Vaccines Against Leprosy

Vaccination has proved to be a valuable strategy for control of epidemics and containment of infectious diseases. The diligent use of a vaccine enabled the eradication of smallpox from the surface of the earth. In the case of leprosy, human beings by and large constitute the foyer of infection and the source of transmission to others. If humans could be rendered "inhospitable territory" for the proliferation of *Mycobacterium leprae*, the approach employed successfully for eradicating smallpox could theoretically help to eradicate leprosy. It is therefore no wonder that a number of laboratories have been engaged in the development of anti-leprosy vaccines. The WHO-IMMLEP task force has also devoted its major effort towards developing a leprosy vaccine. As a result of these world-wide studies, seven candidate vaccines have been proposed. They fall into two categories; three of them are based on *M. leprae* and four on cultivable mycobacteria. In the first category are (i) killed *M. leprae*,[1] (ii) killed *M. leprae* + BCG,[2] and (iii) aceto-acetylated *M. leprae*.[3] In the second category are (iv) BCG,[4] (v) BCG + *M. vaccae*,[5] (vi) ICRC bacillus[6] and (vii) *Mycobacterium w*.[7] Each vaccine is based on a hypothesis and is backed by either studies on experimental animals or clinical evaluations. There is feedback on some of these vaccines at both levels. However, the stage is not set to conclude that any one of these vaccines can serve as an effective vaccine for control of the polar form of lepromatous leprosy. The attributes of these candidate vaccines will be briefly recalled before giving a critique.

Killed *M. leprae* is no doubt immunogenic in mice[8] and rabbits.[9] It induces protection against challenge with live *M. leprae* in mice[10] and armadillo[11] and elicits delayed type hypersensitivity (DTH) response in guinea pigs.[12] It has not been tried clinically. In a way, it may be considered as a macroversion of the lepromin test. Previous experience over several decades indicates that repeated lepromin injections do not convert the truely polar lepromatous leprosy patients to lepromin positivity status. Lepromin negativity is in fact employed as a criterion in the categorisation of such patients. Whether an increased inoculum (as proposed in the case the killed *M. leprae* vaccine) would break this barrier remains to be seen.

M. leprae + BCG has been employed with benefit by Convit *et al*[13] in several hundred leprosy patients. It has shown immunotherapeutic potential, but again it is not serviceable in every case of lepromatous leprosy.

BCG alone has had an interesting field record as an immunoprophylactic agent against leprosy. In Uganda, the protection was on the order of 80 per cent.[14] However, in Burma as well in South India, the protection provided by BCG trial was of a lower order: 20-30 per cent.[15,16] Stanford[17] believes that the immunomodulating role of environmental mycobacteria is the reason for the variability of protection in different countries. He has proposed the use of *M. vaccae* along with BCG as a vaccine. This combination has been tried mostly for DTH response in some parts of India and Nepal. Its potential as a vaccine has not yet been clearly demonstrated. BCG is a powerful potentiator of the reticulo-endothelial system and enhances resistance to a variety of antigens. It has been in use in humans for several decades and the incidence of contraindications is low. Besides its use in cases of leprosy, it has a variable record from country to country with regard to the degree of protection that it confers against tuberculosis.

Aceto-acetylated *M. leprae* was devised on the grounds that a known deficit in lepromatous leprosy provides immunological tolerance or anergy of response to some *M. leprae* antigens. Immunological tolerance in experimental animals has been successfully broken either by modification of the antigen with haptens[18] or by linkage to immunogenic carriers.[19] As the type of immunity desired to be abrogated in leprosy is primarily the cell mediated response, modification of *M. leprae* by aceto-acetylation was tried. Parish[20] reported that the properties of these haptenic groups enhance CMI. It was observed that aceto-acetylated *M. leprae* evoked leukocyte migration inhibition with peripheral cells of polar lepromatous leprosy patients, which normally did not produce these lymphokines in the presence of *M. leprae* antigens. Aceto-

acetylated *M. leprae* has been evaluated on a limited scale in lepromin-negative contacts of lepromatous leprosy patients.[21] A single intradermal injection of 5 x 10^7 modified bacilli converted 88 per cent of lepromin-negative subjects to lepromin positivity.

About eight years ago, we tested 16 cultivable mycobacteria for their ability to induce lymphocyte blast transformation and leukocyte migration inhibition of peripheral blood cells taken from a panel of tuberculoid leprosy patients. The choice of this category of donors was based on the deduction that in these subjects clinical evidence of *M. leprae* infection was available with their demonstrated ability to localise the infection and eliminate the mycobacteria. *M. leprae* was used as a reference and cultivable mycobacterial strains giving a response similar to *M. leprae* with the donor cells were selected. Five mycobacteria from amongst the 16 tested fell into this category. These were *Mycobacterium w.*, ICRC bacillus, *M. vaccae*, *M. phlei* and *M. gordonae*. Two of these have undergone limited clinical evaluation. *M.w.* is a nonpathogenic atypical mycobacteria which belongs to Runyon's group IV on the basis of its growth characteristics and metabolic properties.[22] A single intradermal injection of 5 x 10^7 autoclaved *M.w.* cells converted about 62 per cent of repeated lepromin-negative lepromatous leprosy patients to lepromin positivity status. In converted cases, the Mitsuda reaction was clearly positive (8.0 ± 1.0 mm); the positivity was not transient but was shown on retest 6-11 months after immunisation. An *in vitro* CMI test conducted by another under a double blind code with cells of these patients showed a good match between the *in vivo* DTH reaction and *in vitro* leukocyte migration inhibition. In recent studies involving the use of this vaccine, Dr. Chaudhary also observed an immunotherapeutic benefit of *M.w.* inactive BL to LL leprosy cases. The field studies of ICRC bacillus vaccine were conducted mostly in Bombay.[23,24] The results of recent studies show that ICRC vaccine is able to bring about lepromin conversion in 50 per cent of LL and 80 per cent of BB/BL cases four months after vaccination; 30 per cent of LL patients developed ENL.

The lepromin conversion rate of the candidate vaccines tested in clinics or in the field is limited to about 60 per cent. Whether this limit can be by-passed, using a combination of these vaccines, remains to be determined. Alternatively, it may be hypothesised that a subclass of lepromatous leprosy is non-convertible by these approaches and may have to be treated primarily with a combination of drugs.

Development of vaccines against leprosy is a complex and a challenging proposition. The majority of the population (98%) is intrinsically resistant to the disease and the latent period of the disease is long (five years or more). Therefore, efficacy testing of any vaccine will demand a fairly large study conducted over a long period of time. No faithful experimental model is available for human lepromatous leprosy. The precise nature of the immune defect is not well known, although progress has been fairly good during the last 15 years. Thus, research must continue in order to enable us to understand the lesion, so that rational criteria are available to evaluate under stringent conditions the candidate vaccines. A complementary route to the containment of the disease may be the development of sensitive methods for diagnosis of subclinical carriers of infection, who may be potential transmitters to others. Fluorescent antibody assay,[25,26] radioimmunoassay[27] and last but not least enzyme-immunoassays[28,29] based on detection of the IgM type of antibodies reactive with phenolic glycolipid unique to *M. leprae* are the main methods currently under evaluation for discriminatory diagnosis. Their relative utility to indicate with high fidelity carriers or patients loaded with *M. leprae* should be established on larger samples within a year or so. Identification of potential transmitters of infection by immunodiagnosis could pave the way to their isolation and radical treatment with a combination of drugs. This route may be a practicable strategy in the short run, while research and field testing continue eventually to develop a vaccine(s).

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