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Multifactorial Nature of Human Immunodeficiency Virus Disease: Implications for Therapy

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The immunopathogenic mechanisms underlying human immunodeficiency virus (HIV) disease are extremely complex; the disease process is multifactorial with multiple overlapping phases. Viral burden is substantial and viral replication occurs throughout the entire course of HIV infection. Inappropriate immune activation and elevated secretion of certain cytokines compound the pathogenic process. Profound immunosuppression ultimately occurs together with a disruption of the microenvironment of the immune system, which is probably unable to regenerate spontaneously. Thus, therapeutic strategies in HIV disease must not be unidimensional, but rather must be linked to the complex pathogenic components of the disease and must address where feasible each of the recognized pathogenic processes for the possibility of therapeutic intervention.

Over the past several years, researchers, clinicians, and health care providers have gained considerable experience in studying and caring for individuals infected with HIV throughout the often prolonged course of HIV disease and the acquired immunodeficiency syndrome (AIDS). On the basis of this experience, it has become clear that the pathogenic mechanisms underlying HIV infection and disease are not unidimensional, but rather are extremely complex (*1*). Any attempt to design a comprehensive therapeutic strategy for HIV disease must take this fact into account. The mechanisms producing perturbation of the immune system must be fully delineated, and therapies must be directed not only at blocking HIV replication but also, where possible and appropriate, at the selective pathogenic processes that may be only tangentially related to the direct infection of a given target cell. In the present discussion, we will not attempt to review exhaustively the literature dealing with pathogenic mechanisms of HIV disease, but rather we will focus on those recognized pathogenic mechanisms potentially amenable to therapeutic intervention and develop a framework for the design of a comprehensive therapeutic strategy based on an understanding of these mechanisms.

Viral Infection, Burden, and Replication

Initial infection. A few weeks after primary HIV infection, there is a burst of virus replication and high levels of viremia (*2*). This is most readily recognized in those individuals (up to 70%) who manifest an acute symptomatic syndrome associated with primary infection (*3*). It is highly likely that this state of heavy viremia is responsible for the seeding of virus to various organs, including the brain (*4*) and lymphoid tissues (see below). There is a dramatic perturbation in the numbers of peripheral blood mononuclear cell (PBMC) subsets, usually with a substantial decrease in $CD4^+$ T lymphocytes (*2, 3*). Within weeks to months, a humoral and cellular immune response to HIV is detected, and the levels of culturable virus decrease dramatically (*2, 3*). Most PBMC subsets return to normal levels—except the $CD4^+$ T cells, which may rebound somewhat, but which rarely return to pre-infection levels (*3*). Patients then enter a phase of clinical latency, which is characterized by a lack of symptoms, only moderately decreased levels of $CD4^+$ T cells, and low levels or absence of culturable virus in the blood.

Viral burden and replication. Owing to the relative absence of viral parameters in the PB compartment during the period of clinical latency, it was assumed that clinical latency was synonymous with low viral burden and microbiological latency (Fig. 1) (*1*). Hence, the rationale for aggressive treatment with antiretroviral agents at this phase was felt to be weak. However, in recent studies of HIV-infected individuals at various stages of disease, the use of sensitive molecular techniques combined with careful histopathologic examination (*5, 6*) has indicated that there is a high burden of HIV in the lymphoid tissues both as extracellular virus trapped in the follicular dendritic cell (FDC) network of the germinal centers (Fig. 2A) (*5–7*) and as intracellular virus (Fig. 2B) (*5–7*), usually in a latent form (*6*). Furthermore, HIV is persistently replicating even during the early, asymptomatic phase of disease (*5*). As disease progresses, viral burden and levels of replication increase in the lymphoid tissue, and only later in the course of disease are parameters of active virus replication again readily detectable in the PB (Fig. 1) (*5*).

Peripheral lymph nodes are not the only lymphoid reservoirs for virus burden and replication. The gut is one of the major lymphoid organs in the body, and as many as 50 to 60% of all of the body's lymphocytes are contained in the lymphoid tissue of the gut, which is distributed as Peyer's patches, lamina propria lymphoid cells and aggregates, and intraepithelial lymphocytes (*8*). Infection in the gut-associated lymphoid tissue is similar to that in the peripheral lymph nodes, with trapping of virus on FDC and reservoirs of latent and replicating virus (*9*). In addition, it is possible that other reservoirs for HIV exist in the body

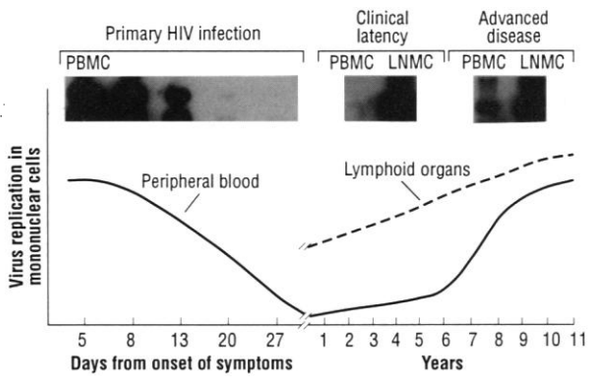

Fig. 1. HIV replication in peripheral blood and lymph node mononuclear cells (PBMC, LNMC) during the various stages of HIV disease. RNA PCR using a gag primer was performed on 200,000 PBMC from different patients during primary HIV infection and on PBMC and LNMC during the periods of clinical latency and advanced disease. A heavy signal was seen in PBMC during the first several weeks after primary infection. The signal was barely detectable in the PBMC after 20 weeks and throughout the period of clinical latency. The signal in LNMC, however, was readily detectable during the period of clinical latency and increased as advanced disease occurred. During advanced disease virus replication was once again readily detectable in PBMC as indicated by the heavy RNA PCR signal.

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and that virus produced in these locations contributes to the accumulation of virus in lymphoid tissue.

Most recently, by means of highly sensitive molecular techniques of quantitative competitive polymerase chain reaction (PCR) on plasma and PCR-driven in situ hybridization on PBMC (*10*), it has become clear that the quantity of virus in the plasma as well as in the PBMC of HIV-infected individuals is much higher than was formerly thought. Taken together, these data indicate that high levels of viral burden are present from the earliest stage of HIV infection and that these levels as well as the degree of virus replication increase as HIV disease progresses. The degree of $CD4^+$ T cell depletion that can be attributed to direct killing of cells by the virus as compared with indirect cytotoxic effects triggered by the virus is at present unclear (see below). However, there is no question that the presence of virus and its active replication is at least associated with $CD4^+$ T cell depletion, and thus HIV is a primary component of the disease process.

Rationale for antiretroviral therapy. The above discussion provides a sound scientific basis for blocking the initial burst of virus replication and dissemination as well as the persistent replication throughout the course of disease by treating HIV-infected individuals with antiretroviral agents from the earliest time that HIV infection is recognized through the entire course of infection. Unfortunately, currently available agents are only partially effective in suppressing virus replication, and this effect is transient (*11*). Clear-cut, but limited, benefit is seen when zidovudine (azidothymidine, AZT) is given to a patient with advanced HIV disease. However, the benefits of early intervention are usually only temporary and do not result in significant long-term advantages with regard to course of disease and death. In the decision-making process of considering whether to start antiretroviral therapy with currently available drugs in an asymptomatic HIV-infected patient, these facts must be balanced against the cost and toxic side effects of treatment in addition to the likelihood of selecting for drug-resistant strains. However, strategies aimed at blocking virus dissemination, decreasing viral burden, and inhibiting virus replication at the earliest possible time after infection are scientifically justified. When safer and more effective antiretroviral drugs become available, they should be used in this context.

Immune Cell Activation in HIV Infection

Chronic activation of the immune system. Activation of the immune system is an essential component of an appropriate immune response to a foreign antigen. Once the immune response adequately deals with and clears the foreign antigen, the system returns to a state of relative quiescence until the next stimulus is introduced (*12*). This is essential for the optimal functioning of the immune response. In HIV infection, however, the immune system is chronically activated. Spontaneous hyperactivation of B cells in AIDS patients has been reported (*13, 14*), as well as persistent activation of multiple components of the immune system. Such components of immune activation include spontaneous lymphocyte proliferation; activation of monocytes; expression of T cell activation antigens on $CD4^+$ and $CD8^+$ T cells; lymph node hyperplasia early in the course of disease; increased cytokine expression, elevated levels of neopterin, β_2-microglobulin, acid-labile interferon, and interleukin-2 receptors; and autoimmune phenomena (*15*). This is particularly true during the early stages of infection when a vigorous immune response to HIV is being mounted. The persistence of virus and viral replication throughout the course of HIV disease (*5, 6*) may play a primary role in the maintenance of this state of immune activation.

In addition, it has been proposed that a superantigen of microbial origin encoded either by HIV or an unrelated microbe might be involved in the pathogenesis of HIV disease (*16*). Since stimulation by superantigens requires binding only to the variable (V) region of the T cell receptor (TCR) β chain in association with binding to the β chain of the major histocompatibility (MHC) class II molecule, superantigens can induce massive stimulation and expansion of all those T cells that bear the specific β chain regions. This is in contrast to conventional antigens, which require interaction with specific components of all regions [V, diversity (D), and joining (J)] of the TCR α and β chains and thus stimulate only a small fraction of T cells (*17*). The finding that HIV-infected individuals manifest massive deletions of a large proportion of V_β families (*18*) has not been confirmed in studies that have reported either no perturbations in the V_β repertoire or selective changes in one or two V_β families (*19*). Therefore, in HIV infection it is likely that superantigens, if indeed they are present and have an impact on pathogenesis, act as potent activators of T cells [producing the negative consequences associated therewith (see below)] rather than as agents directly responsible for the deletion of selective subsets of T cells.

Finally, it has been hypothesized that autoimmune phenomena are initiated and propagated throughout the course of HIV disease and that these contribute substantially to the state of inappropriate hyperactivation. In addition, cross-reactivity between viral proteins and self components such as MHC molecules could trigger immunological responses that eliminate immune competent cells or impede immunological function such as antigen recognition (*15, 20*).

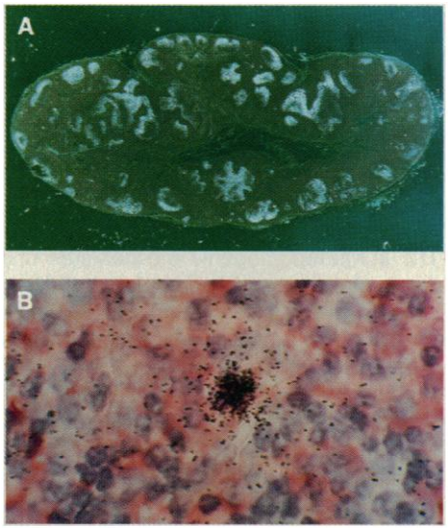

Fig. 2. Viral burden and replication in lymph node of an HIV-infected individual with early stage disease ($CD4^+$ T lymphocyte count >500 per cubic millimeter). (**A**) Cross section of hyperplastic lymph node illustrates well-demarcated germinal centers. In situ hybridization analysis demonstrates large numbers of extracellular virions (white areas) trapped within the follicular dendritic cell network of the germinal centers. (**B**) Individual cell expressing HIV mRNA as demonstrated by in situ hybridization.

Negative consequences of persistent immune system activation. Although the ability to activate the immune system in response to antigenic stimulation is critical for normal immune function (*12*), persistence of immune activation may have a number of negative consequences (*15*). From a virologic standpoint, although quiescent $CD4^+$ T cells can be infected with HIV, reverse transcription, integration, and virus spread is much more efficient in activated cells (*21*). Furthermore, cellular activation induces expression of virus in cells latently infected with HIV (*21, 22*).

From an immunologic standpoint, repeated or persistent exposure of the immune system to an antigen may ultimately lead to immune system dysfunction and loss of the ability to maintain an adequate immune response to the antigen (*15, 23*). Furthermore, the general functional capability of immune competent cells may be impaired if they are maintained in a chronically activated state (*15, 23*). In addition, chronic activation of the immune system may induce an abnormal

program of cell death (apoptosis) as well as the secretion of certain cytokines that can induce HIV expression (see below).

Apoptosis is a form of programmed cell death that may serve as a normal mechanism to eliminate effete cells in organogenesis as well as in the cellular proliferation that occurs in an immune response; it was originally described in the context of the intrathymic elimination of autoreactive T cell clones (*24*) and is closely dependent on cell activation. It has been proposed as a mechanism whereby $CD4^+$ and even $CD8^+$ T cells can be killed in HIV-infected individuals without invoking direct infection of the cell by HIV (*25*). In this model, large numbers of cells, particularly those in the microenvironment of the lymphoid organs where there is close cell-to-cell contact, would be exposed to virus or virus products (particularly gp120) without necessarily becoming infected. On subsequent activation by conventional antigen or a putative superantigen, these cells would undergo apoptosis (*25*).

Rationale for determining the feasibility of inhibiting immune activation. The above discussion indicates that it is reasonable to pursue the feasibility of selectively blocking immune activation without compounding the immunosuppressed state of HIV infection. This approach might be particularly appropriate during the early stages of HIV disease before the stage of profound immunodeficiency.

Cyclosporine A (CsA) is a noncytotoxic immunosuppressive agent that has been used successfully in the prevention and treatment of organ transplantation rejection (*26*). It suppresses T cell activation by blocking the formation of the T cell transcription activating factor NF-AT (*27*). In 1986, CsA was shown to block binding of HIV to its target cells (*28*). In addition, it was shown to inhibit HIV expression and cell growth of chronically infected cells (*29*). There have been conflicting reports of the in vivo effects of CsA in HIV-infected individuals, with some studies showing improvement (*30*) and others clinical deterioration (*31*). The negative consequences of CsA on HIV infection were felt to be due to the compounding of immunosuppression in patients whose immune systems were already substantially compromised. However, a recent review of 53 patients who were infected with HIV either by an infected transplanted organ or by blood transfusions during or shortly after transplantation indicated that the group (n = 13) that did not receive CsA as part of its immunosuppressive regimen had a significantly higher incidence of advancement to AIDS by 66 months than did the group (n = 40) that received CsA (*32*). Because CsA was administered early in the course of infection and was continued throughout the infection, it is conceivable that blocking immune activation before severe immunosuppression had a beneficial effect.

Recent studies indicate that the mechanisms underlying the action of CsA on HIV infection may be more complex than that of merely blocking cellular activation. It has been demonstrated in vitro that CsA interferes with the binding of cellular cyclophilin A and B to HIV gag protein and in this manner might interfere with HIV replication (*33*). Furthermore, nonimmunosuppressive analogs of CsA are now being tested in transplantation patients and may prove to be more appropriate for testing in HIV-infected individuals.

Since the triggering of $CD4^+$ T cells by gp120 alone or complexed with antibody to gp120 may deliver an anergic signal to the cell or prime it for subsequent activation-induced apoptosis, the strategy of blocking the gp120-CD4 interaction might prove beneficial. Whether by the administration of soluble CD4 (*15*) or other therapeutic modalities, the scientific rationale exists for interrupting this interaction. Furthermore, if apoptosis results from a signal that occurs after this initial gp120-$CD4^+$ T cell interaction, strategies should be pursued to block the apoptotic event either by administration of certain cytokines that interfere with apoptosis (*34*) or by pharmacologic means (*35*). Finally, if a putative microbial superantigen contributes to the pathogenic process in vivo, elimination of the superantigen either by antiretroviral therapy (if it is a product of HIV) or by treatment of the relevant non-HIV microbe if and when it is identified should be undertaken.

Cytokines in HIV Infection

Cytokine modulation of HIV expression. Cytokines are peptide hormones that are critical for generating inflammatory responses and maintaining the homeostatic regulation of the immune system (*36*). Infection with HIV is associated with increased production of a number of cytokines in vitro and in vivo (*37*). B cells isolated from HIV-infected individuals spontaneously secrete high amounts of tumor necrosis factor–α (TNF-α) and interleukin-6 (IL-6) in vitro (*38*). These and several other cytokines have been shown in vitro to modulate the expression of HIV in infected cells of both T lymphocytic and monocytic lineages (*39*) (Table 1). Since activated B cells within the germinal centers of lymph nodes of HIV-infected individuals are in close proximity to latently infected $CD4^+$ T cells in the paracortical areas of the nodes as well as to those infected $CD4^+$ T cells that infiltrate the germinal centers (*5, 6*), it is likely that cytokine secretion plays a major role in the activation of HIV expression in the microenvironment of the lymph node.

Table 1. Cytokine regulation of HIV expression and replication. T, T lymphocyte; M, monocyte or macrophage; TGF-β, transforming growth factor–β; M-CSF, monocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor. [Adapted from (*39*) with permission]

Cytokine	Target cell or cells	Effect
Bulk supernatant	T,M	↑
IL-1	T,M	↑
IL-2	T	↑
IL-3	M	↑
IL-4	T,M	↑ ↓
IL-6	M	↑
IL-10	M	↑ ↓
IL-13	M	↓
TNF-α, TNF-β	T,M	↑
TGF-β	T,M	↑ ↓
M-CSF	M	↑
GM-CSF	M	↑
IFN-α, IFN-β	T,M	↓
IFN-γ	M	↑ ↓

TNF-α is of particular interest and potential importance in HIV infection since it also has the property of causing wasting and cachexia in animal models (*40*). It is hypothesized that the wasting syndrome seen in certain HIV-infected patients may be due at least in part to high levels of TNF-α. In addition, TNF-α has been correlated with deleterious effects in other diseases such as tuberculosis, lepromatous leprosy, leishmaniasis, and malaria (*41*).

Rationale for inhibiting cytokine secretion. Attempts to selectively inhibit cytokine secretion or effects (or both) have been made in certain diseases in which cytokines are felt to play a pathogenic role. IL-1 has been shown to be a mediator of endotoxin shock (*42*). Clinical trials have utilized IL-1 receptor antagonist to block the tissue effects of IL-1 with some clinical benefit and very little toxicity (*43*). Soluble TNF-α receptors that block the effects of TNF-α are currently being tested in animal models of endotoxemia as well as in clinical trials in inflammatory conditions such as autoimmune diseases (*44*). Soluble TNF receptors have been shown to inhibit TNF-α–induced HIV-1 transcription and expression in vitro (*45*). Thalidomide selectively inhibits the production of TNF-α in vitro in human PBMCs that have been induced with lipopolysaccharide and other agonists (*46*). Thalidomide also reduces serum levels of TNF-α in lepromatous leprosy patients with erythema nodosum, and this reduction is associated with an amelioration of symptoms (*47*). With regard to HIV infection,

in vitro thalidomide inhibits TNF-α mRNA levels and protein as well as the expression of virus in chronically infected cell lines and in the PBMCs of HIV-infected patients (*48*). Pentoxifylline is an agent that has been used successfully in the treatment of peripheral vascular disease (*49*); it has more recently been demonstrated to block the secretion of TNF-α in cancer patients and in bone marrow transplant patients in whom symptoms were associated with elevated levels of TNF (*50*). Pentoxifylline has also been shown to inhibit the replication of HIV in human PBMCs and in cultured T cells (*51*), and preliminary clinical trials have demonstrated that the administration of pentoxifylline to HIV-infected individuals was safe and was associated with a decrease in TNF-α expression in PBMCs (*52*). Finally, IL-1 receptor antagonist has been shown to block the IL-1–dependent induction of HIV in vitro (*39*). Thus, given the clear-cut demonstration of the role of cytokines in HIV pathogenesis and the apparent lack of serious toxic side effects associated with pharmacologic attempts to selectively block cytokine secretion or action, this approach should be explored vigorously in clinical trials for the treatment of HIV-infected individuals.

Immunodeficiency in HIV Disease

Degrees of immunodeficiency. Varying degrees of immunodeficiency are associated with the different stages of HIV disease. In early stage disease (stages 1 to 3), before the occurrence of profound decreases in numbers of circulating $CD4^+$ T cells, selective defects in antigen-specific T cells are observed (*53*). Over time there is a gradual and progressive decrease in numbers of circulating $CD4^+$ T cells accompanied by severe immune function abnormalities, and in advanced stage disease abnormalities of virtually every component of the immune system have been reported (*1*, *54*). Although depletion of $CD4^+$ T cells is a critical factor in the development of the profound immunodeficiency associated with HIV disease (*1*), a major role in the transition from the phase of immune activation (that is, early stage disease) to the phase of progressive and severe immunodeficiency (intermediate and advanced stage disease) is played by the HIV-mediated destruction of the microenvironment of the lymphoid organs.

Destruction of the microenvironment of lymphoid organs. The immune system is comprised of labile cellular elements capable of freely circulating among or populating a variety of lymphoid organs. In addition, individual lymphoid organs have a sessile component or microenvironment that is necessary for the maturation and propagation of cellular elements. The integrity of the microenvironment is crucial for optimal presentation of antigen as well as for the execution of specific immune functions (*55*). It is well recognized that HIV may be directly or indirectly involved (or both) in the destruction of labile immune competent cells (see above). However, it is also true that certain elements of lymphoid organ architecture and microenvironment are severely disrupted in HIV infection.

Over the prolonged course of HIV disease, the complex FDC network within the germinal centers of lymphoid tissue is gradually and progressively disrupted and ultimately destroyed (*5–7*) (Fig. 3). Since the FDCs serve as the major antigen-presenting cell network for germinal center B cells and are responsible for the initiation of B cell responses and memory, disruption of the microenvironmental network is incompatible with an effective humoral immune response. In addition, the disruption of the lymph node architecture results in an ab-

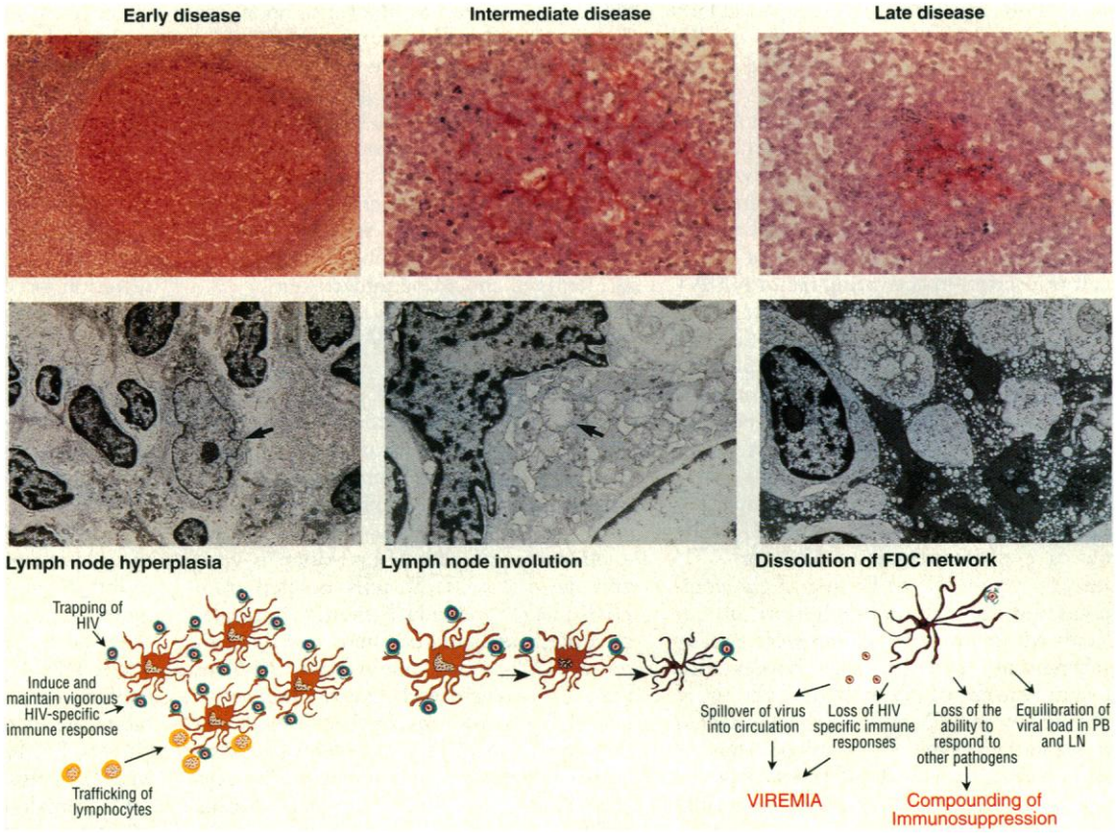

Fig. 3. Lymph node germinal centers during various stages of HIV disease. During early disease an intact follicular dendritic cell (FDC) network (staining pink with a CD21 monoclonal antibody) is seen within the germinal center (upper panel). At this point individual FDCs appear healthy by electron microscopy (arrow, middle panel). During this period HIV particles are trapped by the processes of the FDC and initiate a vigorous humoral immune response by the germinal center B cells. $CD4^+$ T cells migrate into the area and are exposed to virus (lower panel). During intermediate stage disease FDCs begin to degenerate, as indicated by clumping of the fine dendritic network (clumped red staining by antibody to CD21, upper panel) and by swollen organelles on electron microscopy (arrow, middle panel). At this point the efficiency of the FDC in trapping virions is diminished (lower panel). During advanced stage disease the FDC network is virtually destroyed, with minimal staining by antibody to CD21 (upper panel) and necrotic-appearing, amorphous cells by electron microscopy (dark staining material, middle panel). At this point, the destroyed FDCs are incapable of trapping virus, which now is readily detectable in blood. The loss of FDC function contributes to the profound immunosuppression of advanced stage disease (lower panel).

normal distribution of lymphocytes within the lymphoid tissue, and it is likely that the function of accessory cells such as macrophages and interdigitating reticular (dendritic) cells that present antigen to T lymphocytes is profoundly impaired.

The thymus is comprised of a complex microenvironment of thymic epithelial cells that form a stromal network extending from the subcapsular to the cortical to the medullary areas of the gland. At least six different types of thymic epithelial cells populate the thymus; they are rich in cytokines and are critical in the nurturing and maturation of thymocytes (*56*). After the direct injection of HIV into a fully developed human thymus resident in the severe combined immunodeficiency (SCID)–human (hu) mouse model, there is progressive infection and destruction of multiple subsets of thymocytes (*57, 58*), as well as widespread destruction of thymic epithelial cells (*58*). The SCID-hu mouse offers the potential for studying the effect of HIV on the thymic microenvironment; it should serve as an excellent model for HIV infection of the human thymus since the morphologic and histopathologic appearance of the HIV-infected thymus in the SCID-hu mouse is similar to that of thymuses examined at autopsy from simian immunodeficiency virus–infected monkeys (*59*) and from patients with advanced HIV disease (*60*).

In the bone marrow microenvironment, a network of stromal cells of monocytic lineage is vital for optimal sustenance and maturation of stem cells and progenitor cells of myeloid and lymphoid lineage (*61*). There is evidence that in HIV infection bone marrow stromal cells are adversely affected (*62*). In addition, we have demonstrated that in advanced HIV disease, $CD34^+$ progenitor cells within the bone marrow can be infected with HIV (*63*).

Role of lymphoid tissue microenvironment in the regeneration of the immune system. It is unclear at present whether the severely damaged immune systems of patients with advanced HIV disease would be capable of spontaneous regeneration even if virus replication could be completely inhibited by a totally effective antiretroviral agent. In fact, there is suggestive evidence that spontaneous regeneration would not occur under these circumstances. In clinical trials of antiretroviral agents in HIV-infected individuals in which there is at least a temporary inhibition of virus replication, a complete reconstitution of normal levels of $CD4^+$ T cell counts, even transiently, is rarely if ever observed (*11*). This is in contrast to the situations in which immune competent cells are suppressed or destroyed iatrogenically by the administration of immunosuppressive regimens for a variety of diseases. Under those circumstances, complete regeneration of the immune system generally occurs after cessation of immunosuppressive therapy (*64*). Furthermore, it has been demonstrated in the SCID mouse model that collaboration between T and B cells and the factors that these cells produce is essential for the normal development of FDC (*65*). Thus, unless regeneration of a normal balance between T and B cell elements also occurs, spontaneous regeneration of normal FDC development would likely be compromised.

One of the most problematic areas related to the ability of the immune system to spontaneously regenerate in HIV infection concerns the role of the thymus in adults. It is generally, although incorrectly, assumed that the thymus is not necessary in adults. This assumption is based on the observation that individuals who undergo thymectomies for medical reasons generally can lead normal lives with relatively intact immune function. However, patients treated with thymectomy for myasthenia gravis develop a moderate lymphopenia even in the absence of subsequent obvious stresses to the immune system (*66*).

HIV-infected individuals not only have destruction of their thymuses, but also experience a gradual and persistent destruction of mature $CD4^+$ T cells over a period of years (*1*). This would be equivalent to surgically thymectomizing an individual and chronically administering antilymphocytic globulin for a prolonged period of time. In several animal species, adult thymectomy is associated with a gradual decrease over months in circulating lymphocytes (*67*). Relevant to the situation with HIV in humans is the observation that thymectomized, irradiated, bone marrow–reconstituted adult mice do not achieve normal immune function without co-implantation of a fetal thymus (*68*). The thymic microenvironment is apparently critical for complete immunological reconstitution despite the fact that stem cells and precursor cells were supplied by the bone marrow transplant. Similarly, HIV-infected individuals with advanced disease (and perhaps even with early stage disease) are functionally thymectomized (see above). Hence, even if precursor cells are still present in HIV-infected individuals or supplied by bone marrow transplantation, it is questionable whether the reconstitution of normal immune function would occur in the absence of an intact thymic microenvironment. Furthermore, it is unclear at present how the infection of bone marrow stromal cells would contribute to the lack of regenerative capability of the immune system in HIV infection.

Rationale for attempts to reconstitute the immune system. Certain cytokines are capable of inducing the replication of HIV; therefore, selective blocking of cytokines is an important strategy in the treatment of HIV disease (see above). Nonetheless, cytokines are also important for the expression and regulation of normal immune function. In fact, defects in the production of IL-2 and interferon-γ (IFN-γ) have been reported in HIV infection (*69*). Therefore, the administration of cytokines in order to partially reconstitute or stimulate the defective immune system in HIV disease is a reasonable strategy that is being pursued (*70*). Recent reports suggest that there is a progressive imbalance in the T cell limbs of the immune systems of HIV-infected individuals, with a selective defect in TH-1 responses mediated by IL-2 and IFN-γ and a predominance of TH-2 responses mediated by IL-4, IL-5, IL-6, and IL-10 (*71*). The potential exists for correcting this imbalance by the administration of TH-1–type cytokines such as IL-2 or IL-12 (*72*). In this regard, dramatic and sustained (several months) increases in numbers of circulating $CD4^+$ T cells have been noted in a limited number of HIV-infected patients treated with intermittent (5 days every 2 months) doses of IL-2 intravenously (*73*). The mechanisms underlying this enhancement of $CD4^+$ T cell numbers are currently being investigated and may reflect a combination of direct expansion of T cell subsets, correction of the IL-2 defect of HIV disease, as well as the potential beneficial effects of intermittent stimulation of the immune system (see below).

Recent studies have suggested that IL-12, a potent cytokine that enhances T cell and natural killer cell capabilities and that is involved in the differentiation of TH-1 $CD4^+$ T lymphocytes (*74*), might be useful in the treatment of HIV-infected individuals. PBMCs from HIV-infected patients are defective in the production of IL-12, and treatment of these cells with IL-12 in vitro significantly enhanced the cytotoxic capability of the cells (*75*). Finally, a number of chemical immune enhancers have been proposed for the treatment of HIV-infected individuals, with clinical trials generally showing variable results (*70*).

The most direct and potentially most complete form of immunologic reconstitution is the replacement of cellular elements of the immune system. Allogeneic and syngeneic bone marrow transplantation have been attempted in HIV-infected individuals without notable success (*76*). We have performed syngeneic bone marrow transplantation from uninfected to infected identical twins together with the transfusion of syngeneic PB lymphocytes (*77*) and have noted a transient increase in $CD4^+$ T cells. The lack of complete reconstitution could be explained by infection of the

transplanted elements by HIV, inadequacy of marrow take owing to the fact that the recipient was not conditioned, or lack of an intact thymus microenvironment for the maturation of transplanted T cell progenitor cells. Other attempts to reconstitute cellular elements include the transfusion of ex vivo IL-2–expanded, syngeneic $CD4^+$ T cells, HIV-specific $CD8^+$ T cells, and HIV-specific $CD8^+$ T cell clones (*78*). Results are too preliminary for conclusions to be reached concerning the feasibility and long-term benefit of these approaches.

Experience with thymic transplantation in congenital immunodeficiency diseases as well as in AIDS has not been promising, but the extent of experience has been minimal (*79*). The loss of thymic cellular elements and the disruption of the thymic microenvironment in HIV infection provides a compelling argument to aggressively pursue the feasibility of this approach as a component of attempts directed at immunologic reconstitution of HIV-infected individuals. Furthermore, recent studies have suggested the existence of alternative, extrathymic development pathways for T lineage cells, particularly in the gut (*80*). Delineation of the integrity of these pathways in HIV-infected individuals would be important.

Although chronic, intermittent stimulation of the immune system as a therapeutic modality in HIV infection might seem counter-intuitive given that immune activation has potentially negative consequences, the possibility exists that under certain circumstances and in association with the administration of effective antiretroviral agents, intermittent stimulation of the immune system might have a beneficial effect in partially reconstituting immune competence. It is noteworthy that earlier trials with continuous infusions of IL-2 in HIV-infected individuals did not show clear-cut benefit (*72*); however, recent studies with intermittent IL-2 stimulation in which the immune system was allowed to rest for 7 to 8 weeks between 5-day courses of IL-2 resulted in dramatic increases in $CD4^+$ T cells in some patients (*73*). Sensitive measurements of virus activity in plasma by a branched DNA technique revealed transient increases in virus replication associated with each course of IL-2, which usually returned to baseline. This observation underscores the need for the simultaneous administration of antiretroviral agents with this approach. It is unclear why the immune system must rest between courses of stimulation, but this may be related to the requirement for optimal expression of IL-2 receptors. Other approaches at intermittent stimulation of the immune system with materials such as polio vaccine (*81*), typhoid vaccine (*82*), and dinitrochlorobenzene (DNCB) (*83*) have yielded variable results. Finally, the use of killed HIV or its protein components as a therapeutic vaccine is currently in clinical trials, and there have been reports suggesting beneficial effects on $CD4^+$ T cell counts or viral burden (or both) (*84*). However, available data do not allow conclusions to be reached regarding immunologic, virologic, or clinical benefit. Despite the fact that these studies were designed to stimulate HIV-specific immune responses, these products could also nonspecifically stimulate the immune system. Taken together, these studies provide the basis for pursuing cautiously the feasibility of intermittent immune system stimulation, preferably in combination with an antiretroviral agent.

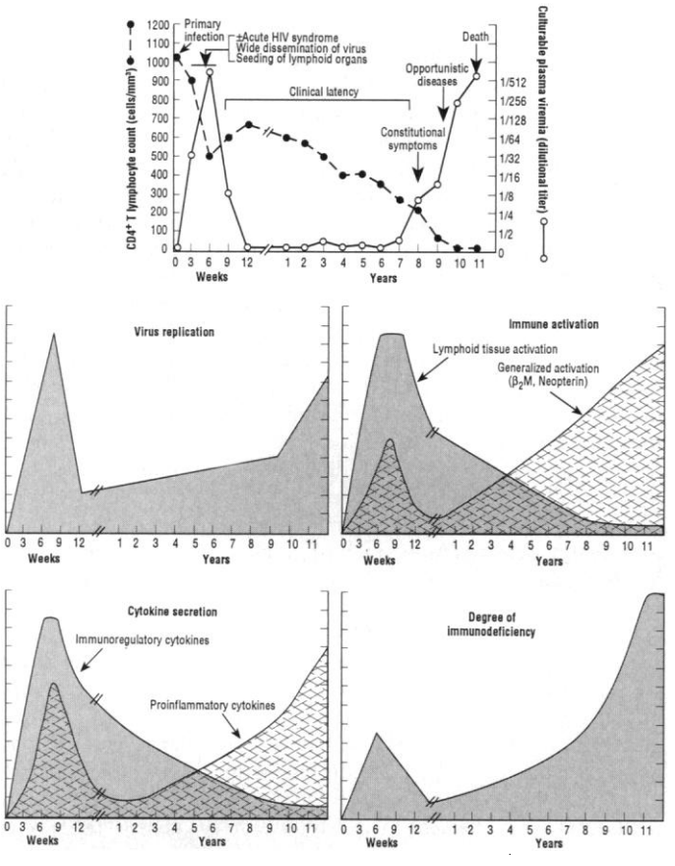

Fig. 4. The multifactorial, multiphasic, and overlapping components of the pathogenic mechanisms of HIV disease. Virus replication occurs throughout the entire course of HIV infection. Immune activation and cytokine secretion are major components of the pathogenic process and are noteworthy for their variability among patients and for the fact that they may occur at different stages of disease. They are prevalent at the time of primary infection, particularly in patients with an acute syndrome. These processes may increase dramatically in certain patients as disease progresses. Immunosuppression progresses throughout the course of disease, resulting in the profound immunosuppression of late stage disease. [Upper panel reproduced from G. Pantaleo *et al.*, in (*1*), with permission.]

Conclusions

Any comprehensive therapeutic strategy must consider the complexities of the pathogenic mechanisms of HIV disease. Suppression of HIV replication is only one of several possible approaches to the therapy of an HIV-infected individual; certain stages of the disease may benefit more than others from an intensive regimen of antiretroviral drugs. The early phase of wide viral dissemination seems particularly amenable to such an approach. Inappropriate and sustained immune activation, cytokine secretion, disruption of the microenvironment of the immune system, and the profound immunodeficiency are all potential targets of therapeutic intervention. Such an approach is particularly problematic, however, since these multifactorial components of HIV pathogenesis occur in phases that may overlap (Fig. 4). Certain types of interventions may be appropriate at one stage of disease and contraindicated at another. This may be particularly relevant with regard to the overlap in certain patients of aberrant cellular activation and profound immunosuppression. Some approaches may be undertaken in temporal sequence, whereas others might be undertaken simultaneously. It is only through the process of carefully conducted clinical trials based on the expanding knowledge of HIV pathogenesis that answers to these important questions will be forthcoming.

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