Introduction
Studies of HIV infection in the past decade have revealed a great deal about the organisation of our immune system and basic cell biology, as well as about the pathogenesis of HIV disease. The integration of the retroviral genome into that of T-cells results in a major disruption of host-cell gene expression and protein synthesis. HIV results in the destruction and dysfunction of CD4+ T-cells, and many other cells of the immune system. Recent studies have emphasised not only the tremendous scale and rate of viral replication, but also an unexpectedly high rate of destruction and compensatory regeneration of CD4+ T-cells. Some functional abnormalities, including decreased (antigen-specific) T-cell proliferation and cytokine synthesis (such as interferon-γ), appear in the early stages of infection before there has been any significant depletion of CD4+ lymphocytes. Despite the widespread cellular functional defects observed in individuals with HIV disease, the number of viable cells infected with the virus is relatively low. Estimates of the number of peripheral blood mononuclear cells (PBMC) infected with HIV range from 0-1% to 13-5%; most of these cells contain integrated provirus, usually in a latent or defective form. Recent studies have shown that fundamental cell processes such as cell cycle regulation are similarly affected among uninfected cells, resulting in premature programmed cell death, or apoptosis. The precise mechanisms by which the virus affects the survival or function of uninfected cells are at present unclear. In this review, we explore some of the key cellular and molecular mechanisms of the host-virus interaction which ultimately lead to such profound damage to the immune system. While some of these are interlinked and some appear to proceed in parallel, it is not yet possible to state precisely what their relative contribution is. Rather we attempt to outline some of the mechanisms that appear to contribute and weave them into a tentative model.

Perturbations of cytokine profiles
Following HIV infection, abnormalities can be observed in cytokine production and the intracellular mechanisms that lead to cytokine gene expression in lymphocytes. Cytokine-producing T-helper (Th, CD4+) cells can broadly be classified into three groups according to the cytokines they produce on stimulation: Th1 cells, which are responsible for delayed-type hypersensitivity and macrophage activation, produce interferon [IFN]-γ, interleukin [IL]-2, tumour necrosis factor [TNF]-β and IL-12; Th2 cells (associated primarily with humoral responses) which produce IL-4, IL-5, IL-6, IL-10 and IL-13; and intermediate Th0 cells which co-express both Th1 and Th2 cytokines in various combinations. Lymphocytes from HIV-infected subjects who progress to develop AIDS have been found to express predominantly Th2-type cytokines. It has been suggested that Th1-type cells may be protective against disease progression, whereas Th2/Th0 CD4+ T-cell clones tend to support HIV replication. In a recent study, the cytokine secretion pattern was assessed in T-cell clones from HIV-infected individuals before and after seroconversion. There was a decrease in the proportion of Th1 cytokine-secreting clones following seroconversion, while Th2 clones increased. Moreover, antigen-specific CD4+ T-cell clones from HIV-infected individuals have a predominantly Th0 cytokine profile, with a reduced proportion of Th1 cytokine-producing clones, compared with uninfected controls.

The changing cytokine profiles have recently been linked to changes in other cell surface markers and their soluble counterparts. Thus, a Th2 cytokine secretion profile is associated with increased CD30 expression (and the release of CD30 in its soluble form, sCD30, into circulation) and a lack of CD7 expression on CD4+ cells. Rapid progression to AIDS is correlated with higher circulating sCD30 levels. The induction of Th1/Th2 cytokine gene expression requires the interactions of specific DNA-binding factors with the promoter/enhancer regions of cytokine genes. The nuclear factor of activated T-cells (NF-AT) complex, in response to extrinsic signals such as T-cell receptor (TCR) stimulation, binds to the IL-2 gene promoter element to enhance its expression. The NF-AT complex involved in the induction of the Th2-specific IL-4 gene differs from the Th1-specific IL-2 NF-AT complex in lacking a component called activating protein (AP-1). AP-1 is a protein which, following cell activation, moves into the nucleus from cell cytoplasm and binds to a specific gene sequence (present in, for instance, the IL-2 gene promoter and the HIV-1 Long Terminal Repeat (LTR) region), and may therefore lead to increased host gene/HIV-1 expression. Several key enzymes, including protein kinase C (PKC) and the mitogen activated protein (MAP) kinases, involved in the biochemical signalling pathways.
ways responsible for AP-1 induction, are affected by various HIV gene products, in particular gp41 and Nef (see also the section below on "HIV gene products"). Interactions between viral gene products and these signalling proteins may in part explain the HIV-related defects that predominantly affect Th1 cell survival and cytokine synthesis.

The correlation between disease progression and changes in cytokine secretion may be accounted for by considering the specific roles of Th1 cytokines in the immune system. One of the functions of IFN-γ is to prime macrophages for the intracellular killing of organisms such as Toxoplasma gondii which cause infections in AIDS. Th1 (but not Th2) cytokine secretion by lymphocytes from patients co-infected with HIV and *T. gondii*, when challenged ex vivo with *T. gondii*-specific tachyzoite antigens, was shown to be greatly impaired. Decreased secretion of macrophage-activating cytokines, coupled with a reduced capacity of HIV-infected macrophages to phagocytose *T. gondii*, helps to explain the reactivation of such organisms in AIDS. Strategies which restore the balance of Th1/Th2 cytokine synthesis could provide a useful approach to prevent or treat opportunistic infections.

Activation-induced T-cell apoptosis

Apoptosis is a normal regulatory process by which cells self-destruct and may be increased or decreased in specific cells in various disease states. It is characterised by chromatin condensation, fragmentation of genomic DNA and blebbing of the surface membrane. It is involved in the selection process that occurs during the development of lymphocyte precursors in the thymus. In contrast to immature thymocytes, mature T-cells are more resistant to the "suicide signal" induced by T-cell receptor (TCR) triggering. Infection with HIV-1, interaction of CD4 with HIV gp120-antigen-antibody complexes or simply gp120 can lower the threshold for TCR-induced apoptosis. This increased susceptibility to activation-induced cell death will interfere with T-cell functions such as antigen recall and immune surveillance. Memory T-cells, which respond to a lower level of antigen than naive T-cells, are particularly prone to this effect of HIV. For instance, exposure of lymphocytes from HIV-infected asymptomatic individuals to recall antigens results in the deletion of the corresponding specific memory T-cells. This may partly explain the decreased responses to vaccination with tetanus toxoid and influenza in HIV-infected individuals. However, while increased CD4+ lymphocyte apoptosis appears to be an important feature, several studies (and Johnson et al, manuscript in preparation) have shown conflicting results regarding the relationship between the intensity of lymphocyte apoptosis and disease progression.

Recent work points towards a possible interplay between HIV-induced susceptibility to activation-induced apoptosis and other T-cell defects. Th1 cytokines suppress apoptosis in T-cells from HIV-infected individuals. Following in vitro infection with HIV-1 and TCR stimulation, the percentage of apoptosis was 10-fold higher in Th1 T-cell clones than in Th0/Th2 clones. Using T lymphocytes from HIV-seropositive donors at various stages of infection, we have shown an inverse relationship between TCR-induced apoptosis and cellular proliferation in response to TCR/Integrin costimulation (Ng, et al, manuscript submitted). These functional defects are probably linked at the subcellular level and may be related to disruption of expression and/or function of key intracellular enzymes involved in proliferation and cytokine synthesis.

Unlike cell necrosis, programmed cell death may be prevented by modifying the biochemical signals generated by cell activation. Accessory, or antigen-presenting cells such as macrophages and dendritic cells (DC) supply the "regulatory" signal that enhances or prevents T-cell apoptosis through surface adhesion molecules (such as B7, vascular cell adhesion molecule (VCAM), etc.) that interact with corresponding molecules on T-cells (such as CD28, integrins, etc.). Anti-CD28 stimulation prevents apoptosis of lymphocytes derived from HIV-infected individuals as well as prevents HIV-1 infection of CD4+ T-cells. Anti-CD2 stimulation has also been shown to abrogate gp120-induced T-cell apoptosis. Our own data suggest that stimulation via CD29 (the β subunit of β1-integrins) may also provide a "rescue" signal which prevents TCR-induced cell death in lymphocytes from individuals with asymptomatic HIV infection, but not those with AIDS. Failure to deliver an appropriate accessory signal to TCR-activated CD4 + T-cells may constitute a potential mechanism for activation-induced cell death in HIV infection. HIV induces changes in the surface expression of several adhesion/costimulatory molecules on CD4+ T-cells, monocytes and dendritic cells. In addition, the enzyme cascades responsible for conveying the message from adhesion co-receptors, such as CD29, to the cell nucleus are blocked to a variable degree in patient-derived T lymphocytes, depending on disease severity, even if receptor expression is normal. A thorough understanding of these processes may provide potential means for restoring or maintaining a more balanced cytokine profile in HIV-infected patients.

Imbalance between Ca2+-induced and protein kinase C-mediated signals

The intermediate messengers that mediate the suicidal event in CD4+ mature T-cell apoptosis has recently been shown to be Fas (Apol1/CD95). The early biochemical events that cause activated T-cells to undergo apoptosis rather than proliferation, however, remain undetermined. In immature T-cells or thymocytes, an "orphan" signal defined by a sustained increase in intracellular Ca2+ (as is
Effects of HIV gene products on the host immune system

The functions of the major genes and proteins of HIV-1 are summarized in the table. The U region of the HIV-1 LTR (at each end of the viral genome) presents an important site for host-virus interactions at the molecular level and encodes potential binding sites for host transcription factors, such as nuclear factor-kB (NF-kB) and the NF-AT complex (composed of NF-ATp, and AP-1).57 In healthy CD4+ T cells, activation of the TcR and PKC results in increased binding of NF-ATp, AP-1 and NF-kB to their corresponding DNA binding sites and induces IL-2 secretion, which increases lymphocyte proliferation. The interaction of HIV gp120 with CD4, however, abolishes the binding activity of these nuclear factors leading to reduced proliferation and cytokine production.58 59 This is possibly related to the suppression of TcR-induced Ca2+ release and PKC activation by HIV gp120.60 The binding activity of these nuclear factors in uninfected CD4+ lymphocytes may also be impaired indirectly through altered cytokine profiles such as an increase of IL-10.60

Several viral regulatory and accessory genes interact with components of host cell transcriptional machinery. Nef inhibits the induction of NF-kB DNA-binding activity by T-cell mitogens61 as well as TcR-mediated IL-2 gene transcription.62 The recruitment of AP-1 DNA-binding activity in stimulated T-cells is also blocked in the presence of Nef.63 In addition, lymphocytes from healthy uninfected donors that had been pretreated with the HIV-1 Nef gene demonstrated HIV-1 Tat-responsive element (RRE) RNA (initiation and elongation of viral transcripts) in uninfected CD4+ lymphocytes, possibly through a direct effect on a cell cycle-related regulatory enzyme.64

### Genes and proteins of HIV-1 (adapted from Luciw and Shacklett, 1993')

<table>
<thead>
<tr>
<th>Gene</th>
<th>Dispensable for replication</th>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>gag</td>
<td>no</td>
<td>Pp55vax</td>
<td>polyprotein precursor for virion core proteins: matrix protein p17, capsid protein p24, nucleocapsid protein p9, p7</td>
</tr>
<tr>
<td>pol</td>
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</tr>
<tr>
<td>vif</td>
<td>yes</td>
<td>p23</td>
<td>viral infectivity factor</td>
</tr>
<tr>
<td>vpr</td>
<td>yes</td>
<td>p15</td>
<td>viral protein, unknown function</td>
</tr>
<tr>
<td>tat</td>
<td>no</td>
<td>p14</td>
<td>transcriptional activator, binds c-acting Tat-responsive (TAR) RNA (initiation and elongation of viral transcripts)</td>
</tr>
<tr>
<td>rev</td>
<td>no</td>
<td>p19</td>
<td>post-transcriptional transactivator, binds c-acting Rev-responsive element (RRE) (splicing and/or transport and translation of viral mRNA)</td>
</tr>
<tr>
<td>vpu</td>
<td>yes</td>
<td>p16</td>
<td>influences virus release, augments turnover of CD4 antigen, downregulates MHC Class I molecule expression</td>
</tr>
<tr>
<td>env</td>
<td>no</td>
<td>gp160</td>
<td>precursor for envelope glycoprotein, surface subunit gp120/130—receptor binding, transmembrane subunit gp41/32—membrane fusion</td>
</tr>
<tr>
<td>nef</td>
<td>yes</td>
<td>p27</td>
<td>down-regulates viral transcription, downregulates CD4, inhibits T-cell activation</td>
</tr>
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between cell surface molecules of antigen-presenting cells and CD4+ T lymphocytes. In addition, a number of critical defects in antigen-presenting cell function have been identified in HIV infection. Antigen processing/presentation by dendritic cells (DC, the most potent antigen-presenting cells, and essential for primary immune responses) may be affected by HIV and other retroviruses. Human peripheral blood DC are susceptible to HIV infection, and CDC Group II/IV HIV-infected individuals have reduced numbers of DC. The subpopulation of DC with high-intensity HLA class II antigen expression is preferentially depleted in patients with progressive immunodeficiency. In addition, the expression of ICAM-1 on DC has been shown to be decreased following retroviral infection. Functionally, DC from HIV-infected individuals have impaired ability to stimulate uninfected T-cells. Recent data suggest that the depletion and dysfunction of DC may be reversed by antiretroviral treatment with zidovudine. Binding and activation of CD4+ T lymphocytes by HIV-1-exposed mature DC may result in viral transmission and cytopathic effects, and this may be a critical route of cell-to-cell infection in vivo.

Towards the later stages of HIV infection, there is an expansion of a subpopulation of CD8+ T lymphocytes that are CD28-negative, HLA DR-positive and CD25 (IL-2 receptor α-chain)-negative. This subpopulation of CD8+ T-cells has a poor proliferative response to TcR/CD3 stimulation, which may explain the general diminution of cytotoxic T lymphocyte (CTL) responses to other viral antigens (for example of Epstein-Barr virus, cytomegalovirus and influenza). The primary recruitment of T-cells into immune responses has an absolute requirement for dendritic cells. These specialised APC provide the costimulatory signals required for generation of CTL via their surface adhesion molecules, in particular B7-1 (counter receptor for CD28 and CTLA-4 on T-cells) and the intercellular adhesion molecules ICAM-1 and ICAM-3. The latter are counter receptors for leukocyte function antigen (LFA)-1 which is involved in antigen-specific CTL-mediated lysis.

**Destruction of the APC network in lymphoid organs and subsequent impairment of lymphocyte regeneration**

During the asymptomatic stage of HIV disease, active viral gene expression and replication are largely confined to the lymphoid tissues. A large proportion (up to 30% in one report) of CD4+ lymphocytes in the germinal centres of lymph nodes are latently infected during this period of clinical latency. Within the germinal centres, HIV particles are trapped on the surfaces of follicular dendritic cells (FDC) which surround and are intimately associated with lymphocytes as they migrate through lymphoid follicles. The recently discovered ability of FDC to convert neutralised HIV into an infectious form, even in the presence of an excess of neutralising antibodies, makes them the ideal vehicle for viral transmission to CD4+ lymphocytes. The immunological function of FDC is to capture and retain foreign antigens, which eventually bind to and are presented by germinal centre B-cells to stimulate the memory Th cell population. As disease progresses, the lymphoid organs that provide the APC microenvironment necessary for the renewal of antigen-specific Th cells undergo atrophy, which is characterised by the destruction of the FDC network and possibly the release of entrapped HIV particles into the circulation.

**Adhesion and chemokine receptors in HIV infection**

Various adhesion receptors play a pivotal role in lymphocyte activation. The same surface molecules which supply the accessory signal to augment TcR stimulation are also involved in cell-free viral transmission as well as in syncytium formation in HIV infection. Stimulation of β1-integrin in infected T-cells may potentially increase the availability of AP-1 for DNA binding and promote HIV transcription by enhancing c-fos transcription through MAP kinase activation. There are several HIV-induced defects in β1-integrin signalling among patient-derived T lymphocytes that involve the expression and/or function of important enzymes such as PKC, MAP kinases and focal adhesion kinase (FAK), a protein tyrosine kinase. At the cellular level, some of these signalling defects correlate with the loss of T-cell proliferative responses. The interactions between lymphocyte activation, adhesion receptor expression and viral replication in HIV disease may influence viral latency at the postintegration level.

The ability of patient-derived HIV-1 isolates to induce syncytium formation in vitro has been shown in several studies to correlate with clinical progression, a more rapid CD4+ cell decline and increase in cellular viral load in PBMC. The formation of syncytia involves the initial HIV envelope protein-mediated cell membrane fusion between infected and uninfected cells and later events leading to multinucleated giant cell formation which are dependent on the function of adhesion receptors such as LFA-1 and ICAM-1.

Recently, additional receptors for HIV have been identified in CD4+ cells. These include several receptors for the CC family of chemokines/small cytokines (CCR5, receptor for Rantes, macrophage inflammatory protein-1 (MIP)α and MIP-1β; CCR3, receptor for eotaxin, an eosinophil chemotacticant; CCR2b, expressed on monocytes) have been shown to be fusion coreceptors for HIV-1. The type of receptor utilised by the virus differs between isolates and appears to be determined by the characteristic of the viral envelope glycoprotein (syncytium-inducing property). Rantes has been shown in vitro selectively to attract (and costimulate) memory T lymphocytes and K. Bacon, Fourth International Chemokine Symposium.
1995) and inhibit HIV-1 infection by interfering with the virus-cell fusion process.\textsuperscript{113} Besides the chemokine receptors, other cell surface molecules that are involved in HIV gp160-mediated cell fusion include the fusion regulatory protein (FRP)-1 and FRP-2.\textsuperscript{117,118} FRP-2 is probably identical to the α chain of α5 integrins\textsuperscript{119} while FRP-1 (CD98)\textsuperscript{120} possibly induces fusion by activating the integrins. The induction of synctium formation in HIV-infected cultures coincides with CD4+ cell depletion in vitro.\textsuperscript{119} Although experiments conducted on human PBL-SCID mice (immunodeficient strains reconstituted with human lymphoid cells) indicate that the loss of CD4+ T cells does not correlate with the cytopathicity of the infecting virus type,\textsuperscript{120} synctium formation has nevertheless been proposed as an important virus-mediated cytopathic mechanism. Further characterisation of the molecular processes that mediate cell fusion and synctium formation may provide a possible target for therapeutic intervention.

A hypothetical model and its implications for therapy (figure)

The schematic diagram outlines a possible/ hypothetical model that seeks to relate the molecular events involved in antigenic stimulation, viral transactivation, host cell gene expression and cell cycle control as a framework for further analysis. One of the chief obstacles facing the immunological approach to HIV therapy relates to the intricacy of the host-virus relationship. The molecular details of this interaction have been described in the preceding sections and summarised in the figure-legend. The enzymatic activities that occur within a T-cell challenged by foreign antigens are indispensable for eliciting a normal immune response, yet these are the same molecular events which may enhance the susceptibility of T-cells to HIV infection and maintain viral replication.\textsuperscript{120,121} HIV transactivation leads to the translation of several viral proteins which may suppress the function and/or expression of intracellular enzymes that are involved in lymphocyte activation and survival. This process may be followed by a shutdown of the host transcription machinery and cell death by apoptosis. Strategies that are designed to restore the integrity of the immune system should be based on agents which are capable of differentiating between HIV-infected and uninfected cells.

For instance, ex vivo CD28 costimulation of CD4+ T-cells from HIV-infected donors was recently shown to enhance lymphocyte proliferation but not viral replication.\textsuperscript{122} One possible explanation is that CD28 costimulation selectively induces the proliferation of a subset of T-cells that do not support infection. Alternatively, this effect could be explained...
by the CD28-stimulated production of an "endogenous" substance (such as the chemokines) that blocks cell-virus fusion. The problem with the latter explanation in terms of clinical application is, given that some of these substances are produced physiologically in response to a variety of extracellular stimuli (inflammatory ones in particular), a therapeutic strategy that aims to increase their levels may not have additional benefits over what is already achieved physiologically. The effects of these molecules on the expression or function of other cell membrane ligands/lipids which mediate the process of fusion/syncytium formation need to be established. The important message from recent development is that biological substances which are secreted physiologically to modify the immune system may be part of the defence system that deters viral entry into cells. Clearly it is of paramount importance to obtain a better understanding of the mechanisms involved and more importantly, the reason why this defence system fails, in many HIV-exposed individuals, to block virus entry.

Autoimmune reactions in HIV infection

A diverse variety of clinical manifestations of autoimmunity appear quite frequently in individuals with HIV disease.132-134 These phenomena may be attributed to generalised disruption of regulatory T cell circuits and/or specific cases of molecular mimicry (for example, there are regions of amino acid sequence homology between the nef gene product and the MHC DR region,135-137 the p17 gag protein and α1-thymosin,138 gp120 and IgG heavy chain,133,137,138 and p24 and platelet antigens139). Of particular importance to the central theme of this review is that dysfunction and loss of CD4+ cells may be due to specific autoimmune reactions.

The presence of anti-lymphocyte antibodies (ALA) in the sera of HIV-infected individuals has been recognised for over a decade.133,134 However, little information was available regarding the specificity of these antibodies and their clinical significance remained uncertain.

Some subsequent studies have attempted to define the cellular and molecular targets of ALA. Stricker and colleagues140 observed sera from the majority of patients with ARC and AIDS had ALA that bound to an 18 kDa antigen on CD4+ T cells. The anti-18 kDa antibodies reacted with HIV-infected and stimulated CD4+ T cells but not with unstimulated CD4+ cells or stimulated CD8+ cells. In vitro studies with affinity-purified antibodies showed that they would lyse cells bearing the 18 kDa antigen in the presence of complement and would also suppress mitogen-induced proliferation of CD4 (but not CD8) cells. A strong association between the presence of antibodies and the clinical status of the infected individual was found: the autoantibody was virtually absent in HIV-infected, asymptomatic individuals and almost always present in patients with AIDS or ARC. We have determined by n-terminal amino acid analysis that the 18 kDa antigen is histone H2B141 (and manuscript in preparation). Furthermore in longitudinal studies of patients with HIV disease, anti-histone antibodies were shown to correlate well with disease activity and the loss of CD4+ cells.142 It is noteworthy that anti-18 kDa antibodies have also been detected in Rhesus monkeys infected with the simian immunodeficiency virus (SIV) which develop an AIDS-like disease143,144 but not in Sooty mangabeys which do not become sick following infection with the virus. Furthermore, asymptomatic HIV-infected chimpanzees do not have anti-18 kDa antibodies in their sera although they were detected in one animal with profound lymphopenia.145

The origins of the anti-18 kDa antibodies are unknown and their contribution to the pathology of HIV infection remains to be fully elucidated. Nevertheless it is tempting to speculate that they may arise as a result of histones being co-presented to the immune system with HIV, perhaps during the course of apoptosis (see above). Indeed a high incidence of autoantibodies to nuclear proteins, including histones, occurring in HIV-infected individuals has been described.146

The presence of antibody with a similar specificity (reactive with a 22 kDa antigen) in the sera of patients with ARC was described in a separate study147; however, the majority of HIV-infected individuals examined in these investigations had antibodies that reacted with a 73 kDa antigen. Because of the techniques used in this latter study to examine the specificity of the anti-lymphocyte response it is difficult to compare the 22 kDa antigen with the 18 kDa molecule described above.140-142

Molecular mimicry and the gp120-CD4 interaction

For some time it has been thought that molecular mimicry arising from structures associated with the gp120-CD4 interface may potentiate autoimmune responses. Ziegler and Stites148 initially postulated that an autoimmune response could result from antigenic similarities between the CD4-binding receptor site on the gp120 envelope of the virus and HLA class II molecules (HLA DR is the natural ligand for the CD4 molecule, as it interacts in the process of presenting antigen).

The Ziegler-Stites hypothesis has been extended by Hoffmann and colleagues, who consider regulatory T cells bearing internal image idiotypes of class II MHC determinants to be the "center pole" of the immune network.149-152 The pole is supported and stabilised by a "canvas" of anti-self class II cells. These authors note that the immunological network predicts the existence of both cell types and go on to hypothesise that, while most people do not apparently make pathologically significant responses to their own MHC, it may be easier to develop immunity to cells bearing the subtly different internal image of class II. These authors further propose that the anti-lymphocyte responses are further
exacerbated by allogeneic reactions resulting from lymphocytes present in the blood of or in the ejaculates from contact individuals. Responses directed against the foreign class II molecules may also recognise host class II and act in synergy with the anti-gp120/host class II response. The loss of crucial subsets of regulatory T cells may lead to chaos in the immune system as the “center pole” collapses.

To explore this theory they conducted experiments in alloimmune and autoimmune mice.153 Alloimmune animals (mice that had been exposed to cells from another mouse strain) were shown to make antibodies against HIV gp120 and p24 while mice of the autoimmune-prone strains MRL-+/− and MRL-+/+ made antibodies to gp120. None of these animals had been exposed to HIV proteins. Furthermore, anti-anti-MHC antibodies (immunoglobulins bearing structures similar to those of MHC molecules) were detected in both alloimmune sera and MRL mice. The authors claim that the presence of both types of antibodies in alloimmune sera supports the idea of synergy between immune responses to allogeneic cells and HIV antigenic stimuli as postulated; however these results remain to be confirmed by independent investigators.

Conversely, del Guercio and Zanetti124 have suggested that autoimmune reactions leading to anti-lymphocyte antibodies may result from the formation of anti-idiotypic antibodies to the gp120 receptor site. The resulting anti-idiotypic antibodies would have specificity for CD4-bearing cells. This hypothesis has been substantiated in part by the finding of anti-CD4 autoantibodies in HIV-infected patients.154 155 However, the origin of these antibodies may not have been anti-idiotypic: both groups demonstrated that sera containing anti-CD4 activity did not inhibit the binding of Leu3a, a mouse monoclonal antibody which maps very closely to the HIV attachment site on CD4.156 This conclusion is supported by Wilks and colleagues157 who failed to find anti-idiotypic antibodies in the sera of 97 HIV-infected subjects.

It is possible that antibodies arising from molecular mimicry of gp120 or anti-idiotypic control mechanisms may have indirect pathological consequences. For example a study by Karpatkin and Nardi158 noted that autoimmune anti-idiotypic-like antibody (Ab2) directed against anti-HIV-1 gp120 antibody (Ab1) was present in high titre of 21 HIV-infected patients with immune thrombocytopenia. These authors did not perform epitope mapping studies to determine the specificity of these antibodies (therefore they could not necessarily be attributed to originate from images of the gp120-CD4 molecules) but they concluded that they were pathogenic as they were found as Ab1-Ab2 immune complexes associated with platelets and thus involved the destruction of this cell population.

Graft-versus-host (GvH) disease
The hypothesis that HIV could induce a GvH-like syndrome was first proposed by Shearer and colleagues162 163 and indeed similarities in symptoms between HIV disease and GvH reactions have been described.164 165 While this theory has undergone re-evaluation and reintroduction of the gp120/CD4 binding region (CD4+ lymphocyte population. The GvH model has been extended by Hounsell and coworkers who suggest that a region of the carboxy terminus of HIV gp120 resembles structurally a T-cell alloepitope.160 Recognition of gp120 expressed on infected CD4+ cells as an alloepitope may thus induce a GvH reaction; a process that would accelerate as the pool of infected cells expands.

Mimicry associated with MHC molecules outside the gp120-CD4 binding site
Deleterious immune responses resulting from structures on the HIV envelope outside the CD4 attachment site of gp120 may also occur. Golding et al157 166 have described homologous sequence regions of HIV gp41-derived and human MHC class II β1 domain. Affinity purified IgG antibodies from patients' sera exhibited immunosuppressive activity of lymphocyte proliferation to antigen stimulation.168 Similarly, a homology between class II MHC molecules and gp120169 has been noted and reports which describe the presence of anti-class II MHC antibodies and antibody-dependent cellular cytotoxicity (ADCC) reactions which eliminate class II-bearing cells170 171 in patients with AIDS reinforce these suggestions and further suggest a role for autoimmunity in the pathogenesis of the disease. More recently Zagury and colleagues172 using novel software, identified regions of homology between gp120 and sites on both CD4 and HLA (class II β chain) molecules. A synthetic peptide based on the gp120 domain may inhibit the activation of CD4+ lymphocytes as well as induce humoral and cellular responses from HIV-1-infected individuals. The authors proposed that these gp120 segments may contribute to HIV-induced immunosuppression by two mechanisms affecting CD4+HLA interaction during immune cell activation: (i) an autoimmune reaction against CD4 and (ii) direct interference with the CD4-HLA cistimulation signal, thus inducing anergy in the CD4+ cell population. Homology with gp120 (C5 region) has also been found with the αβ peptide-binding domain of the HLA class I molecule.173

Conclusions
The pathogenesis of HIV infection is a dynamic process driven by various mechanisms which may predominate at different points of the virus life cycle. In this paper, rather than giving an extensive review of all the
pathological mechanisms involved, we have focused on a few molecular interactions between HIV and host lymphocytes which may have adverse effects on the survival and/or functioning of the latter. Despite the wide recognition of cellular dysfunction in HIV infection, most of the intracellular signal defects that give rise to changes in lymphocyte production and cell cycle regulation remain to be determined. Furthermore, since only a minority of infected CD4+ lymphocytes actively produce full-length HIV RNA, it may be necessary to study the effects of latent HIV genome on mechanisms of lymphocyte activation. A better understanding of the complex host-virus interplay will be important clinically in identifying appropriate targets for immune-based interventions.

Addendum added in proof

Recently, another receptor for the chemokine family (C-C chemokine receptor 5 also known as LESTR/fusin) which specifically binds to the stromal cell-derived factor-1 (SDF-1, a lymphocyte chemoattractant) was identified as a cofactor for HIV entry (Bleul et al, Nature 1996;382:22–5; Liu et al, Cell 1996;86:367–77).

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Molecular immunopathogenesis of HIV infection


