

Editorial

A VACCINE FOR LEPROSY

An effective vaccine for leprosy is undeniably desirable as a prophylactic reagent to prevent the clinical manifestations of infection and perhaps as a therapeutic reagent to upgrade patients at the lepromatous end of the disease spectrum. Besides being effective, such a vaccine would have to be safe, cheap, easy to administer and a real improvement over BCG.

Taken at its simplest, an effective vaccine for leprosy will be a reagent that induces a circulating clone of thymic lymphocytes capable of instructing macrophages in the art of destroying leprosy bacilli. In principle a vaccine will consist of the antigens (x) of *Mycobacterium leprae* necessary for the induction of protective immunity together with an adjuvant which will particularly enhance the cell mediated rather than humoral immune mechanism. The obvious adjuvant is BCG and alternatives should only be considered if for some reason BCG proves unsuitable. Nevertheless, during the development stages of the vaccine in which vaccinated animals are experimentally challenged a non mycobacterial adjuvant such as *Corynebacterium parvum* could be used to advantage. Leaving aside the practical aspects of experimentation let us assume the vaccine to be BCG + x which could replace BCG alone in the vaccination programme against tuberculosis in leprosy endemic countries. If this is to be the case then not only do we have to find and prove the effectiveness of x against leprosy, but we must also show that it is stable in a freeze dried preparation with BCG and does not impair protection from tuberculosis.

Mycobacteria possess at least 4 groups of antigens (Fig. 1) those which they share amongst themselves and with related genera such as *Nocardia* and *Gordona* (group i antigens); those shared by slow growing mycobacterial species (group ii antigens); those shared by fast growing mycobacterial species (group iii antigens) and those limited to individual species (group iv antigens) (Stanford, 1973a). So far as we know there is little or no cross protection between *Nocardia* and *Mycobacterium* or between fast growing and slow growing mycobacteria. There appears to be considerable cross protection between slow growing species which also show some cross reactivity to Tuberculin PPD, but so far there is no evidence of cross protection between fast growing species. The best protection, however, is afforded by members of the same species. Thus BCG immunization affords somewhat better protection from tuberculosis than does the so-called "non-specific" sensitization to Tuberculin PPD attributed to contact with *M. avium* and *M. gordonae*, and immunization of mice with *M. avium intracellulare* affords better protection from *M. lepraemurium* than does BCG vaccination (Brown, personal communication). One may conclude from this that antigens inducing protective immunity amongst slow growing mycobacterial species may belong to

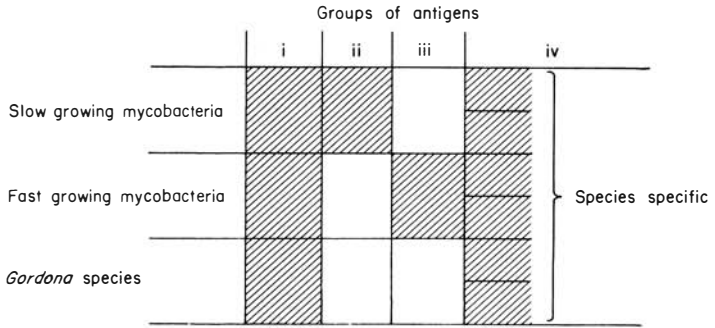


Fig. 1. The antigens of *Mycobacterium* and *Gordona* species demonstrable by immunodiffusion arranged in groups. The antigens of group i are shared by all members of both genera and the group iv antigens are limited to individual species.

the antigenic groups ii and iv, although this does not necessarily mean that the protective antigens are themselves precipitated in immunodiffusion analysis.

On the basis of these observations it would be best to use the antigens of *M. leprae* itself in any proposed vaccine since the use of antigens obtained from related culturable species might be expected to afford less good protection. Until such time as the leprosy bacillus can be readily cultured *in vitro* it will be necessary for the organism to be extracted from tissues. It is not only necessary to free the organism of host tissue antigens, but it is also necessary to leave the leprosy antigens chemically intact and not complexed with host antibody. Even if a suitable extraction technique is used there is still the problem of the majority of leprosy bacilli in tissues, even armadillo tissues, having been dead for some considerable time. If any parallel can be drawn from experience with BCG we can expect little immune protection to be induced by the antigens of long dead organisms. Thus a lysate of bacilli extracted from tissue will contain a comparatively small proportion of the desired antigens, possibly necessitating the use of some fractionation and concentration procedure before a useful product is obtained.

Induction of cellular or humoral immunity to the wrong antigens of *M. leprae* may itself be hazardous since in some forms of the disease these very phenomena are a part of pathogenesis. Their superimposition on a person already subclinically infected with the leprosy bacillus might precipitate a worse form of the disease than would otherwise have developed. Because of the many difficulties associated with the production of a vaccine from tissue derived leprosy bacilli serious consideration should be given to alternative approaches.

It has already been pointed out that a vaccine from a related culturable species might be expected to be less effective than one prepared from *M. leprae* itself. Nevertheless, such a vaccine might provide a very useful amount of protection. What then do we know of the relationships existing between *M. leprae* and other mycobacterial species?

Immunodiffusion analyses have not so far demonstrated the presence of group ii or iii antigens in the leprosy bacillus so that it cannot clearly be related to either the fast or slow growing subgenera of *Mycobacterium* (Stanford *et al.*, 1975). This

	i	ii	iii	iv									
<i>M. avium avium</i>	hatched	hatched		hatched	hatched	hatched	hatched	hatched	hatched	hatched	hatched		
<i>M. avium intracellulare</i>	hatched	hatched		hatched	hatched	hatched	hatched	hatched	hatched	hatched	hatched		
<i>M. lepraemurium</i>	hatched	hatched		hatched	hatched	hatched	hatched	hatched	hatched	hatched	hatched	hatched	hatched
Other slow growers	hatched	hatched											
Fast growers	hatched		hatched										

Fig. 2. The group iv (species specific) antigens of *M. avium* variants shown in relation to the antigens they share with other species. The group iv antigens are shared vertically where this is indicated by hatching.

lack of groups ii and iii antigens is also a feature of *M. vaccae* and of members of the genus *Gordona*. Studies on the mycolic acids of these organisms have shown *M. leprae* and *M. vaccae* to possess those of the mycobacterial type whereas *Gordona* species possess mycolic acids with smaller numbers of carbon atoms, similar to the nocardomycolic acids (Etemadi and Convit, 1974; Alshamaony *et al.*, 1976). Studies of delayed hypersensitivity in leprosy patients and their family contacts using a range of very specific skin test reagents produced from 2 *Gordona* species and 20 mycobacterial species have shown the leprosy bacillus to be more closely related to *M. vaccae* and *M. nonchromogenicum* than with the other species tested (Paul *et al.*, 1975). Similar conclusions have been reached from studies of delayed hypersensitivity in experimentally immunized animals.

I have it on the authority of Dr S. Browne that there is no evidence for the existence of leprosy prior to 600 B.C. If this is so and if we allow a margin of 5 millenia then the leprosy bacillus has only been with us some 8000 years—a very short time indeed compared with the antiquity of man himself. Presumably *M. leprae* arose as a naturally selected mutant of another mycobacterial species. It is highly likely that this progenitor is still in existence and there is no reason to think that it need be a pathogen. In fact there is good reason to believe that it was not. With the exception of *M. tuberculosis* and possibly *M. lepraemurium*, which is passed directly from the infected to the uninfected, the other mycobacterial pathogens of mammals are all opportunists coming from the environment. In many cases strains causing infections are probably the same as environmental strains, but in one species, *M. fortuitum*, the serotype usually involved in human infections differs from those generally present in soil and it has been shown that the soil serotypes throw off the potentially pathogenic type at a low rate, probably by a process of deletional mutation (Grange and Stanford, 1974). With the exceptions of *M. fortuitum* and *M. chelonae* which are fast growing species giving rise to infections unaccompanied by the development of positivity to Tuberculin PPD, all the culturable pathogens of mammals are slow growing species infection with which does produce positivity to Tuberculin PPD. *M. lepraemurium* belongs to the slow growing mycobacteria possessing antigens of group ii. This species is closely related to *M. avium* from which it almost certainly arose, possibly by a process of deletional mutation (see Fig. 2) (Stanford, 1973b).

Thus the leprosy bacillus does not appear to be closely related to the other pathogens. However, it may well bear a relationship to a culturable environmental

species similar to that of *M. lepraemurium* to *M. avium* or the pathogenic to the nonpathogenic serotypes of *M. fortuitum*.

It is particularly unfortunate that the two organisms found to be related to the leprosy bacillus, *M. nonchromogenicum* and *M. vaccae* are themselves little understood. Both are common in certain natural environments and both were first described relatively recently. There has been only one reported case of a human infection with *M. nonchromogenicum* and none are known with *M. vaccae*. Unfortunately both species are incompletely characterized and so variable that in fact each may really comprise several species.

Research is currently going on to try to sort out the various strains of these species and to determine which of them is most closely related to *M. leprae*. This should shortly be completed and then animal protection experiments can begin. Both organisms are so easily cultivated that large quantities can be readily prepared. Their lack of pathogenicity makes them easy to handle and even the possibility of a live vaccine might be considered.

The numbers of persons producing positive reactions to skin tests with the antigens of *M. nonchromogenicum* or *M. vaccae*, in regions where these organisms are common in the environment is low in comparison with those reacting to other environmental mycobacteria suggesting that, like the leprosy bacillus itself, they are not readily allergenic (Stanford *et al.*, 1976). Perhaps they lack some of the adjuvanticity associated with other mycobacteria, however, this could readily be provided by BCG. A small study of the environmental mycobacteria of Uganda found *M. nonchromogenicum* to be widely distributed, but strains of *M. vaccae* were only encountered around Lake Kyoga in regions close to those where the trial of BCG against leprosy was carried out (Brown, *et al.*, 1969). Perhaps the good results obtained in the trial were in part due to enhancement of reactivity to these environmental species by BCG.

In conclusion it is likely that a vaccine for leprosy will consist of BCG. together with antigens able to induce specific protective immunity from the disease. Although these antigens would theoretically be best obtained from *M. leprae* the practical difficulties in their extraction and purification from infected tissues—even of armadillos—may be difficult to overcome. In view of this an alternative source should be sought amongst the leprosy bacillus' closest culturable relatives. Some success in identifying these organisms has already been achieved and experimental vaccines employing them will shortly be tested in animals. This in itself will be problematical since the intact rather than the immunologically suppressed mouse will have to be used and there is very little latitude for protection in such animals. In view of this the vaccine may well have to be assessed in the only animal known to be naturally susceptible to leprosy—man.

J. L. Stanford

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