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EDITORIALS

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Immunological Approach for Control of Mycobacterium avium-intracellulare Infections in AIDS—an Hypothesis

Acquired immunodeficiency syndrome (AIDS), characterized by a wide spectrum of opportunistic infections, is caused by a group of lymphocytotropic retroviruses, now designated as human immunodeficiency viruses (HIV).[1-3] These cytopathic viruses preferentially infect CD4+ cells.[4, 5] Among the opportunistic infections, infections due to atypical mycobacteria, chiefly the *Mycobacterium avium-intracellulare* (MAI) group of organisms, are frequently observed in the developed countries.[6-8] In drug abusers, Haitians in the U.S.A., and in Africans, AIDS is often associated with a high inci-

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dence of tuberculosis.[9-12] It thus appears that AIDS patients exhibit increased susceptibility to mycobacterial infections.

The MAI group of organisms are ubiquitous environmental mycobacteria of very low virulence.[8, 13] Their frequent isolation in AIDS patients could simply be attributed to severe T-cell immune deficiency caused by the virus. This is to some extent supported by the observation that, besides MAI, a host of opportunistic agents have also been isolated from these patients.[1-3] However, certain features of MAI infections cannot be explained merely on the basis of this assumption. Infections due to MAI and *M. tuberculosis* occur even in AIDS-related complexes (ARC), suggesting that a severe immune deficiency is not a prerequisite for the occurrence of such infections.[14, 15] Further, observations suggest that immunity against MAI may be selectively affected in AIDS. The types of atypical mycobacteria isolated from AIDS patients are somewhat different from those seen in immunodeficiencies associated with other conditions.[16] Thus *M. kansasii* and *M. tuberculosis*, which are frequently isolated from patients with silicosis and terminal renal transplantation cases, are rare in Caucasian AIDS patients in the U.S.A.[17, 18] Likewise, *M. scrofulaceum* infections, which are relatively common in children, are virtually absent in AIDS patients.[16, 19, 20] Even within MAI, certain serotypes are more frequently isolated. In one study 77% of the isolates were serovar 4, which is in contrast to the serotypes of MAI isolated from a variety of other human diseases.[21, 22]

These features suggest that MAI may not just be a passenger opportunistic infection, but that HIV has, in certain cases, a special preference for T cells involved in immunity against mycobacterial infections.[9, 12, 16] The outcome of the host-parasite interaction is decided by the balance between host immunity and the virulence of the organism. The genetic background of the host plays a dominant role in host immunity. This is best illustrated in mice, in which animals of specific genetic combinations can be bred at will. The immune response is governed by Ir genes located in the H-2 complex.[23] Resistance of mice to bacterial (including MAI), viral, protozoal, and fungal infections is dependent upon their genetic makeup.[24-32] Several studies have been conducted in man to determine the relationship of

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the HLA pattern to susceptibility to infections.[33, 34] Human beings exhibit a broad range of susceptibility for the development of leprosy, a mycobacterial disorder widely prevalent in developing countries.[35, 36] Depending upon their immunity, individuals could be completely resistant or can develop the mild, localized tuberculoid or the severe, disseminated lepromatous varieties of leprosy.[37] In the same way, there could be differences in host susceptibility to MAI. Normally, even subjects with a very weak immunity are resistant to MAI. However, an attack of HIV may tilt the balance, particularly in individuals with a weak immunity, favoring a disseminated MAI infection. As a consequence, there would be antigenic overloading. Also, proliferating MAI would put an additional burden on the host's nutrition and, in some cases, generate "immunosuppressive" metabolites,[38] further compromising host immunity and making such individuals susceptible to fresh attacks of the HIV infection. A vicious circle may thus be established, culminating in unabated multiplication of MAI which results in full-blown AIDS. Boosting of the MAI-

specific immunity in such individuals either before the HIV infection or in the pre-AIDS stage, could strengthen their defenses against MAI infection.

No single laboratory immunological parameter is diagnostic of AIDS. The disease is, however, consistently associated with lymphopenia, a reduction in the T4:T8 ratio as a result of loss of the former, anergy to a variety of recall antigens, diminished *in vitro* T-cell responses, and a paradoxical aberrant increase in the level of circulating immunoglobulins. In addition to these features, there are also reports of diminished production of interleukin 2 (IL-2) and defective expression of IL-2 receptors.[39]

Immunology of leprosy vis-à-vis AIDS. The tissue lesions induced by MAI in AIDS patients are predominantly composed of macrophages,[40, 41] lack lymphocytes, and resemble those seen in patients with lepromatous leprosy (LL) which is a disorder due to defective immunity to *M. leprae*.[42-44] As in AIDS, LL lesions are loaded with slow-growing mycobacteria—*M. leprae*. Also, immunological changes in the LL patients have many similarities with those observed in AIDS patients. For example, as in AIDS, in LL also there are reports of lymphopenia,[45] a reduction in the T4:T8 ratio,[46, 47]

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depression of both *in vivo* and *in vitro* T-cell responses, and an increase in immunoglobulin levels.[44, 45] Some workers have reported diminished production of IL-2 and defective expression of IL-2 receptors in LL patients.[43] However, unlike AIDS, the immune nonresponsiveness in LL is highly specific to *M. leprae*.[42, 44, 48] A reduction in helper (T4) cells and, consequently, in the T4:T8 ratio is observed only in untreated LL patients who are highly bacilliferous. In treated cases with a low bacterial index, the number of circulating T4 cells and the blood T4:T8 ratio return to normal.[46] In other words, alterations in T4 as well as the T4:T8 ratio are dependent on the tissue bacillary load. By the same analogy, a heavy tissue load of MAI could aggravate immune deficiency in AIDS patients.

If, as has been suggested by Collins,[16] MAI infection has a putative role in the pathogenesis of AIDS, a suitable vaccine to boost immunity, particularly in the high-risk subjects, could protect them against MAI even when they are infected with HIV. There are hardly any laboratory parameters which could be used to identify subjects with weak immunity to MAI. However, in view of the many similarities in the immunological profiles and local tissue responses between AIDS and LL patients, some of the lessons learned from leprosy might be useful specifically to identify those individuals with weak immunity against MAI.

Generally, a 48–72 hour skin test response to recall antigens has been used as a laboratory parameter of cell-mediated immunity (CMI), which is the dominant host defense against intracellular parasites. However, it often denotes sensitization and may not necessarily be a reflection of the host defense. This is best illustrated by the results of the tuberculin reaction. In leprosy, two types of tests are employed.[36, 49] Soluble antigens induce a tuberculin-type reaction that reaches a peak between 48 and 72 hours. Like the tuberculin reaction, the response to the soluble antigens is an indication of exposure to *M. leprae*. On the other hand, in the Mitsuda test a particulate antigen of *M. leprae* is used which gives a biphasic reaction. The response at 48–72 hours is weak and inconsistent, but at the site of injection a small induration, which peaks at 3–4 weeks, is observed.

Mitsuda reactivity is observed in more than 80% of the healthy population residing in leprosy-endemic areas.[36] The proportion of responders is not very much different even in leprosy-free areas, although in them the reaction tends to be weaker. No significant differences are observed in the proportions of responders between household contacts of LL patients and those who did not reside with the patients.[50] These observations indicate that constitutional rather than environmental factors (exposure to *M. leprae* antigens) play a dominant role in the genesis of the Mitsuda reaction. Although the mechanism of the Mitsuda reaction is not fully understood, the available clinical, laboratory and experimental evidence clearly shows that the reaction is closely linked with the capacity of the host to effectively handle *M. leprae*.[36, 37, 51, 52] Thus, in LL patients, who represent one end of the leprosy spectrum, the Mitsuda reaction is consistently negative; the patients exhibit diffuse lesions; and their tissues are laden with *M. leprae*. On the other hand, in the paucibacillary tuberculoid (TT) variety the Mitsuda reaction is strongly positive.[37] TT patients exhibit one or two hypopigmented anesthetic skin patches and their tissues contain very small numbers of *M. leprae*. Epidemiolog-

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ical studies have shown that Mitsuda-negative individuals in leprosy-endemic areas run a high risk of contacting the lepromatous or near lepromatous forms of the disease which are not seen in those who are Mitsuda positive.[51] Leprosy has been successfully induced in armadillos[53] and monkeys.[54] However, not all armadillos inoculated with *M. leprae* develop the disease. According to Job and his coworkers,[52] Mitsuda-positive animals are relatively resistant to the disease. Experimentally induced lepromatous leprosy is observed only in lepromin-negative monkeys.[54] The interpretation of the Mitsuda test could be further improved if histology is taken into account.[49] On the basis of the histology, the locally induced granuloma can be classified as: a) predominantly consisting of macrophages with a paucity of lymphocytes and b) well-formed granulomas with giant cells, epithelioid cells, and lymphocytes. The second category represents an immune granuloma.

Reference has already been made to the similarity in the immunological profiles of AIDS and LL patients. Further, in immunocompromised individuals, both *M. leprae* and MAI induce granulomas consisting predominantly of macrophages and lacking lymphocytes.[40, 41] For these reasons, we feel that a Mitsuda-type reaction, using particulate antigen(s) of MAI, might be useful to screen the high-risk groups. Those who show a weak response, as evidenced by a small induration and a histology consisting predominantly of macrophages, are probably the subjects with weak immunity to MAI. Such subjects could be given a suitable vaccine to boost their immunity.

Principles of vaccine development. Two approaches that have been used in the development of an antileprosy vaccine could be followed. Intradermal administration of killed *M. leprae* induces in LL patients only a macrophage granuloma lacking lympho-

cytes. But when a mixture of *M. leprae* plus BCG is used, a lymphocyte-rich, epithelioid-cell granuloma consisting of giant cells (immune granuloma) is formed.[55] This observation forms the basis of the "mixed" antileprosy vaccine containing heat-killed *M. leprae* plus BCG that is curently undergoing field trials in Venezuela.[56] A similar approach could be followed to develop a suitable mixed vaccine to boost immunity against MAI, especially in the high-risk subjects with weak immunity. Such a mixed vaccine could contain either two or more members of the MAI complex or a member of the complex plus allied immunogenic mycobacteria. Appropriate combination(s) could be selected using the above-mentioned procedure followed in the development of the mixed antileprosy vaccine.

At the Cancer Research Institute in Bombay, a somewhat different approach using a cultivable organism antigenically closely related to *M. leprae* has been followed. The Institute has repeatedly isolated, during the last 30 years, a group of slow-growing cultivable mycobacteria, named ICRC, from human lepromas. The "Mycobacterium ICRC," which belongs to the MAI complex, has many biochemical and immunological characteristics in common with leprosy bacilli.[57, 58] A number of other nonpathogenic mycobacteria have been isolated from lepromas.[59] The cultivable leprosy-derived mycobacteria are probably "passenger organisms" that could be described in a broad sense as "local opportunistic infections" restricted only to lepromas.

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Interestingly, a vaccine prepared from killed ICRC bacilli has been able to break the nonresponsiveness to *M. leprae*, even in the highly bacilliferous LL patients, so that after vaccination these patients are able to mount cellular immunity against the organisms.[58, 60] Studies from this laboratory indicate that the vaccinated patients exhibit an increase in the T4:T8 ratio, as well as an improvement in both *in vivo* and *in vitro* T-cell responses. Circulating anti-*M. leprae* antibodies are also decreased after vaccination.[61] A vaccine prepared from the ICRC bacillus, a "passenger organism," has thus been able to reverse the immune defect in LL, even in the presence of tremendous mycobacterial load.

We are conscious of the fact that, in the present state of knowledge, the mechanisms of immune deficiency in the two disorders, namely, AIDS and lepromatous leprosy, are different. However, as discussed below, even the AIDS patients, who exhibit severe immune deficiency, are still able to respond to a number of vaccines. In light of this, attempts could be made to develop a suitable vaccine against the MAI infection using the principle followed in the preparation of antileprosy vaccines.

Immunoprophylaxis and immunotherapy against mycobacteriosis in AIDS. AIDS has a long incubation period during which HIV lies dormant in the infected T4 cells, the main target for the virus. Although the exact mechanisms by which a carrier or an AIDS-related complex (ARC) patient develops full-blown AIDS are not understood, considerable importance is being attached to cofactors, especially to concurrent infections.[1, 62, 63] It is believed that the cofactors induce proliferation of the already infected CD4+ cells, resulting in their destruction and hence the concomitant immune deficiency. However, it has been shown that only 5% to 10% of the CD4+ cells actually carry the receptor for HIV.[64] Further, using radioactive nucleotide probes, it has been demonstrated that only 1:100,000 peripheral blood mononuclear cells express viral RNA, even in AIDS patients.[65] These studies indicate that the immune deficiency cannot be totally ascribed to the direct cytopathic effects of the HIV.

Probably due to preoccupation with HIV, the possibility of concurrent infections being responsible for aggravating the immune deficiency has not received the attention it deserves. As mentioned earlier, there is evidence which shows that MAI infection could play a putative role in the pathogenesis of AIDS.[16] Recent studies have shown the frequent occurrence of tuberculosis in AIDS patients, particularly in drug abusers,[66] Haitians,[10] and Africans.[9] Often tuberculosis has been diagnosed even before the overt demonstration of immune deficiency.[14, 15] The association is so strong that it is now being debated whether *M. tuberculosis* infection is not a predisposing factor for AIDS in certain groups.[15] In fact, it has recently been proposed that tuberculin-positive, high-risk groups be given chemoprophylaxis with the daily administration of isoniazid.[12] Chemoprophylaxis, as a control modality, has not only many lacunae but also serious operational problems. What is true for tuberculosis may be equally applicable to MAI infections. Being organisms of low virulence, MAI infections may remain subclinical for a long time. Like tuberculosis, therefore, MAI infection may occur long before the immune system is seriously compromised. There is, thus, a good case for attempting immunoprophylaxis against mycobacterial

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infections in high-risk groups, particularly in individuals with weak immunity if they could be identified by a suitable laboratory, Mitsuda-like test.

What about vaccination of HIV carriers, ARC, or even AIDS patients? It may be argued that vaccination may precipitate the disease in the first two conditions, and in the last it may worsen the clinical course by activating the already virally infected CD4+ cells, resulting in their destruction. In fact Radfield, *et al.*[67] have recently reported a case of an HIV seropositive military recruit who developed AIDS after a smallpox vaccination. That this is coincidental, however, cannot be ruled out when one weighs other evidence, particularly the data on other vaccines. Thus, Nelson (quoted by Halsey and Henderson)[68] found no evidence of progression of HIV disease or a rise in the level of p24 antigen in 105 HIV-seropositive men given the polyvalent pneumococcal vaccine and four influenza vaccines. Likewise, no adverse reactions to immunization with live oral poliomyelitis, measles, mumps or rubella vaccines have been observed. Even in infants who received live vaccines after the onset of symptomatic HIV infection no worsening was observed, and the infants exhibited good immune response to vaccination.[68]

Another point to consider is that the AIDS patient may be nonresponsive to vaccines because his immune system could be suppressed due to heavy MAI infection, especially when it is considered that components of some mycobacteria can induce immunosuppression.[38] However, it has been shown that heavy mycobacterial infection does not totally suppress the immune system in experimental animals. Thus, mice heavily infected with *M. kansasii* and MAI continue to respond to other antigens.[69, 70]

This may be true also in the AIDS patient who, as mentioned above, is able to mount an immune response even to vaccines against viruses which, like MAI, are intracellular parasites. These observations indicate that the immune system of the AIDS patient is still capable of responding to a variety of antigens/vaccines.

As mentioned above there is a preponderance of certain strains of MAI in AIDS, and perhaps the immune system associated with other strains remains unaffected. According to Mackness,[71] vaccination with an intracellular parasite results also in a nonspecific stimulation of macrophages which then exhibit enhanced killing of unrelated organisms. By the same analogy, vaccination with a member of MAI other than the one isolated from the patient could result in destruction of the MAI organisms already present in the ARC or even in the AIDS patient. Therefore, a vaccine containing antigenically crossreacting MAI might not only induce antigen specific immunity but also stimulate nonspecific effector mechanisms.

Recently, it has been reported that a 29-year-old AIDS patient developed disseminated *M. bovis* infection following BCG vaccination.[72] Live mycobacterial vaccines should therefore be avoided in AIDS patients.[73] However, it has been shown that, in the case of some mycobacteria, antigenicity is not destroyed by heat killing.[74, 75] If this were true of the MAI, a killed vaccine, which would be safe, could be given even to AIDS patients.

A number of strains (serotypes) of MAI have been identified.[76] Ideally, the vaccine

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should give protection against all of the strains. One of the ways this could be achieved would be to use a polyvalent vaccine containing a large number of killed MAI serotypes. On the other hand, if the immunogenic components of different strains could be identified, a polyvalent vaccine containing such components of different strains of MAI could be used. This approach has been used for the development of a polyvalent pneumococcal vaccine which contains capsular polysaccharide from a number of strains of pneumococci.[77] From the ICRC bacilli, we have recently isolated a very high molecular glycolipoprotein, named PP-1, with an apparent molecular weight of 1,000,000.[57] PP-I appears to be the dominant immunogen of the organism because it brings about lepromin conversion in both LL patients and their lepromin-negative, healthy, household contacts.[78, 79] The chemical nature of PP-I suggests that it is probably a component of the cell membrane. Several studies have shown that cell-surface glycoproteins are good immunogens, and they have been used in the preparation of vaccines.[77, 80-82] A similar approach could be followed for vaccination against MAI infection in AIDS patients. A polyvalent vaccine containing PP-I fractions of a number of strains of MAI could be used. Being a non-live vaccine, it could be given even to ARC and AIDS patients without the danger of producing disseminated mycobacterial disease.

On the practical side, the vaccine should be used in small antigenic doses and its effects on the immune system assessed by using suitable laboratory parameters, especially with reference to T-cell functions. Simultaneously, investigations using full-vaccine doses could be conducted in suitable animal models (chimpanzees, macaques, etc.[83-85]) to see if they could be benefitted by a polyvalent vaccine containing a number of killed strains of MAI or their PP-I fractions. The macaques are especially suitable because a naturally occurring AIDS-like syndrome due to a retrovirus (simian T-lymphocytotropic virus or STLV-III), which has many similarities with HIV, has been described in them. The affected animals show clinicopathological features, including MAI infections, similar to those seen in human AIDS.

Concluding remarks. The best way to prevent AIDS would be to develop a vaccine specific against the causative agent. Attempts are being made in that direction by a number of laboratories around the world. However, a major problem in the development of such a vaccine is the marked antigenic variation observed in different isolates of HIV. Simultaneous attempts should therefore be made to develop strategies to contain some of the major opportunistic infections that may play putative roles in the pathogenesis of AIDS. MAI is one such infection which accounts for about 30% of the opportunistic infections in AIDS. In certain groups, AIDS is also frequently associated with *M. tuberculosis* infection. Association of mycobacteria is so strong that it is considered by some workers as a predisposing factor for AIDS. Further, it has

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been suggested that tuberculin-positive, high-risk subjects be given chemoprophylaxis for tuberculosis. Chemoprophylaxis has several conceptual and operational problems. Also, such an approach is not feasible for MAI infection, which is one of the most difficult infections to treat, since the organisms are resistant to most of the available drugs. In light of the above, immunoprophylaxis, which would be a cost-effective and operationally feasible preventive strategy, should be seriously considered—provided a suitable, preferably polyvalent, vaccine could be developed.

This editorial may appear somewhat speculative but our hypotheses are entirely testable. In the absence of any fully effective strategy, some novel approach is needed to tackle the AIDS problem, a problem that is acquiring alarming dimensions and threatens to be the worst killer of mankind in the years to come. For these reasons, in our view, both approaches—a) identification of subjects with weak immunity against MAI, and b) vaccination of high-risk healthy subjects, as well as HIV carriers and ARC and AIDS patients, using the above-mentioned modalities—are worthy of serious consideration. Such vaccines may not be curative, but by providing immunity against a common opportunistic infection they may prolong disease-free life, giving host defenses a better chance to cope with the deadly virus.

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