18. Titti, F. *et al. J. med. Virol.* **23**, 241-248 (1987).
19. Goedert, J. J. *et al. Science* **231**, 992-995 (1986).
20. Eyster, M. E. *et al. Ann. intern. Med.* **107**, 1-14 (1987).
21. Rothenberg, R. *New Engl J. Med.* **317**, 1297-1302 (1987).
22. Reeves, G. K. & Overton, S. E. *Lancet* **i**, 880 (1988).
23. Piot, P. *et al. Science* **239**, 573-579 (1988).
24. Pedersen, C. *et al. Br. med. J.* **295**, 567-569 (1987).
25. Goudsmit, J. & Paul, D. A. *Epidem. Inf.* **99**, 701-710 (1987).
26. May, R. M., Anderson, R. M. & Johnson, A. M. (in preparation).
27. Blythe, S. P. & Anderson, R. M. *IMA J. Math. appl. Med. Biol.* (in the press).
28. May, R. M. *Nature* **331**, 655-656 (1988).
29. Anderson, R. M. & Johnson, A. M. in *AIDS and Sex: An Integrated Biomedical and Behavioural Approach* (Kinsey Institute, in the press).
30. Blythe, S. P. & Anderson, R. M. *IMA J. Math. appl. Med. Biol.* **5**, 1-19 (1988).
31. Johnson, A. M. *J. Roy. Stat. Soc. Ser. C.* (in the press).
32. Peterman, T. A. *et al. J. Am. med. Ass.* **259**, 55-58 (1988).
33. Padian, N. *et al. J. Am. med. Ass.* **258**, 788-790 (1987).
34. Redfield, R. R. *et al.* III Int. Conf. on AIDS, Washington (1987).
35. Steigbigel, N. H. *et al.* III Int. Conf. on AIDS, Washington (1987).
36. Fischl, M. A. *et al. J. Am. med. Ass.* **257**, 640-644 (1987).
37. Taelman, H. *et al.* III Int. Conf. on AIDS, Washington (Abstr.) (1987).
38. Miller, E. J. *et al.* III Int. Conf. on AIDS, Washington (Abstr.) (1987).
39. Jones, P. *et al. Br. med. J.* **229**, 695-699 (1985).
40. Allain, J. P. *New Engl. J. Med.* **315**, 517 (1986).
41. Kreiss, J. K. *et al. Ann. intern. Med.* **102**, 623-626 (1985).
42. Winklestein, W., Wiley, J. A. & Padian, N. *J. Am. med. Ass.* **255**, 901-902 (1986).
43. Jason, J. M. *et al. J. Am. med. Ass.* **255**, 212-215 (1986).
44. Peterman, T. A. & Curran, J. W. *J. Am. med. Ass.* **256**, 2222-2226 (1986).
45. Saltzman, B. R. *et al.* II Int. Conf. on AIDS, Paris (Abstr.) (1986).
46. Sewankambo, N. K. *et al. AIDS* **1**, 113-116 (1987).
47. Bikerfield, G. *et al. Scan. J. infect. Dis.* **18**, 497-500 (1986).
48. Weller, I. V. D. *et al. J. med. Virol.* **22**, 91-98 (1987).
49. Grant, R. M. *et al. J. infec. Dis.* **156**, 189-193 (1987).
50. Johnson, A. M. *et al. Lancet* (in the press).
51. *AIDS Advertising Campaign. Report on Four Surveys During the First Year of Advertising 1986-87* (British Market Research Bureau, London, 1987).
52. Centres for Disease Control *A Review of Current Knowledge and Plans for Expansion of HIV Surveillance Activities* (30 November, 1987).
53. Quinn, T. C. *et al. N. Engl. J. Med.* **318**, 197-203 (1988).
54. Albert, J. *et al. AIDS* **2**, 107-111 (1988).
55. Blythe, S. P. & Anderson, R. M. *IMA J. Math. Med. Biol.* (in the press).
56. Greenblatt, R. M. *et al. AIDS* **2**, 47-50 (1988).
57. France, A. J. *et al. Br. med. J.* **296**, 526-529 (1988).
58. Evans, B. A. *et al. Br. med. J.* **296**, 473-475 (1988).
59. Srinwasan, A. *et al. Blood* **69**, 1766-1770 (1987).
60. Cheng-Mayer, C. *et al. Science* **240**, 80-82 (1988).

Mysteries of HIV: challenges for therapy and prevention

Jay A. Levy

Department of Medicine and Cancer Research Institute, University of California School of Medicine, San Francisco, California 94143-0128, USA

A number of problems still surround infection by the human immunodeficiency virus and the pathogenesis of AIDS. Solutions to the problems would provide valuable information for the development of antiviral therapy and a vaccine.

DESPITE substantial progress in our understanding of the human immunodeficiency virus (HIV), a number of mysteries remain concerning the virus, its target cells and the responses of the infected host. If a rational approach to treatment and therapy of AIDS is to be successful, solutions to the mysteries must be found. From my perspective, the four major questions are: what are the viral and cellular determinants of infection, what mechanisms generate the different HIV strains, how does HIV cause disease, and what determines the course from infection to disease?

What governs viral tropism?

Recognition that the CD4 antigen on the surface of human helper T lymphocytes is a major cellular receptor for the HIV envelope protein gp120[1] led to the inference that endocytosis of the virus by cells expressing the CD4 molecule is an initial step in infection. But although mouse cells expressing human CD4 (as a result of experimental transfection) can bind HIV to the cell surface, they do not produce virus[2]. Moreover, HIV can infect cells lacking CD4, such as brain astrocyte cell lines[3] and human fibroblasts[4], and the virus is detected in endothelial[5] and epithelial[6] cells of seropositive individuals. Together, these observations strongly suggest that there are also mechanisms that do not involve CD4 by which HIV initially interacts with some cells.

Fusion of the target cell membrane with the HIV transmembrane envelope protein gp41 is one possible alternative means of virus entry. It may operate alone or in concert with gp120. In support of a fusion process, infection by HIV appears to be *p*H-independent[7]. Moreover, part of the sequence of gp41 is similar to a sequence coding for the fusogenic glycoproteins of paramyxoviruses[8], and antibodies to the gp41 protein neutralize HIV[9]. In addition, antibody-dependent enhancement of virus infection can mediate HIV infection of cells[10]. As previously described for dengue and other viruses[11], virus-antibody complexes permit HIV infection of macrophages and T cells, most likely via the complement and/or Fc receptor.

These findings should prompt re-evaluation of the likelihood that soluble CD4 will be of major value in the prevention of HIV infection of cells and encourage the further search for methods to control the first steps in virus infection. It could be worth directing attention to the second conserved region of the viral gp120, which is not involved in CD4 attachment but is essential for early stages of infection[12].

The establishment of HIV infection requires several processes that are influenced by both viral and cellular factors. Strain variations in specific viral genes may, for example, account for the fact that, compared with blood isolates of HIV, isolates from the central nervous system replicate better in macrophages—the main HIV-expressing cell type of the brain[5]—than in T lymphocytes[13]. The properties of brain isolates may be reflected in the clinical observation of some infected individuals who have neurological defects without signs of immune deficiency[14]. Strain variations in specific viral genes such as the heterogenous *orf-B* region (see below) may also account for the lack of replication of some HIV isolates despite their efficient attachment to human $CD4^+$ T cells[15].

In other studies, cellular factors appear to determine virus replication. For instance, a single HIV isolate displays different levels of productive infection in peripheral blood mononuclear cells from various individuals[15]. Cultured mouse cells, in contrast to human cells, do not produce a substantial number of virus progeny after transfection with a biologically active DNA clone of HIV[16]. Cellular factors, such as the NF-κB protein, have been shown to interact with regulatory regions of HIV and enhance virus replication[17].

Defining the viral and cellular genes governing the host-range specificity of HIV is a major avenue of study. Experiments using

recombinant HIVs, in which portions of macrophage-tropic and lymphocyte-tropic strains are combined, or using site-directed mutagenesis of biologically active DNA clones of these viruses should help clarify the viral genes involved. Assays of proteins found in selected cells or the use of somatic cell hybrids (mouse-human, for example) could uncover cellular factors influencing viral tropism. Clearly, the wide host range of HIV and the factors affecting virus replication are important variables to be defined for therapeutic strategies against viral infection of all cell types.

What causes HIV heterogeneity?

Biological heterogeneity of HIV is reflected by differences in host range, replicative properties and cytopathic effects in infected cells[18]. Restriction enzyme[19] and sequence analyses[20] of HIV isolates, as well as the patterns of neutralization of different isolates by antibodies,[21] also demonstrate genetic diversity, particularly in the envelope glycoprotein. (This is true not only of HIV-1 but also of the more recently identified HIV-2 subtype[22]). The mechanism responsible for generating these varying strains of virions is puzzling. One theoretical possibility is that the unintegrated proviral copies of HIV that accumulate during acute replicative infection[23] can undergo efficient genomic recombination leading to the evolution of infectious variants. The lack of genetic changes in HIV during long-term passage of the integrated virus in persistently infected cells[24] is consistent with this hypothesis.

Three explanations may account for the occurrence of envelope variants. First, the immunological reaction of the host selects specific spontaneous mutants which differ in their external envelope region. Thus far, this mechanism has only been observed with certain animal lentiviruses[25]. Second, mutations in the envelope, in contrast to other structural genes, can be tolerated during HIV replication. Third—and most speculatively—the HIV reverse transcriptase may be most error-prone when dealing with sequences for glycosylated proteins.

What determines pathogenesis?

An understanding of how HIV causes disease is a major research objective. As with any infectious agent, both viral and host determinants are involved.

Neuropathy. The disease in the central nervous system has been attributed by some investigators to the production by infected macrophages of cytokines that affect normal brain function[5,26]. HIV-infected brain capillary endothelial cells could compromise the maintenance of the blood–brain barrier, so permitting entry of toxic materials from the blood[5,26]. HIV also infects oligodendrocytes and astrocytes[3,5,14]. Compared with brain macrophages, only a small number of these glial cells produce viral RNA[4,5] but persistent or low replication of HIV in glial cells might affect their function. Since astrocytes maintain the integrity of the blood–brain barrier[27] and oligodendrocytes produce myelin, which is required for nerve conduction, the participation of these infected cells in AIDS neuropathy should be further evaluated. Finally, whether the neurologic disease results from long-term effects of HIV infection or specific pathogenic properties of a neurotropic strain[13,14] remains to be elucidated.

Enteropathy. HIV infection of enterochromaffin cells in the intestinal mucosa[6], perhaps by a process similar to that in the brain, could explain the chronic diarrhoea and malabsorption (particularly with duodenal involvement) observed in AIDS patients in the absence of any known bowel pathogens. These neuroendocrine cells migrate during embryogenesis from the neural crest and help regulate motility and digestive functions of the intestine. How their infection specifically accounts for the pathology is not known and the possible toxic effects of cytokines secreted by infected macrophages in the lamina propria needs to be considered.

Immunopathology. How HIV causes immune suppression presents the greatest enigma. The immune dysfunctions identified in HIV infection were first linked to the cytopathic effects of HIV on helper T lymphocytes that play a vital role in regulating immune function. These cells infected with HIV *in vitro* undergo syncytial formation by recruiting many uninfected cells before proceeding to cell death[1].

Table 1 Immune function abnormalities in AIDS

T lymphocytes
(1) Decreased proliferative responses to mitogens, soluble antigens, and allogeneic cells.
(2) Decreased lymphokine production (IL-2, gamma interferon) in response to antigen.
(3) Decreased cytotoxic T lymphocyte activity against virus-infected cells.

B lymphocytes
(1) Polyclonal activation with hypergammaglobulinaemia and spontaneous plaque forming cells.
(2) Decreased humoral response to immunization.
(3) Production of autoantibodies.

Monocytes
(1) Decreased chemotaxis.
(2) Decreased IL-1 production (or production of an inhibitor of IL-1).
(3) Decreased microbiocidal activity.

NK cells
(1) Decreased cytotoxic activity.

These abnormalities appear to begin with acute depletion of T helper cells and proliferation of B cells; other defects, many revealed by *in vitro* studies, accumulate over time. Several of the immune abnormalities may result from the decrease in $CD4^+$ lymphocytes and cytokine production[32].

Several observations, however, have challenged this suggested explanation for HIV-induced immunopathology. First, despite extensive histopathological studies of infected individuals, little evidence exists for syncytial cell formation *in vivo*[28]. Second, the number of HIV-infected cells in the blood (10^2–10^3 per ml)[29] does not account for the quantity of cells lost over time in the infected host; moreover, $CD4^+$ cells infected by HIV can survive several weeks in culture[30]. Third, many HIV isolates obtained from immunologically suppressed individuals are not highly cytopathic *in vitro*[18,31] and non-cytopathic isolates of HIV have sometimes been associated with disease[22]. Finally, abnormalities of immune function are observed not only in HIV-infected helper T cells and macrophages but also in uninfected cells of the haematopoietic system (Table 1)[32].

What other mechanisms could explain the immunological features of HIV pathogenesis (Table 2)? HIV infection is known to cause epiphenomena including decreased expression of immunological recognition sites, such as CD4 and the interleukin-2 (IL-2) receptor, and reduced production of cytokines such as IL-1, IL-2, and gamma interferon (Table 2)[32]. Loss of these molecules could have far reaching effects on other cells of the immune system. Moreover, HIV infection of progenitor cells could reduce the replenishment of circulating lymphocytes and macrophages. The disarray in immune function could generate T suppressor cells or factors[33] that further compromise the immune response. HIV envelope proteins have been found to be toxic or inhibitory to immune cells[34]. By circulating in the blood, these proteins may block the ability of lymphocytes to recognize or respond to foreign antigens and may interfere with the function of antigen-presenting cells.

In addition, HIV is associated, often early in the infection, with a polyclonal activation of B cells resulting in hypergammaglobulinaemia[32]. Some of these antibodies form immune complexes that can be detrimental to the immune system; some react with self-proteins, leading to autoimmunity[35]. The destruction of activated helper T cells by lymphocytotoxic autoantibodies directed against a normal cellular protein (p18) has been suggested as one mechanism for the substantial loss of $CD4^+$ cells in advanced disease[35]. Antibodies and/or cytotoxic cells directed

against other shared antigens on immune cells can induce further abnormalities in immune function or haematopoiesis[36,37]. Finally, antibody-dependent cellular cytotoxicity reacting against envelope proteins bound to ligands on uninfected $CD4^+$ cells could be a factor in the pathogenic process[38]. Clearly, multiple effects of HIV infection on the immune system, both direct and indirect, need to be fully evaluated to appreciate their potential role in the immunological abnormalities observed.

Cytopathology. A critical question surrounding HIV pathogenesis is how the virus kills the cell. In general, helper T lymphocytes are most susceptible to the cytopathic effects of HIV; in culture, they often undergo fusion before cell death. Macrophage killing by some strains of the virus has also been observed[1]. Syncytial formation by T cells, however, does not always preceed cell death; infected cells can die without undergoing fusion[39]. The viral envelope gp120, alone or through its interaction with CD4, could be responsible for cell death[34,40,43]. Direct inoculation of inactivated virus or the envelope gp120 onto peripheral blood mononuclear cells can also produce cytopathic effects[34,41]. Cell death may result from direct membrane disruption involving calcium channels[42] and/or phospholipid synthesis[43]. The accumulation of unintegrated proviral copies of HIV DNA is an attractive explanation for cytopathology since it is associated with cell death in other retrovirus systems[44]. Finally, whether the cytopathology of HIV in cell culture mirrors pathogenesis in the host awaits development of an appropriate animal model.

What influences progression to disease?

Long-term follow-up studies of HIV seropositive individuals indicate that about a third will remain free of symptoms for at least seven years[45]. Moreover, some healthy seropositive individuals lose a large proportion of their $CD4^+$ lymphocytes, yet do not develop symptoms[46]. Several AIDS patients (many with Kaposi's sarcoma) have remained clinically stable for up to six years. Two patients followed at our medical center have had only 5% of their normal $CD4^+$ cell number for over a year without any new symptoms. Thus, predictions on the development of opportunistic infections or cancers based solely on a decrease in $CD4^+$ cells could be misleading; other presently unrecognized functions of the immune system may be fundamental in warding off disease.

$CD8^+$ cell activity. What determines the resistant state? Cytotoxic T lymphocytes that react with cells expressing HIV proteins[47,48] have been noted in infected individuals, but the clinical importance of this antiviral response is unknown. In our laboratory, studies of asymptomatic individuals have revealed that their peripheral blood mononuclear cells do not readily release HIV when placed in culture. Nearly all, however, yield virus when a subset of their $CD8^+$ lymphocytes is removed from the blood sample[49]. Similar observations have recently been made with the primate immune deficiency virus[50]. These $CD8^+$ cells apparently prevent HIV replication not by killing infected cells, but by producing a diffusible suppressor factor or factors. Among seropositive individuals, the level of this $CD8^+$ cell activity varies, and can be reflected in clinical status. Peripheral blood mononuclear cells cultured from many patients with disease readily produce virus and their $CD8^+$ cells show very little antiviral activity.

This variation in HIV replication in cultured cells probably mirrors the increase of viral p25 antigen in the plasma of individuals as they advance in disease[51]. Whether this observation reflects enhanced virus production or a decrease in antibodies to p25 is still not clear. Nevertheless, the information does suggest that the resistant state in infected individuals is mediated by cellular immune responses operating soon after infection; once these are reduced, renewed production of HIV can occur. The resumption of HIV replication could enhance progression to disease because of the emergence, by mutation or selection, of new HIV variants that replicate rapidly to high titre in a variety of cell types, and that are highly cytopathic[18]. This observation correlates clinically with the increased loss of $CD4^+$ cells[46] and the high levels of p25 antigenaemia[51] associated with development of disease. Nevertheless, whether the progression to disease results first from a reduced immune response or from the eventual emergence of a more pathogenic HIV strain, or from both, needs to be clarified.

Taken together, the data suggest steps in HIV infection that might explain variations in the course of the disease (Fig. 1). Levels of antiviral immune response, the inherent sensitivity of the host cell to virus replication and the relative virulence of the virus strain are major variables to be defined. What ends the resistant state (that is, triggers progression to disease) is not known, but could be a variety of factors including antilymphocyte antibodies, enhanced production of virus by activating events, progressive destruction of $CD4^+$ lymphocytes by inter-

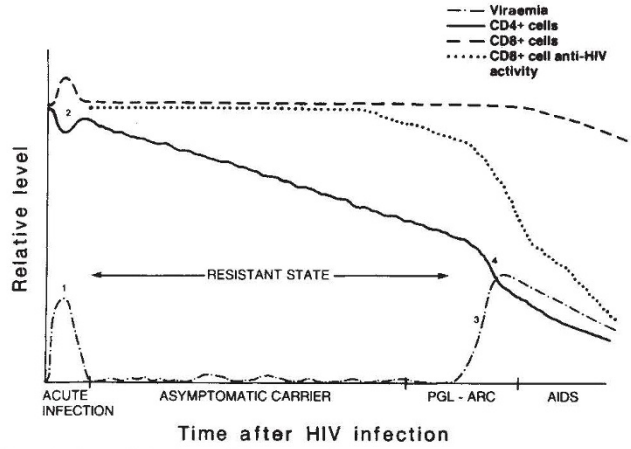

Fig. 1 A model of possible stages in the course of HIV infection. (1) Acute infection is characterized by the presence of free-virus (or its antigen) in the blood in the absence of antibodies to HIV. (2) A $CD8^+$ cells increase rapidly with a concomitant decrease in $CD4^+$ cells; thus the helper/suppressor ratio is dramatically reduced. After a short period (2–12 weeks) a resistant state develops in which $CD8^+$ cells return to above normal levels, $CD4^+$ cells decrease at a slow rate, and free virus is not readily detected in the blood, probably because it is produced episodically. Subsequently, after a variable time lag, the resistant state wanes for reasons that are not known. (3) The virus enters multiple replicative cycles during which a variant strain that can be resistant to the immune response and highly cytopathic can emerge and further compromise the antiviral state. (4) Viraemia is accompanied by enhanced destruction of $CD4^+$ cells and progression of disease.

Table 2 Mechanisms of immune suppression by HIV infection

Direct mechanisms
(1) HIV cytocidal effect on $CD4^+$ lymphocytes.
(2) Functional defects in infected $CD4^+$ cells:
  (*a*) decreased expression of cell surface proteins (for example, IL-2 receptor, CD4);
  (*b*) impaired production of lymphokines such as IL-2 or gamma interferon.
(3) Impaired antigen presentation and/or monokine production by infected macrophages; cell death.

Indirect mechanisms
(1) Generation of suppressor T cells and/or factors.
(2) Toxic or inhibitory effects of viral protein
(3) Immune complex formation.
(4) Induction of autoimmune phenomena:
  (*a*) autoantibodies resulting from polyclonal B cell activation or antigen mimicry;
  (*b*) virus mediated, enhanced immunogenicity of normal cellular proteins.
(5) Cytotoxic cell activity against viral or self proteins.

mittent periods of HIV replication and a decreased production by $CD4^+$ lymphocytes of cytokines required for the growth and function of antiviral $CD8^+$ cells.

Cofactors in pathogenesis. A major unresolved issue is whether other infectious agents can affect this asymptomatic period. Concomitant viral or parasitic infections may activate immune cells so they produce more virus, or become more sensitive to HIV infection[1]. Such events might lead to the suggested intermittent periods of HIV production. As demonstrated *in vitro*, agents such as the herpes viruses may act on the regulatory regions of HIV to enhance virus replication within the cell[52]. Continued surveillance of individuals with long asymptomatic periods, as well as studies of infected chimpanzees that have not yet shown any clinical abnormalities, should provide insight into factors influencing resistance to HIV.

Latency. A long incubation period might also be explained by a latent infection. During the latent period of retrovirus infection very little viral protein or RNA is made and no infectious progeny are produced by the infected cell[53]. When cells that have been latently infected with HIV in culture are treated with activating agents, such as halogenated pyrimidines and cytokines, virus replication begins and is then either maintained or reverts to latency[14,54].

Studies of the *orf-B* (or *3' orf*) gene of HIV suggest it could be responsible for latency. Deletion of *orf-B* leads to a 5–10 fold increase in virus replication compared with the wild-type virus[55]. Conceivably, the *orf-B* gene product (p27 protein), which has GTPase and phosphorylating properties[56], interacts with cellular factors to down-regulate virus replication (see above) in a continuum that can proceed to latency.

In rare cases, individuals who have been HIV seropositive become seronegative. In some of these individuals the presence of a latent HIV infection in peripheral mononuclear cells can be detected by means of the polymerase chain reaction; in others no HIV can be detected[57]. This potentially encouraging observation suggests that HIV infection in some individuals might be eliminated completely, but most likely the virus remains latent at other sites. Defining the factors governing latency should provide valuable information for the development of antiviral strategies. Moreover, the importance of latency to viral transmission must be assessed in 'false negative' serological states.

Conclusions

Answers to many questions about the viral and host determinants of HIV pathogenesis could assist the prospects for therapy and prevention of AIDS. On current information, there are several features of HIV that need to be taken into account (Table 3).

Table 3 Features of HIV of relevance to antiviral therapy

(1) Virus infection involves integration of the viral genome into the chromosome of the infected cell. This cell is a protective environment for the virus and a reservoir for persistent virus production.
(2) The infected cell is a major source of virus transmission and can pass HIV by cell-to-cell contact.
(3) The infected cells can remain "latent" and express very few viral antigens. Can these cells be recognized and eliminated by an antiviral response?
(4) HIV transmission occurs at specific sites in the host (such as the rectum). Prevention requires immune response at these local sites.
(5) Several independent serotypes and subtypes of HIV can be identified. Can they all be controlled by one strategy?
(6) Portions of HIV proteins resemble normal cellular proteins. Immunization may induce autoantibodies.
(7) Vaccination may induce antibodies that enhance HIV infection.

We should target antiviral drug strategies at the vulnerable sites of HIV replication, both before and after integration. In this regard, understanding how an HIV strain evolves into a more cytopathic (and potentially pathogenic) agent[18] would be valuable. We must find methods for inducing strong intracellular and cellular host responses against the virus: intracellular production of the *orf-B* protein or stimulation of the $CD8^+$ cell population responsible for suppresssing HIV replication might produce long asymptomatic periods. Preventing the formation of antibodies to lymphocytes would be another promising direction. For vaccine development we need novel approaches that will define both specific epitopes of HIV and the appropriate adjuvant to elicit strong cross-reacting immune responses not generally observed in natural infection. Toward this objective, elimination of those epitopes responsible for antibody-dependent enhancement[10] would appear important. The immunized host must respond not only against free virus, but most importantly against productively and latently infected cells that can be major sources of HIV transmission[58]. Concentration on these areas of research should provide valuable information to help in the attack against HIV. In the process, we will learn a great deal more about viruses and the function of the immune system.

Studies conducted by the author were supported by the California State Universitywide Task Force on AIDS, the American Foundation for AIDS Research, and the National Institutes of Health. I would like to thank Drs S. Levy and J. Ziegler as well as Drs C. Cheng-Mayer, L. Evans, J. Homsy, J. Hoxie, J. Leong, M. McGrath and C. Walker for their helpful comments on this article, and C. Beglinger for its preparation.

1. Fauci, A. S. *Science* **239,** 617–622 (1988).
2. Maddon, P. J. *et al. Cell* **47,** 333–348 (1986).
3. Cheng-Mayer, C. *et al. Proc. natn. Acad. Sci. U.S.A.* **84,** 3526–3530 (1987).
4. Tateno, M. & Levy, J. A. IV Int. Conf. AIDS, Stockholm (abstr.), (1988).
5. Wiley, C. A. *et al. Proc. natn. Acad. Sci. U.S.A.* **88,** 7089–7093 (1986).
6. Nelson, J. A. *et al. Lancet* **i,** 259–262 (1988).
7. Stein, B. S. *et al. Cell* **49,** 659–668 (1987).
8. Gallaher, W. R. *Cell* **50,** 327–328 (1987).
9. Chanh, T. C. *et al. EMBO J.* **5,** 3065–3071 (1986).
10. Robinson, W. E. *et al. Lancet* **i,** 790–795 (1988).
11. Halstead, S. B. & O'Rourke, E. J. *J. exp. Med.* **146,** 201–217 (1977).
12. Ho, D. D. *et al. Science* **239,** 1021–1023 (1988).
13. Gartner, S *et al. Science* **233,** 215–219 (1986).
14. Levy, J. A. *et al. Ann. Inst. Pasteur* **138,** 101–111 (1987).
15. Evans, L. A. *et al. J. Immun.* **138,** 3415–3418 (1987).
16. Levy J. A. *et al. Science* **232,** 998–1001 (1986).
17. Nabel, G & Baltimore, D. *Nature* **326,** 711–713 (1987).
18. Cheng-Mayer, C. *et al. Science* **240,** 80–82 (1988).
19. Hahn, B. H. *et al. Science* **232,** 1548–1553 (1986).
20. Starcich, B. R. *et al. Cell* **45,** 637–648 (1986).
21. Weiss, R. A. *et al. Nature* **324,** 572–575 (1986).
22. Evans, L. A. *et al. Science* **240,** 1522–1525 (1988).
23. Luciw, P. A. *et al. Nature* **312,** 760–763 (1984).
24. Robert-Guroff, M. *et al. J. Immun.* **137,** 3306–3309 (1986).
25. Carpenter, S. *et al. J. Virol.* **61,** 3783–3789 (1987).
26. Price, R. W. *et al. Science* **239,** 586–592 (1988).
27. Fontana, A. *et al. Nature* **307,** 273–276 (1984).
28. Cohen, M. B. & Beckstead, J. in *AIDS: Pathogenesis and Treatment* (ed. Levy, J. A.) (Dekker, New York, in the press).
29. Harper, M. E. *et al. Proc. natn. Acad. Sci. U.S.A.* **83,** 772–776 (1986).
30. Hoxie, J. A. *et al. Science* **229,** 1400–1402 (1985).
31. Asjo, B *et al. Lancet* **2,** 660–662 (1986).
32. Koenig, S. & Fauci, A. S. in *AIDS: Etiology, Diagnosis, Treatment and Prevention*, 2nd edn. (eds DeVita, V., Hellman, S. & Rosenberg, S.) (Lippincott, Philadelphia, in the press).
33. Laurence, J. *et al. J. clin. Invest.* **72,** 2072–2081 (1983).
34. Shalaby, M. R. *et al. Cell Immun.* **110,** 140–148 (1987).
35. Stricker, R. B. *et al. Nature* **327,** 710–713 (1987).
36. Ziegler, J. & Stites, D. P. *Clin. Immunol. Immunopathol.* **41,** 305–313 (1986).
37. Donahue, R. E. *et al. Nature* **326,** 200–203 (1987).
38. Weinhold, K. J. *et al. Lancet* **i,** 902–904 (1988).
39. Somasundaran, M. & Robinson, H. L. *J. Virol.* **61,** 3114–3119 (1987).
40. Hoxie, J. *et al. Science* **234,** 1123–1127 (1986).
41. Rasheed, S *et al. Virology* **154,** 395–400 (1986).
42. Gupta, S. & Vayuvegula, B. *J. clin. Immun.* **7,** 486 (1987).
43. Lynn, W. S. *et al. Virology* **163,** 43–51 (1988).
44. Keshet, E. & Temin, H. M. *J. Virol.* **31,** 376–388 (1979).
45. Rutherford, G. W. & Werdegar, D. in *AIDS: Pathogenesis and Treatment* (ed. Levy, J. A.) (Dekker, New York, in the press).
46. Lang, W. *et al.* Abstr. Int. on Conf. AIDS, Stockholm (abstr.) (1988).
47. Walker, B. *et al. Nature* **328,** 345–348 (1987).
48. Plata, F. *et al. Nature* **328,** 348–351 (1987).
49. Walker, C. M. *et al. Science* **234,** 1563–1566 (1986).
50. Kannagi, M. *et al. J. Immun.* **140,** 2237–2242 (1988)).
51. Lange, J. M. A. *et al. Br. med. J.* **293,** 1459–1462 (1986).
52. Mosca, J. D. *et al. Proc. natn. Acad. Sci. U.S.A.* **84,** 7408–7412 (1987).
53. Rojko, J. L. *et al. Nature* **298,** 385–388 (1982).
54. Folks, T. M. *et al. Science* **231,** 600–602 (1986).
55. Luciw, P. A. *et al. Proc. natn. Acad. Sci. U.S.A.* **84,** 1434–1438 (1987).
56. Guy, B. *et al. Nature* **330,** 266–269 (1987).
57. Farzadegan, H. *et al. Ann. int. Med.* **108,** 785–790 (1988).
58. Levy, J. A. *J. Am. med. Ass.* **259,** 3037–3038 (1988).