Vaccine Development in Leprosy

To The Editor:

I read your editorial "The Lepromatous Macrophage Defect as Related to Vaccine Development in Leprosy" with great interest (IJL **44** [1976] 485-490). You stated that, "if the primary defects lie in T cell clones in lepromatous leprosy and if the lepromatous macrophages do, indeed, process the ingested bacilli, then it is difficult to see how an attenuated live vaccine can be effective." Our studies on attempts to repair the immunologic deficit in lepromatous leprosy by cellular engineering support your views in many ways.

Years ago, Dharmendra demonstrated that lepromatous leprosy developed almost exclusively among those individuals who were not capable of showing any late lepromin reactivity. Also this specific unresponsiveness to *M. leprae* in patients with lepromatous leprosy is long-lasting and probably life-long, but generalized impairment of cell-mediated immunity towards unrelated antigens may revert with treatment. Due to this poor immune status, these individuals are unable to eliminate lepra bacilli which tend to grow within the hosts at an accelerated rate. As the bacillary load increases, there is frequent release of mycobacteria or their products in the circulation causing onset of *erythema nodosum leprosum* (ENL). This tremendous bacterial load further throws these patients into a state of immunologic paresis, which is initially specific to *M. leprae,* but as the disease progresses onward this becomes generalized towards other unrelated antigens. Thus a vicious cycle is set up which shifts them to the extreme polar form of lepromatous leprosy commonly associated with repeated attacks of ENL and its usual consequences. This compels many patients to become dependent on cortisone. Moreover, these patients often become dapsone resistant due to lack of adequate intake of the drug for a prolonged period. Furthermore, some also develop drug intolerance to such a degree that they avoid taking DDS due to fear of devęloping painful episodes of ENL. Thus, usual antileprosy therapy alone appears to hold limited promise in these active lepromatous patients.

Armed with these facts and the concept of cellular engineering to fortify immunologic responses in immunodeficient diseases; we treated 1) 12 such active cases with three infusions of viable allogenic blood lymphocytes obtained from normal donors showing late lepromin reactivity, and 2) 10 similar patients by successive grafting of three thymuses taken from 15–18 week old human fetuses obtained from women undergoing hysterectomy. Each patient was assessed clinically, bacteriologically, histologically and immunologically before and five months after immunotherapy.

Both repeated infusion of allogenic lymphocytes as well as implantation of fetal thymus dramatically brought about improvement of the clinical status of patients, resolution of skin lesions, subsidence of ENL reaction, clearance of bacteria from skin, and reconstitution of only those immunologic deficiencies which are not related to *M. leprae.* Regrettably, late lepromin reactivity did not develop in any of the so-treated cases.

Mitomycin C treatment prevents cellular DNA replication. However, similarly treated blood lymphocytes may act as a vehicle of transfer factor. In a third set of experiments,

3) 7 lepromatous cases with severe ENL and dapsone intolerance were given three successive infusions of mitomycin C-blocked allogenic blood lymphocytes. Also in another experiment, 4) 4 similar patients were infused with transfer factor prepared from leucocytes taken from healthy donors with positive lepromin reactivity. However, the last two immunologic interventions proved to be futile, although immunologic unresponsiveness towards unrelated antigens developed in almost all cases. Also, in a current pilot experiment, human fetal thymic tissue encased in millipore chambers and inserted in a few lepromatous cases having severe ENL, did not alter their downhill course though some unrelated immunologic responsiveness did develop.

These experiences suggest that an allogenic encounter between the recipient and donor lymphocytes, with viable lymphocyte infusion, may help the lepromatous macrophages to process *M. leprae*. Moreover, all these four immunologic interventions could only restore those immunologic reactivities which were not related to *M. leprae*, e.g., tuberculin and streptokinase-streptodornase sensitivities, dinitrochlorobenzene contact sensitivity, and even 48-hour lepromin (armadillo) hypersensitivity. What is lamentable is that the 30 day lepromin responsiveness never developed, although in a few cases there was influx of lymphocytes at the site of lepromin test.

Thus there is always high risk of reactivation (relapse) of the active illness, which promptly subsides after the lymphoid tissue replacement therapy. In fact, the disease relapsed with full intensity in two patients after about two years of thymus grafting. Therefore it is possible that the primary immunologic defect related to *M. leprae* lies neither in T cells nor in the thymus, but may stay in some bone marrow or fetal liver precursor cells. Thus, it is difficult to see how an attenuated live vaccine can be effective in controlling this dreadful disease on the earth. The equivocal results on controlled trials on leprosy prevention by BCG vaccination lend further support to the above notion. BCG vaccination indeed potentiates late lepromin reactivity which is the hallmark of resistance against leprosy; but it may fail to protect those who may be genetically deprived of this unique late reactivity towards *M. leprae*.

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