Lepr Rev (1985) **56,** 1–3

Editorial

VACCINATION AGAINST LEPROSY; RECENT ADVANCES AND PRACTICAL IMPLICATIONS

Leprosy control, using the current approach of mass treatment, has important limitations which are well recognized. The long incubation period of the disease, the insidious onset, the chronic course, and the need for prolonged treatment have made control a formidable task, bringing out the urgent need for improved tools. Primary prevention through immunization has thus attracted considerable attention in recent years, and efforts are being made to develop a vaccine against leprosy with high efficacy, acceptability and cost-effectiveness.

BCG itself was the first vaccine to be considered against leprosy following the report of Fernandez in 1939 on lepromin conversion among lepromin negative healthy children following BCG administration. Shepard later provided the first experimental evidence in favour of BCG in the mouse foot-pad model. However, it was not until the 1960s that major field trials on the value of BCG were started in Uganda, Burma, Papua New Guinea, and India. The trial in Uganda involving over 60,000 children showed an overall protective effect of 80% during the 8 years of follow-up. The Burma trial involving over 28,000 subjects showed a protective effect of about 20% at the end of 14 years of follow-up. In Papua New Guinea, the protective effect observed among 5000 subjects over a 12-year period of follow-up was about 46%. The Indian trial, which is still in progress, involves over 180,000 subjects and has so far shown a protective effect of 28%. Thus it can be concluded that the protective effect of BCG has generally been modest except in Uganda. The factors that might have contributed to the observed variations remain to be explained.

A major impetus to research on antileprosy vaccines was the possibility in the 1970s of obtaining large quantities of *Mycobacterium leprae* through the then discovered model of the nine-banded armadillo and preparing a vaccine based on killed *M. leprae*. Partly as a result of this development, a Scientific Working Group on the Immunology of Leprosy (IMMLEP), a component of the UNDP/World Bank/WHO Special Programme for Research and Training in

0305-7518/85/056001+03 $01.00

Tropical Diseases, came to be established in 1975 with vaccine development as one of its major goals. Since then IMMLEP has made substantial progress.

An important premise on immunization in leprosy is that induction of cell-mediated immunity will lead to protection against the disease. This premise is based on the wide spectrum of disease that leprosy manifests, and the relationship of the different types in the spectrum to cell-mediated immunity. The next premise, which is based on experimental evidence, is that *M. leprae* and certain other cultivable mycobacteria are capable of producing cell-mediated immunity to antigens of *M. leprae.*

The availability of adequate quantities of *M. leprae* being a major prerequisite for vaccine development, IMMLEP has been able to produce large quantities through its armadillo colonies, store and distribute them through an *M. leprae* bank in London. This dependence on armadillos is expected to continue until other methods, such as production of *M. leprae* antigens in *E. coli* or other bacterial hosts through use of recombinant DNA technology, become possible.

As the vaccine preparation requires *M. leprae* in a purified form, IMMLEP has been able to develop an optimal method of purification of the organisms from host tissues which gives maximum yields of tissue-free bacteria with minimum damage to the organisms. Extensive *in vitro* and *in vivo* testing of the preparation has shown no loss of identifiable mycobacterial antigens. The vaccine preparation itself has involved both irradiation of the infected tissue and autoclaving of the final product.

Studies so far have established that the killed *M. leprae* preparation, even in the absence of adjuvants, is capable of producing good delayed-type hypersensitivity in mice as well as guinea-pigs. In addition, the preparation has been found in the mouse foot-pad model to be capable of protecting against challenge with live *M. leprae*.

The next vital step in vaccine development is testing of the vaccine preparation in human beings. Before considering any field trial it is essential to demonstrate that any preparation has the capability of converting normal individuals from non-endemic countries to positive and lasting immunological reactivity for delayed-type hypersensitivity or cell-mediated immunity, and that optimal doses for skin test conversion can be arrived at with minimal side-effects. Similar studies are also necessary among healthy individuals in leprosy endemic countries. IMMLEP has been able to initiate activities on this step, and the preliminary results appear to be encouraging.

Even as the original concept of developing a prophylactic vaccine against leprosy through the step-by-step approach was evolving, Convit and his co-workers demonstrated that a vaccine consisting of a mixture of killed *M. leprae* plus BCG was capable of upgrading the immune status of CMI deficient lepromatous and borderline patients, and suggested that such a vaccine should be capable of doing the same in susceptible but healthy individuals and thus prevent the occurrence of manifest disease. Such a study is currently under way in

Venezuela and is expected to involve ultimately about 30,000 contacts. The approaching of immunoprophylaxis through immunotherapy appears to be unique to leprosy. The same approach has been used in studies carried out in India with cultivable mycobacteria, which are slightly different from, and cross-react with, *M. leprae*. Deo and Bapat have used a cultivable mycobacterium designated as the ICRC bacillus for preparing a killed vaccine preparation and have reported on skin test conversion and immune upgrading in lepromatous and borderline patients. Lepromin conversion in lepromatous patients has also been reported by Talwar with a vaccine preparation derived from another cultivable organism designated as *Mycobacterium W*.

It is important to realize that while evaluation of side effects, acceptance and immune response could be studied in small groups of human subjects, the evaluation of the vaccine in terms of its protective capability in the individual, and its capacity to bring about disease control in the community can be effected only through large-scale prospective studies in populations. There appears to be no viable alternative to this approach. The implication of this is that a vaccine that could become available for public health practice is at least 1 decade away. Meanwhile, the tremendous progress that is being made in newer technologies such as DNA recombinant techniques promises even better vaccine preparations.

From the public health point of view, an ideal vaccine should be able to prevent leprosy, particularly the forms responsible for the spread of the disease, among those exposed and susceptible. While the concept of vaccination of selected groups of susceptible subjects is very attractive, the public health practice of this will be closely related to the ease with which such groups can be identified and reached and the proportion of disease in the community that occurs within such groups. The implication of measuring the protective effect of any vaccine against occurrence of multibacillary leprosy is that field trials will have to involve very large populations over long periods of time, in view of the very low incidence of multibacillary leprosy occurring *de novo* in most situations.

It should be pointed out at this stage that no matter how promising are the newer tools such as vaccines, they do not automatically guarantee that leprosy control will be achieved. Experience has shown that the problems in the application of even the most efficient tools for effective control are often more difficult to surmount than the problems in the development of the tools themselves. The implication is that leprosy control programmes should learn to use the existing tools such as modern chemotherapeutic regimens to the maximum effect through improved operational performance and be in a position to accept even better tools and apply them efficiently as and when they become available.

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