INTERNATIONAL JOURNAL OF LEPROSY
and Other Mycobacterial Diseases

OFFICIAL ORGAN OF THE INTERNATIONAL LEPROSY ASSOCIATION

Publication Office: Leahi Hospital, 3675 Kilauea Avenue,
Honolulu, Hi. 96816

VOLUME 45, NUMBER 1 JANUARY-MARCH 1977

EDITORIALS

Editorials are written by members of the Editorial Board, and occasionally by guest editorial writers at the invitation of the Editor, and opinions expressed are those of the writers.

The Rationale Behind a Leprosy Vaccine Research Program

The World Health Organization has initiated an international research program on the immunology of leprosy (IMMLEP).[1] This program has three goals: 1) To develop new methods for identification of risk groups; 2) To develop an antileprosy vaccine; and 3) To study the immunopathology of leprosy and thereby explore the possibilities for corrective methods, such as immunotherapy.

At the invitation of the editor of the INTERNATIONAL JOURNAL OF LEPROSY, I shall give some considerations relevant to the vaccine goal of the program. The effectiveness of leprosy control measures is hampered by limitations of control methods and logistic problems. An additional burden, which has recently come to the surface, is the emergence of DDS resistance. Thus, the need for a greater arsenal of antileprosy weapons is quite apparent. As to the possibility of developing an antileprosy vaccine, this question may be divided into three parts:

A. What is the possibility of artificially inducing immunity to *M. leprae* in normal subjects?
B. Is immunoprophylaxis, if applied, likely to have any impact on the infectious reservoir of leprosy?
C. If developed, is a vaccine likely to have any place in the leprosy control programs?

A. What is the possibility of artificially inducing immunity to M. leprae in normal subjects? Immunity to intracellular parasites like *M. leprae* depends on the T-cell compartment of the immune system,[2] so-called cell-mediated immunity. Experimentally, significant levels of cell-mediated immunity can be induced by live infection or by the help of adjuvants. Consequently, the two main possibilities for inducing cell-mediated immunity to *M. leprae* would appear to be 1) the use of an attenuated strain of *M. leprae* or closely-related live mycobacterium, or 2) nonviable antigens in an adjuvant. Among these alternatives, an attentuated strain of *M. leprae* is unlikely to be produced before *M. leprae* can be cultivated on artificial media. This approach therefore appears to be unrealistic at present. The two other approaches are being pursued at present at various research centers.

With regard to a live cross-reactive mycobacterium, taxonomic studies on *M. leprae*, particularly by Dr. Stanford's group in London, have indicated that *M. leprae* is more closely related to rapidly dividing mycobacteria than to slowly growing mycobacteria, such as BCG.

Initial studies at the Armauer Hansen Research Institute indicated that *M. duvalii* was closely related.[3] However, later studies in which some other rapidly growing strains were included, suggest that *M. leprae* might

[1] Report of the First meeting of IMMLEP Project Group, IMM/74.3, WHO, Geneva.

[2] Mackaness, G. B. Delayed hypersensitivity and the mechanism of cellular resistance to infection. Progr. Immunol. **I** (1971) 413-424.

be more closely related to *M. vaccae* and *M. non-chromogenicum*.[4,5] In the later studies, Stanford and his group have mainly used skin-reactivity in human populations with ultrasonicates of bacilli in their taxonomic studies. However, more information is needed on cell wall and surface antigens, since these may well be important in relation to protective immunity. Whether the cross-reactive strains are sufficiently safe to be used in a viable form in man and whether they would be capable of inducing cell-mediated immunity in man remains unknown. If not, they may be considered for use as killed bacilli in an appropriate adjuvant. If a killed vaccine is to be used, it would seem more logical, at least at first sight, to use *M. leprae* itself. This has now become a realistic possibility because of the large number of organisms that can be harvested from armadillos,[6] if these bacilli appear to contain the most important antigens for protective immunity. The potential of a killed vaccine depends on whether sufficiently strong and safe adjuvants can be developed for human use. Various possibilities such as BCG, *C. parvum* and biogradable oils are at present being pursued experimentally. In my view the chance of success in this field of research within a reasonable period of time is good. The reason for this optimism stems from three facts:

1. Recent progress in the field of immunopotentiation, particularly that made by Mackaness and his group with BCG.
2. Earlier observations showing that killed mycobacteria such as *M. lepraemurium* + BCG[7] or *M. tuberculosis* in Freund's incomplete adjuvant can provide protection against experimental infections.[8]
3. In all the three BCG trials undertaken, some protective effect (20-80%) has been observed.

B. Is immunoprophylaxis, if applied, likely to have any impact on the infectious reservoir of leprosy? This question requires first a definition of the infectious reservoir in leprosy. The Fifth Expert Committee on Leprosy[9] (October, 1976) considered that while multibacillary leprosy (BL to LL) was likely to represent the major infectious reservoir, it was also considered that borderline tuberculoid and indeterminate patients in certain areas where the relative proportion of multibacillary leprosy is low, could play a non-negligible part in the transmission of leprosy. Since nonpolar lepromatous leprosy patients (BL-LI) may revert immunologically, simply by antileprosy chemotherapy, it would seem likely that immunization at a pre-infection (and pre-clinical?) stage would have a significant effect on this population (I, BT-LI). This group of patients may well represent 50% or more of the infectious reservoir in a majority of endemic areas.

Then remains the question of whether vaccination could influence lack of resistance in subjects prone to develop polar lepromatous leprosy. If genetic factors should turn out to be of major importance for the development of their immunologic defect, vaccination at a pre-infection stage could be of little value. However, the data supporting the involvement of overriding genetic factors in this defect in my view is limited, e.g., the studies by Chakravartti and Vogel[9] showed that the concordance for lepromatous leprosy in monocygous twins was not more than 50%, a low figure, particularly in the light of the present views on the transmission of leprosy.[10] Moreover, the nature of the defect in lepromatous leprosy, which has been discussed in more detail elsewhere,[3] indicates that the defect has features in common with so-called immunologic tolerance. This type of immunologic unresponsiveness can be restored by immunization with cross-reactive antigens. For these reasons, it would seem likely that vaccination could have a significant impact on the infectious reservoir of leprosy.

[3] Godal, T., Myrvang, B., Stanford, J. L. and Samuel, D. R. Recent advances in the immunology of leprosy with special reference to new approaches in immunoprophylaxis. Bull. Inst. Past. **72** (1974) 273-310.

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

[5] Report of the Second IMMLEP Task Force Meeting, TDR/IMMLEP/75.8, WHO, Geneva.

[6] Kirchheimer, W. F. and Storrs, E. E. Attempts to establish the armadillo (*Dasypus novemcinctus* Linn.) as a model for the study of leprosy. Int. J. Lepr. **39** (1971) 693-702.

[7] Hanks, J. H. and Fernandez, J. M. M. Enhancement of resistance to murine leprosy by BCG plus specific antigen. Int. J. Lepr. **24** (1956) 65-73.

[8] Weiss, D. W. and Dubos, R. J. Antituberculous immunity induced in mice by vaccination with killed tubercle bacilli or with a soluble bacillary extract. J. Exp. Med. **101** (1955) 313-330.

[9] Chakravartti, M. R. and Vogel, F. A twin study on leprosy. *In:* Topics in Human Genetics **1** (1973) 1-123.

[10] Report of the Fifth Expert Committee on Leprosy, WHO Tech. Rep. Ser. (In press)

C. If developed, is a vaccine likely to have any place in the leprosy control program? The most important question in this regard is the cost/effectiveness of a potent vaccine. Costs may be considered at three levels:

1. Costs of development: The vaccine component of the IMMLEP program is likely to cost US$3-5 million from start to the end of the first field trial. This is less than 50 cents per patient today.
2. Production costs: This is likely to be high if based on armadillo-derived *M. leprae* but reasonably accurate estimates are impossible because we do not know the number of organisms needed per dose. The cost of a cultivable cross-reactive organism is likely to be much smaller.
3. Delivery costs: Since the prevalence of leprosy in endemic areas is low, the delivery costs per case protected is likely to be high if isolated leprosy vaccination campaigns on a mass scale were to be undertaken. However, since multiple vaccines (at least six) may be given simultaneously without negative interference, a leprosy vaccine could be incorporated into larger vaccination programs.

Here I have merely pointed to some factors, at present largely unknown, which will have to be considered in due course and balanced against the costs of chemotherapy and other forms of treatment on a per case basis. However, in my view the place of a vaccine in leprosy control cannot be ruled out by presently available cost/effectiveness considerations.

Conclusions. From what has been stated above, it is clear that there are many unanswered questions concerning both the possibilities of developing an effective antileprosy vaccine and its cost/effectiveness. Many of them can only be answered by a vaccine research program.

This research is likely to proceed in a stepwise fashion, involving both experimental research in animals, pilot studies in human volunteers, and finally, vaccination trials in leprosy endemic areas. At the first Task Force meeting of IMMLEP it was estimated that it would take 10 to 19 years before we know whether an antileprosy vaccine has proved to be effective against leprosy. No one should therefore adhere to the misconception that an effective antileprosy vaccine will shortly be at hand. Moreover, because of the long time needed and because of the above-mentioned uncertainties in this area of research, research in other areas relevant to leprosy control, such as the development of new drugs and drug trials, should be given top priority and proceed parallel to research related to the development of a vaccine. After all, leprosy is caused by a mycobacterium, and the best we can hope for is that leprosy research will provide a number of weapons such as new, inexpensive drugs, an effective vaccine and epidemiological tools, all of which may play their part in the fight against leprosy, analogous to tuberculosis control.

—TORE GODAL