AIDS therapy by blocking CD4+ cells

SIR—In a recent *News and Views* article[1], Klatzmann and Montagnier discussed approaches to therapy of patients with acquired immune deficiency syndrome (AIDS), including immunosuppressive drug therapy, and, in particular, the case in which AIDS patients were treated with the drug cyclosporin A[2]. Since AIDS results in an immune-deficient state, most efforts to restore immune function have involved immune-enhancing therapy[3]. However, the rationale for immunosuppressive drug therapy is that the development of AIDS involves a progression of immune disorders of which an early phase may be autoimmune[4].

We suggest an alternative therapeutic approach based on the observation *in vitro* that the virus associated with AIDS, HTLV-III/LAV, is produced in activated but not resting T cells[5]. It seems logical to design therapy that would diminish the pool of CD4+ cells with the potential to produce virus efficiently. This could be accomplished by treating patients as early as possible in the course of the syndrome's development with either monoclonal anti-CD4 or anti-class II HLA reagents, either of which would block the activation of CD4+ T cells. The administration of CD4-specific antibodies would have the added advantage of interfering with the binding of HTLV-III/LAV to the CD4+ cell[6,7].

The mechanism by which HTLV-III/LAV causes the destruction of infected CD4+ T cells is unknown. If the virus is directly cytopathic, addition of CD4-specific reagents should prevent further infection of healthy cells, while permitting the infected cells to be lysed. It is likely that at least part of the destruction of infected CD4+ cells is due to cytotoxic T lymphocytes (CTL) that recognize HTLV-III/LAV antigenic determinants in association with self-HLA products and lyse infected cells[4]. In this case, treatment with antibodies that inhibit CD4+ helper T cell function should block further help provided by anti-HTLV-III/LAV-specific helper cells, but should permit the lysis of infected targets by CTL effectors that have already been activated.

From this perspective, it could be reasoned that immune-enhancing therapy such as administration of interleukin-2 (IL-2) would activate CD4+ cells and increase the number of T cells that would be susceptible to infection with the AIDS virus. Furthermore, since many HTLV-III/LAV infected individuals do not exhibit symptoms[8], it appears that cofactors such as other infectious agents[9], drugs[10], or HLA allogenic stimulation[11,12] contribute to the appearance of the syndrome. A common mechanism by which these various potential cofactors could operate is by the activation of CD4+ T cells, thereby increasing the HTLV-III/LAV target cell pool size.

A therapeutic protocol that blocks CD4+ T cell activation would probably limit the number of CD4+ cells infected by HTLV-III/LAV and subsequently destroyed. However, because these antibodies function to prevent activation of helper T cells, they would be likely to induce immune deficiency, but one that is reversible upon cessation of treatment. Thus, therapy that blocks CD4+ T cell function differs from treatment with immunosuppressive drugs (which can have severe side effects and can be difficult to control) in that it is readily reversible. If therapy that blocks CD4+ T cells were to be attempted, it should be administered as early as possible in the development of AIDS, before depletion of CD4+ T cells has occurred, and probably with agents that have anti-retroviral activity[13,14].

ALFRED SINGER
GENE M. SHEARER

Immunology Branch,
National Cancer Institute,
Bethesda, Maryland 20892, USA

1. Klatzmann, D. & Montagnier, L. *Nature* **319**, 10 (1986).
2. Walgate, R. *Nature* **318**, 3 (1985).
3. Fauci, A.S. *et al. Ann. intern. Med.* **100**, 92 (1984).
4. Shearer, G.M. *Mt Sinai J. Med.* (in the press).
5. McDougal, J.S. *et al. J. Immun.* **135**, 3151 (1985).
6. Dalgleish, A.G. *et al. Nature* **312**, 763 (1984).
7. Klatzmann, D. *et al. Nature* **312**, 767 (1984).
8. Blattner, W.A. *et al. Ann. intern. Med.* **103**, 665 (1985).
9. Frederick, W.R. *et al. J. infect. Dis.* **152**, 162 (1985).
10. Marmot, M. *et al. Lancet* **i**, 1083 (1982).
11. Mavligit, G.M. *et al. J. Am. med. Ass.* **251**, 237 (1984).
12. Tung, K.S. *et al. J. Immun.* **135**, 3163 (1985).
13. Mitsuya, H. *et al. Science* **226**, 172 (1984).
14. Rozenbaum, W. *et al. Lancet* **i**, 450 (1985).

Serotherapy for AIDS and pre-AIDS syndrome

SIR—Acquired immune deficiency syndrome (AIDS) and the related pre-AIDS syndrome continue to spread[1] with as yet no effective treatment. Vaccines are a hope for the future, but it is generally acknowledged that vaccines are unlikely to prove useful in established AIDS. Recent suggestions of using methods of inhibition of gene expression to treat AIDS are theoretically attractive but also somewhat futuristic[2]. There is another and more immediate approach to treating these diseases. McDougal *et al.*[3] and others (including our unpublished observations) have shown that lymphadenopathy-associated virus/human T-lymphotropic virus type III (LAV/HTLV-III) infected T cells and T cell lines established from AIDS patients express the interleukin-2 (IL-2) receptor. This membrane receptor is an 'activation' marker of mitogen and antigen stimulated normal lymphocytes. The virus LAV/HTLV-III causing AIDS on gaining access to T lymphocytes via their CD4 receptors[4] remains within a protected intracellular environment, avoiding the effects of neutralizing antibodies. Such antibodies have been detected in the blood of AIDS and AIDS-risk patients[5,6]. Present indications are that such neutralizing antibodies seem not to influence the course of the disease. This is probably due to the privileged intracellular location of the virus mainly within the helper/inducer T lymphocytes. This is indicated in the experiments of Robert-Guroff *et al.*[6], showing that absorption with virus infected and uninfected H9 cells do not substantially affect neutralizing antibody titres, in contrast to cell-free virus preparations.

We suggest that the expression of the IL-2 receptor by the LAV/HTLV-III infected cells provides an extremely useful target (with a fairly high degree of tissue selectivity) for antibody-directed destruction of such cells. A high affinity anti-IL-2 receptor antibody (several monoclonals exist) selected from the appropriate species and of the appropriate isotype would be lytic-destructive for the LAV/HTLV-III infected target cells. The released virus would then be exposed to the neutralizing antibodies in blood. A good candidate for the anti-IL-2 receptor antibody would be a rat monoclonal of the IgG2b isotype. Such a monoclonal immunoglobulin with predefined specificity for membrane molecules of human and mouse T cells has already been shown *in vivo* and *in vitro* to be highly destructive to target lymphocytes. The antibody activates the recipient's own serum complement and operates in antibody-dependent cell cytotoxicity to give lysis of the targets[7].

The AIDS and pre-AIDS patients' sera may contain enough neutralizing antibody to be effective against the exposed virus following the lysis of IL-2 receptor bearing infected targets. Alternatively, passive anti-LAV/HTLV-III human antibodies could also be infused to boost the patient's own antibody. Passive anti-LAV/HTLV-III antibody for administration can be obtained from pooled AIDS sera by ethyl alcohol fractionation which inactivates the virus[8] without reducing antibody activity.

The combined serotherapeutic approach outlined above can now be put to the test using the recently developed *in vitro* model systems[6,9]. Passive administration of antibodies is a time proven method of therapy, and the side effects are well documented and amenable to prophylaxis and treatment. Ideally this form of therapy should be introduced early after the diagnosis of AIDS and pre-AIDS syndrome, and possibly for patients shown to be LAV/HTLV-III antibody positive, with or without the secondary lymphocyte subset changes. Serotherapy could also be combined with drug treatment with agents such as suramin, which by itself in early clinical trials has proved to be ineffective in the long term, with marked toxic side effects. The early introduction of the ther-