] Bechelli, L. M. The influence of repeated lepromin testing on the Mitsuda reaction in healthy people. Int. J. Lepr. **27** (1959) 228–235.

[5] Chaussinand, R. Tuberculose et lèpre, maladies, antagoniques, éviction de la lèpre par la tuberculose. Int. J. Lepr. **16** (1948) 431–438.

[6] Mitchell, M. S. and Murahata, R. I. Modulation of immunity by BCG. Pharmacol. Therap. **4** (1979) 329–353.



THE FIGURE. Types of leprosy. LL—lepromatous leprosy, BL—borderline lepromatous, BB—mid-borderline leprosy, BT—borderline tuberculoid, TT—tuberculoid.

a) Macrophages—by increasing production of phagocytic, killer, and suppressor macrophages, the relative numbers of each depending on dose. It also increases production of lymphocyte activating factor by macrophages, resulting in increased T cell mitosis.
b) T lymphocytes—by direct mitogenic action, thus increasing numbers.
c) Suppressor lymphocytes—by reducing circulating levels and causing them to be trapped in spleen and lymph nodes.

The result may thus be a higher level of cell-mediated immune response to *M. leprae*.

Lepromin

Much of the early work on BCG vaccination against leprosy used lepromin as a tool to indicate an individual's resistance to *M. leprae*. Lepromin is a semi-standardized extract of bacilli from leprosy nodules, which is injected intradermally and the reaction read after three to four weeks (the Mitsuda response). A positive response is prevalent in areas where *M. leprae* is endemic, increasing with age. Mitsuda-positive responses have been recorded in non-endemic areas[7], and both BCG and other mycobacteria have been shown to cause conversion[8], so that a positive result is not specific for *M. leprae* antigens. Nowadays it is generally accepted that in those individuals without clinical disease a positive Mitsuda reaction indicates a degree of resistance to leprosy. Patients with tuberculoid leprosy are positive, while those with LL and IL give negative results[9]. There is also a small group who remain persistently negative on retesting, indicating a tendency to develop lepromatous leprosy[10].

Trials of BCG

Following the suggestion that BCG vaccination might give some degree of protection against leprosy, three controlled trials were organized in the early 1960s.

[7] Godal, T. Immunological aspects of leprosy: present status. Prog. Allergy **25** (1978) 211–242.

[8] Goihman-Yahr, M., Raffel, S. and Ferraresi, R. W. Cross reactivities of lepromin. Int. Arch. All. Appl. Immunol. **36** (1969) 450–468.

[9] Bechelli, L. M., Gallego Garbojosa, P., Engler, V., Martinez Dominguez, V., Parades, L., Koch, G., Vemura, K. and Sundaresan, T. BCG vaccination of children against leprosy. Preliminary findings of the WHO-controlled trial in Burma. Bull. WHO **42** (1970) 235–281.

[10] Newell, K. W. An epidemiologist's view of leprosy. Bull. WHO **34** (1966) 827–857.

Karimui, Papua New Guinea[11]. BCG vaccination provided 46% protection against leprosy in the general population over a period of six years. The maximum protection was seen in the 5 to 14 age group (56%). No protection was evident until three years after vaccination. No indication was given of the clinical forms of leprosy observed in the vaccinated and the control groups.

Uganda[12]. BCG vaccination had an 80% protective efficacy for contacts of leprous patients in the 0 to 15 age group over a period of six years. No cases of lepromatous leprosy were seen in either the vaccinated or the control groups, and the disease pattern was the same in both groups. There was no variation in protection with age within the 0 to 15 age range. The maximum degree of protection was evident after four years.

Burma[9]. BCG vaccination gave 40% protection in the 0 to 4 age group in the general population over a nine-year period, although this was not evident until they were aged 5 years or older. No significant protection was observed in the 5 to 14 age group. No cases of lepromatous leprosy occurred in either the vaccinated or the control groups and the disease pattern was the same in both groups.

Thus trials of BCG vaccination against leprosy have produced varying degrees of protection, and many factors have been held responsible for the diverse results observed.

Study population

One of the major hurdles in any controlled study in leprosy is the initial survey of the population. Due to the peculiar pathogenesis of the disease, it is very difficult to assess its incidence. Large numbers of bacilli may be present in the tissues for many years before there are any clinical manifestations. This poses great problems in assessing people for inclusion in trials, and frequent examinations are necessary during the study since patients may contract mild forms of leprosy which heal rapidly. The natural history of the disease is altered by treatment, and thus it is difficult to assess the effects of vaccination on its progress in areas where therapeutic aid is available. Comprehensive preliminary surveys were carried out in Burma and Uganda before commencement of the trials, but data, such as annual presentation rate of disease for various age groups, relative incidence of disease forms, and progression of disease, were not sufficiently detailed for a close analysis of some of the results. The Karimui trial suffered even more in these respects. Substantial differences in the populations under study may therefore account for some of the discrepancies in results[9].

Infectious pool

There is a higher incidence of LL in Burma (approximately 6.9 per 1000) than in Karimui or Uganda, and about 40% of leprosy cases in Burma are of multibacillary form, representing a large infectious pool. The risk of exposure to *M. leprae* is great and individuals tend to develop resistance (the usual consequence of exposure) early in life. The effect of vaccination would therefore only be demonstrable in the younger age groups.

In Karimui and Uganda the predominant form of leprosy is tuberculoid, which has a much lower infective potential. Herd immunity may well not achieve a substantial level till later in life, and protection due to early BCG vaccination would be more obvious.

It is difficult to assess at what age exposure is likely to occur in the various populations. Lepromin testing[9] indicates that nearly all the Karimui population give a positive Mitsuda reaction by late adolescence and 99% of Burmese are positive by the age of 15. A similar pattern is believed to exist in Uganda. Whether this is due to previous exposure to *M. leprae* remains equivocal, and work on lymphocyte transformation and leukocyte migration inhibition tests may provide more accurate methods of ascertaining previous mycobacterial infection[2].

Host factors

Variations between the study groups in lifestyle, i.e., urban versus rural, frequency of intermarriage, size of living groups, levels

[11] Russell, D. A., Scott, G. C. and Wigley, S. C. BCG and prophylaxis—the Karimui trial. Int. J. Lepr. **36** (1968) 618.

[12] Brown, J. A. K., Stone, M. M. and Sutherland, I. Trial of BCG vaccination against leprosy in Uganda. Lepr. Rev. **40** (1969) 3–7.

of malnutrition, intercurrent infections, and genetic differences have been explored but no major differences have been identified[9, 13].

Incidence of leprosy after vaccination

In certain trials a higher incidence of leprosy has been noted in the vaccinated than in the control group within the first few months of vaccination. A delay of some years before the maximal protective effect has already been noted.

In Burma at the first follow-up, there were 15% more cases of leprosy in the vaccinated group. A study by Bechelli[9] recorded about 6% more cases immediately among those vaccinated.

This increased incidence may be due to the difficulty of identifying leprous patients before entry into the trial or to individuals who have low levels of *M. leprae* in the tissues without any sign of a response (possibly those with a tendency to develop IL) and in whom vaccination, by increasing antigen levels or by its adjuvant effect, may stimulate a reaction to the latent bacilli—"exteriorization of the disease."

Alternatively BCG may sensitize the "wrong" antigenic clone of cells, or stimulate a damaging cell-mediated response, resulting in a worsened response to subsequent mycobacterial infection[14].

Atypical mycobacteria

The fact that *M. leprae* possesses antigens that cross react with other mycobacteria[15] has been mentioned previously, and it is possible that sensitization to atypical environmental species alters the response to *M. leprae*. Recent work has suggested that the cell-mediated response to mycobacteria can be of two types, one of which provides much better protective immunity than does the other[14]. The Koch-type response is associated with destruction of cells carrying mycobacterial markers and, although this necrosis may be important in containing the disease, in certain cases it may reduce the level of protective immunity and thus enhance the severity of infection.

A true cell-mediated immune response, dependent on activation of macrophages by specifically primed T lymphocytes, is seen in other cases. The macrophages have bactericidal properties and form a much more effective protective mechanism. Mycobacteria vary in their ability to induce the two patterns of response, some species stimulating only the latter, e.g., *M. vaccae, M. leprae*; while others may induce either, depending on their frequency and relative incidence in the environment, e.g., *M. tuberculosis, M. scrofulaceum*. BCG appears to enhance the development of whichever type of response has previously been mounted.

Kwapinski, *et al.*[16] have demonstrated impairment of delayed hypersensitivity to lepromin in individuals vaccinated with certain mycobacterial antigens compared with controls, and subsequent BCG vaccination only partially raised reactivity towards normal. This suggests that some mycobacterial species may have an antagonistic effect to BCG.

In Uganda a high prevalence of sensitization to *M. vaccae* was observed and this may help to explain the good protection afforded with BCG[17]. On the other hand, in Burma the Koch-type response to environmental mycobacterial species is believed to be induced early in life and this may explain why little protection is seen with BCG in this population[14].

Tuberculosis and tuberculin sensitivity

There has been much debate as to the influence of tuberculosis and tuberculin sensitivity on resistance to leprosy infection. Resistance to leprosy has been thought to be conferred by tuberculous infection[5],

---

[13] Godal, T. Recent advances in the immunology of leprosy with special reference to new approaches in immunoprophylaxis. Bull. Inst. Pasteur **72** (1974) 273–310.

[14] Stanford, J. L., Shield, M. J. and Rook, G. A. W. How environmental mycobacteria may predetermine the protective efficacy of BCG—Hypothesis I. Tubercle **62** (1981) 55–62.

[15] Palmer, C. E. and Long, M. W. Effects of infection with atypical mycobacteria on BCG vaccination and tuberculosis. Amer. Rev. Resp. Dis. **94** (1966) 553–568.

[16] Kwapinski, J. B. G., Bechelli, L. M., Haddad, N. and Simao, E. T. Impairment of reactivity to lepromin by mycobacterial antigens related to or identical with *M. leprae*. Can. J. Microbiol. **21** (1975) 896–901.

[17] Stanford, J. L. Editorial. A vaccine for leprosy. Lepr. Rev. **47** (1976) 87–91.

but tuberculosis and leprosy often occur together with a frequency that would be expected from the separate incidences of the two diseases[18]. Epidemiological data on the spread of tuberculosis and leprosy in Asia and Oceania and studies of patients do not suggest that protection is widespread, but it may occur in certain areas[10].

An association has been noted between an individual's response to tuberculin and lepromin[10] which, although not fixed, becomes closer with the use of larger quantities of antigen, in younger individuals, and in areas with high levels of environmental mycobacteria (associated with low-grade tuberculin sensitivity).

In Uganda[12], where TT predominates and there is a high prevalence of tuberculosis, the ability to react strongly to tuberculin bestows some degree of protection, e.g., 38% over six years in one study. An association was also noted between the incidence of leprosy and sensitivity to tuberculin at intake. To assess the relative effects of naturally acquired sensitivity and BCG vaccination, it would have been valuable to have included a group strongly positive to tuberculin in the trial.

The study in Burma[9], where there is a high incidence of progressive forms of leprosy (43% LL and IL as against 8% in Uganda), showed a similar incidence of disease in both vaccinated and control groups and for all degrees of tuberculin sensitivity at intake, except in the 0 to 4 age group, where BCG gave 60% protection in those with a small-sized reaction to PPD. A higher proportion of tuberculoid cases was seen in the vaccinated group with a strongly positive tuberculin reaction. It has been suggested that the children protected by BCG still had their initial, classical, cell-mediated immune response; while those who were strongly positive had developed a Koch-type response from over-exposure to environmental bacteria and thus manifested a different immune response[14].

Tuberculin sensitivity is not believed to give protection in those tending to develop progressive leprosy[19]. Thus only about half the cases in Burma would theoretically gain benefit from BCG with maximum effects being observed in the young who have a greater tendency to develop TT.

In New Guinea[19] natural tuberculous infection and sensitivity to tuberculin give protection against TT, and the frequency of tuberculin-negative individuals is greater among those with TT than in the general population (i.e., tuberculin-negative individuals are more susceptible).

In Karimui[11] there is a low level of tuberculin sensitivity. Leprosy is mainly TT and BCG vaccination has most effect in the 5 to 14 age group, in which the incidence of naturally induced sensitivity is only 2.1 per 1000 males and 0.5 per 1000 females. In older groups there is a higher incidence of sensitivity up to 10.6 per 1000 in males, but the effect of vaccination decreases. It is possible that many of those susceptible to TT gain some protection by natural *M. tuberculosis* infection and BCG has less apparent effect. Alternatively over-exposure to environmental mycobacteria may have stimulated the Koch-type response and altered the disease pathogenesis.

Interpretation of the above data indicates that BCG may give some protection against tuberculoid leprosy when it precedes natural infection by *M. leprae*, but previous infection by *M. tuberculosis* or environmental mycobacteria modifies the response. This protection will decrease the incidence of disease and reduce both the numbers requiring treatment and the infective pool. Even so, a large proportion of those with TT have mild, self-healing disease and recover in any case.

Multibacillary disease

Multibacillary cases are a major problem, being highly infectious with a much poorer prognosis. The data available on the effect of BCG are difficult to assess.

LL tends to occur in older age groups than those studied in the BCG trials and although the Karimui trial included all age groups, the reported incidence of LL was low. Secondly, the incubation period may be up to 15 to 20 years. This necessitates a longer follow-up than has yet been possible.

BCG may survive in the tissues for many years after vaccination, and it is postulated

[18] Gatner, E. M. S., Glatthaar, F. M., Imkamp, J. H. and Kok, S. H. Association of tuberculosis and leprosy in South Africa. Lepr. Rev. **51** (1980) 5–10.

[19] Leiker, D. L. Effects of BCG vaccination on leprosy in Kenya. Lepr. Rev. **39** (1968) 84–86.

that in those individuals with a depressed immune response to *M. leprae* its adjuvant effects may be demonstrated long after vaccination. However, tissue levels of the bacillus wane with time and a point will be reached at which infection by *M. leprae* is able to produce disease. This will occur later in life than in the non-vaccinated case. Some information from trials is available: In Burma[4], ten years after vaccination a smaller number of multi-bacillary cases was seen in the vaccinated than in the control group. In Brazil (1952–1956)[20], a higher proportion of non-LL cases was observed in the vaccinated group although they were examined carefully before inclusion; while the controls were entered without previous examination. In Cuba (1965–1976)[21], there was little decrease in leprosy in the vaccinated group, but of 28 cases of LL, 85% were among controls. All occurred, however, within the first seven years. Information from these studies is obviously inconclusive and further long-term work is needed to assess these effects.

Immunological incompetence

Immune incompetence to *M. leprae* may have a familial or genetic basis[13], although studies on monozygous and dizygous twins suggest these are not of major importance[10]. Racial and ethnic differences are also apparent in the different disease patterns observed within societies[10]. Intensity of exposure to LL may depress the immune system[2], perhaps due to some factor released by *M. leprae*. Host deficiencies in certain cell lines, for example, macrophages, or the presence of suppressor factors could also be responsible[22].

The major defect in lepromatous individuals is the lack of T cells sensitized to *M. leprae* and of macrophage-clearing activity[23]. It is possible to achieve local activation of previously incompetent macrophages in LL by intradermal injection of BCG in combination with killed *M. leprae*, and similar effects have been obtained in IL and with Mitsuda-negative contacts[24]. The Mitsuda response and lymphocyte transformation test become positive after one to four stimulations, more so in the latter two groups than in LL. This suggests that the *M. leprae* specific, T lymphocyte clone is not completely absent in persistently negative individuals. If this is so, BCG in combination with killed *M. leprae* may be important in reducing the risk of developing lepromatous leprosy.

Conclusions

It is obvious that there are still many gaps in our knowledge of BCG and leprosy. One of the priorities must be to elucidate the nature of the immune response to *M. leprae* and the deficiency that exists in those patients who develop LL, for without this knowledge any systematic approach to the development of an effective vaccine is difficult.

A successful vaccine must be able to protect from all forms of the disease and alter their course, reduce the infectious reservoir, provide prolonged protection, and be cost-effective.

At present, research is being conducted with killed *M. leprae*, closely related atypical mycobacteria, and BCG in combination with killed *M. leprae* or atypical mycobacteria[25]. Few conclusive results are yet available and time-consuming controlled trials will be required before the respective efficacy of the vaccines can be truly assessed.

---

[20] De Souza Campos, N. (BCG in the prophylaxis of leprosy. Spontaneous positivity following reinoculation with Mitsuda antigen. Results of practical observations up to date.) Rev. Brasileira Leprol. **24** (1956) 173–187.

[21] Abreu, A., Werthein, L. L. and Ruiz de Zarate, Serafin. Twelve year vaccination with BCG and infantile leprosy in Cuba. Rev. Cu. Hig. Epidem. **16** (1978) 63–72.

[22] Immunological problems in leprosy research: 2. Bull WHO **48** (1973) 483–494.

[23] Convit, J., Pinardi, M. E., Rodriguez Ochoa, G., Ulrich, M., Avila, J. L. and Goihman-Yahr, M. Elimination of *M. leprae* subsequent to *in vivo* activation of macrophages in lepromatous leprosy by other mycobacteria. Clin. Exp. Immunol. **17** (1974) 261–266.

[24] Convit, J., Aranzazu, N., Pinardi, M. and Ulrich, M. Immunological changes observed in indeterminate and lepromatous leprosy patients and Mitsuda-negative contacts after the inoculation of a mixture of *M. leprae* and BCG. Clin. Exp. Immunol. **36** (1979) 214–220.

[25] Convit, J. and Ulrich, M. General ideas concerning a vaccine against leprosy. Int. J. Lepr. **46** (1978) 61–63.

In the meantime the WHO Expert Committee on Leprosy has concluded that the use of BCG as a specific prophylactic measure is not indicated, but suggests that it may be of some value in areas with a high prevalence of TT[26].

—Janet E. Price

Acknowledgment. The author is deeply grateful for the encouragement, patience, and advice of Dr. A. C. McDougall, The Slade Hospital, Headington, Oxford, in reorganizing this essay for publication and in searching out elusive references.

[26] WHO Expert Committee on Leprosy—5th Report. Tech. Rep. Series 607 (1977).