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Pathogenesis of Human Immunodeficiency Virus Infection

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I. INTRODUCTION

Lentiviruses constitute a separate genus of the *Retroviridae* family, which includes a large number of different viruses infecting a diverse group of animal species (Table 1) (190, 419, 663). The human immunodeficiency virus (HIV), the subject of this review, is a lentivirus that has only recently been recognized because of its association with AIDS. In this review, historical aspects of the lentivirus group and the discovery of HIV will be covered. Features of HIV pathogenesis, including aspects of the virus itself, the cells it infects, and the host immune response to this infection, will be discussed. Finally, potential approaches for therapy and a vaccine for HIV infection are considered.

Ironically, one of the first viruses identified in nature was a lentivirus, the equine infectious anemia virus, discovered in 1904 (1211). It induces episodic autoimmune hemolytic anemia in horses, which has had devastating effects on the equine population in many parts of the world, particularly Japan. This agent, although initially demonstrating some characteristics of a retrovirus (661), was only relatively recently identified as an RNA virus containing reverse transcriptase and a member of the lentivirus genus (150). Similarily, lentiviruses of sheep (visna) and goats (caprine arthritis-encephalitis virus) have been known for many years to be associated with a long illness and clinical symptoms not generally characteristic of retrovirus infection (419, 663). Instead of malignancies, they can cause pathologic entities such as autoimmunity and brain and joint disorders (Table 1).

If, with hindsight, researchers on AIDS had looked for an agent that would cause first an immune disorder in humans and somewhat later neurologic syndromes, certainly a lentivirus would have emerged as a prime candidate. Instead, the search for the cause of AIDS in the early 1980s focused on a variety of viruses, including retroviruses but also parvoviruses and herpesviruses, which are known to cause immune deficiency (859, 1020). Even after HIV was discovered, its classification as a lentivirus took almost a year (172, 385, 676, 966).

It is worth noting, however, that the subsequent dedicated efforts to understand the AIDS virus have led to remarkable progress in our appreciation of its pathogenic counterparts in other animal species. HIV research has provided important contributions to veterinary medicine, including the discovery of the primate (simian immunodeficiency virus [SIV]) and cat (feline immunodeficiency virus) lentiviruses (60, 226, 829, 907). The study of HIV has also encouraged further work on the bovine lentivirus (386) (Table 1). Thus, the lentivirus field is one of limited examples in which work on a human virus has led to a better understanding of viruses in other animal species.

II. DISCOVERY OF THE AIDS VIRUS

The first indication that AIDS could be caused by a retrovirus came in 1983, when Barre-Sinoussi et al. at the Pasteur Institute (50) recovered a reverse transcriptase-containing virus from the lymph node of a man with persistant lymphadenopathy syndrome (LAS). At the time, some physicians suspected that this syndrome was associated with AIDS (3), but there was no conclusive evidence. Since enlarged lymph nodes are observed during several viral infections, many physicians believed initially that LAS resulted from infection with a known human virus such as Epstein-Barr virus (EBV) or cytomegalovirus (CMV). In addition, the characteristics described for the retrovirus recovered by the Pasteur Institute group (50) included some reported for the human T-cell leukemia virus (HTLV) (for a review, see reference 1148). Thus, many investigators de-

TABLE 1. Lentiviruses

Virus	Host	Primary cell type infected	Clinical disorder
Equine infectious anemia virus (EIAV)	Horse	Macrophages	Cyclical infection in the first year: hemolytic anemia and sometimes encephalopathy
Visna virus	Sheep	Macrophages	Encephalopathy
Caprine arthritis-encephalitis virus (CAEV)	Goat	Macrophages	Immune deficiency, encephalopathy
Bovine immune deficiency virus (BIV)	Cow	Macrophages	Lymphadenopathy, lymphocytosis, CNS disease (?)
Feline immunodeficiency virus (FIV)	Cat	T lymphocytes	Immune deficiency
Simian immunodeficiency virus (SIV)	Primate	T lymphocytes	Immune deficiency, encephalopathy
Human immunodeficiency virus (HIV)	Human	T lymphocytes	Immune deficiency, encephalopathy

cided initially that the lymph node isolate was a member of this already recognized human retrovirus group. In support of this conclusion was the concomitant publication of a paper by Gallo et al. (343) in the same issue of *Science* reporting the isolation of HTLV from individuals with AIDS.

HTLV as the etiologic agent of AIDS, however, seemed unlikely because of its close cell association and its known poor replication in culture (793, 931, 1148). Since hemophiliacs with AIDS had been reported (142), how could such a virus be transmitted by cell-free plasma products such as factor VIII? Moreover, HTLV does not lyse lymphocytes; in fact, it often immortalizes them into continuous growth (793). Thus, the characteristic loss of $CD4^+$ lymphocytes in AIDS patients (390, 787, 1122) could not be explained by an HTLV infection.

Further studies in 1983 by Montagnier and coworkers clarified these questions in relation to the LAS agent. The results indicated that this human retrovirus, although similar to HTLV in infecting $CD4^+$ lymphocytes, had quite distinct properties. Their virus, later called lymphadenopathy-associated virus (LAV), grew to substantial titer in $CD4^+$ cells and killed these cellular targets (799) instead of maintaining them in culture as does HTLV. These observations on LAV provided important evidence supporting the potential etiologic role of a retrovirus in AIDS.

Several other laboratories were also searching for the agent responsible for this immune deficiency syndrome, and in early 1984, Gallo and associates reported the characterization of another human retrovirus distinct from HTLV that they called HTLV-III (342, 941, 1041, 1065). It was isolated from the peripheral blood mononuclear cells (PBMC) of adult and pediatric AIDS patients. These workers noted the lymphotropic and cytopathic properties of the virus and reported that HTLV-III cross-reacted with some proteins of HTLV-I and HTLV-II, particularly the core p24 protein (342). Thus, they believed it merited inclusion in the HTLV group, although the newly isolated virus was cytolytic and did not induce an established cell line from infected lymphocytes.

Levy et al. (674) also reported at that time the identification of retroviruses they named the AIDS-associated retroviruses (ARV). These viruses were recovered from AIDS patients from different known risk groups, as well as from other symptomatic and some healthy people. Finding ARV in asymptomatic individuals indicated for the first time a carrier state for the AIDS virus. This retrovirus, ARV, showed some cross-reactivity with the French LAV (BRU) strain when examined by immunofluorescence techniques (674). Moreover, it grew substantially in PBMC, killed $CD4^+$ lymphocytes, and did not immortalize them. Thus, the three newly identified retroviruses had similar characteristics. Most importantly, infection by these viruses, as described in 1984, was not limited to AIDS patients. They were also recovered from individuals with other clinical conditions, including lymphadenopathy. This latter observation supported the conclusion that LAS was part of the disease syndrome.

Within a short period, the three prototype viruses (LAV, HTLV-III, and ARV) were recognized as members of the same group of retroviruses, and their properties identified them as lentivirinae (Table 2). Their proteins were all distinct from those of HTLV; their genomes showed only remote similarities to the genome of this agent, no more than that of chicken retroviruses (966). Thus, the initial cross-reactivity of HTLV-III with HTLV proved incorrect. For all these reasons, in 1986 the International Committee on Taxonomy of Viruses recommended giving the AIDS virus a separate name, the human immunodeficiency virus (HIV) (189).

Most recently, the HTLV-III strain has been confirmed as the same virus as the LAV strain (166, 411). The Pasteur Institute group had sent LAV to the National Institutes of Health, where it appears to have contaminated a culture in the National Institutes of Health laboratory (429). This occurrence explains the unique molecular similarities between HTLV-III and LAV, in contrast to the sequence diversities observed with ARV-2 (now called HIV-1_{SF2}) and other strains (59, 106, 822, 974, 1039, 1239). Ironically, the

TABLE 2. Characteristics common to lentiviruses

Clinical
Association with a disease with a long incubation period
Association with immune suppression
Involvement of hematopoietic system
Involvement of the CNS
Association with arthritis and autoimmunity
Biological
Host species specific
Exogenous and nononcogenic
Cytopathic effect in certain infected cells, e.g., syncytia (multinucleated cells)
Infection of macrophages, usually noncytopathic
Accumulation of unintegrated circular and linear forms of viral cDNA in infected cells
Latent or persistent infection in some infected cells
Morphology of virus particle by electron microscopy: cone-shaped nucleoid
Molecular
Large genome (≥9 kb)
Truncated *gag* gene: several processed *gag* proteins
Highly glycosylated envelope protein
Polymorphism, particularly in the envelope region
Novel central open reading frame in the viral genome that separates the *pol* and *env* regions
Presence of accessory/regulatory genes

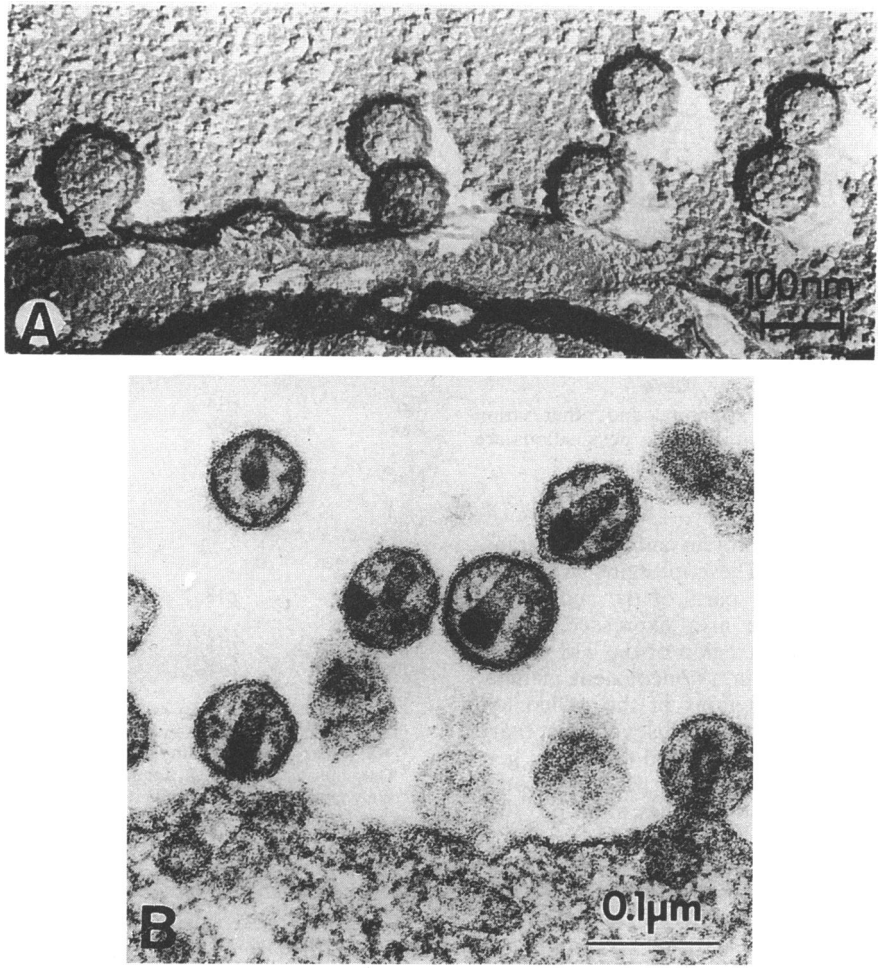


FIG. 1. (A) Scanning electron micrograph of budding particles, most probably HIV, on the surface of a T lymphocyte. This process can incorporate cell membrane proteins onto the surface of the virus (Section XXIV C) and has been considered responsible in part for false-positive reactions in ELISAs (1048). Antibodies to normal T-cell proteins (e.g., HLA, CD4) could show a positive reaction. Photomicrograph courtesy of H. Gelderblom. Reprinted from reference 357 with permission. (B) Transmission electron micrograph of HIV replicating in a T cell. Photomicrograph courtesy of R. Munn.

French agent also was a contaminant in culture. At first considered an isolate from one patient (BRU), its origin was from a different individual (LAI). The LAI strain overgrew the BRU virus in the presumed mixed culture (1240).

HIV isolates were subsequently recovered from the blood of many patients with AIDS, AIDS-related complex, and neurologic syndromes, as well as from the PBMC of several clinically healthy individuals (682, 1033). Thus, the widespread transmission of this agent was appreciated. Soon after the discovery of HIV-1, a separate subtype, HIV-2, was identified in Western Africa (180). Both HIV subtypes can lead to AIDS, although the pathogenic course with HIV-2 might be longer (see Section XIV A).

It is now known that some HIV-1-infected individuals can remain asymptomatic for up to 14 years and still have virus recoverable from their PBMC (691, 1025). Also noteworthy in these long-term survivors is the relative stability of the $CD4^+$ cell numbers, which are not necessarily decreased, as is seen characteristically with HIV-induced disease. The factors that could influence this resistance to progression to AIDS after HIV infection is a major topic of this review.

III. HIV VIRION

A. Structure

By electron microscopy, HIV-1 and HIV-2 have the characteristics of a lentivirus, with a cone-shaped core composed of the viral p25 (or p24) Gag protein (Fig. 1). In this review, this capsid (CA) protein is referred to as p25, as recommended (657). Inside this capsid, or nucleoid, are two identical RNA strands with which the viral RNA-dependent DNA polymerase (Pol, also called the reverse transcriptase [RT]) (p66, p53) and the nucleocapsid (NC) proteins (p9, p6) are closely associated. The inner portion of the viral membrane is surrounded by a myristoylated p17 core (Gag) protein that provides the matrix (MA) for the viral structure and is vital for the integrity of the virion (357, 358) (Fig. 1 and 2). Recent results suggest that MA is required for incorporation of the Env proteins into mature virions (1316).

The viral surface is characteristically made up of 72 knobs containing trimers or tetramers (268, 357, 885, 927, 1263) of the envelope glycoproteins. They are derived from a 160,000 M_r precursor, which is cleaved inside the cell (most probably by cellular enzymes in the Golgi apparatus) into a gp120

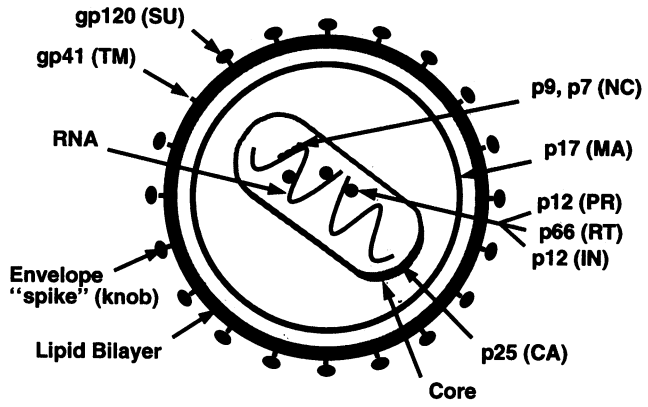


FIG. 2. An HIV virion with the structural and other virion proteins identified. The abbreviated viral protein designations are those recommended (657).

external surface (SU) envelope protein and a gp41 transmembrane (TM) protein (752). These proteins are transported to the cell surface, where parts of the central and N-terminal portions of gp41 are also expressed on the outside of the virion. The central region of the TM protein binds to the external viral gp120 in a noncovalent manner, most probably at hydrophobic regions in the amino and carboxy termini of gp120 (454). Some analyses suggest that a knob- and socket-like structure is involved (1064). In general, the virion has about 100 times more p25 Gag protein than envelope gp120 (649, 805) and 10 times more p25 than the polymerase molecule (649).

The virion gp120 located on the virus surface contains the binding site for the cellular receptor(s) and the major neutralizing domains. Nevertheless, the external portion of gp41 and perhaps part of p17 have also been reported to be sensitive to neutralizing antibodies (146, 222, 839, 1040) (see Sections XIV F and XXII A). The antibodies to p17 could indicate some protrusion of this core protein to the outside of the virion. This possibility, challenged by some (992), has recently received further support (899, 1076).

B. Genomic Organization

Detailed discussions on the basic structure of HIV, its genome, and its molecular features are given in references 400 and 1205. In general, the genomic size of HIV is about 9.8 kb with open reading frames coding for several viral proteins (Table 3) (see Section XII A and Fig. 15). The primary transcript of HIV is a full-length viral mRNA, which is translated into the Gag and Pol proteins. The Gag precursor p55 gives rise, by proteolytic cleavage, to the smaller proteins p25, p17, p9, and p6, cited above. The Pol precursor protein is cleaved into products consisting of the RT, the protease (PR), and the integrase (IN) proteins. PR processes the Gag and Pol polyproteins, and IN is involved in virus integration. The Gag and Gag-Pol products are synthesized in a ratio of about 20:1 (873). Splicing events producing many subgenomic mRNAs are important for the synthesis of other viral proteins. The relative amounts of the unspliced to singly and multiply spliced mRNAs appear to be determined by the *rev* gene, which is itself a product of a multiply spliced mRNA (294, 1110, 1131) (see Section XII A).

The envelope gp120 and gp41 proteins are made from a precursor gp160, noted above, which is itself a mono-spliced mRNA from the full-length viral mRNA. Gene products of other spliced mRNAs make up a variety of viral regulatory and accessory proteins that can affect HIV replication in various cell types (Table 3). One regulatory protein is Tat, a transactivating protein that, along with certain cellular proteins, interacts with an RNA loop structure formed in the 3′ portion of the viral long terminal repeat (LTR) called TAR (Tat responsive region). Tat is a major protein involved in upregulating HIV replication.

TABLE 3. HIV proteins and their functions[a]

Proteins	Size (kDa)	Function
Gag	p25 (p24)	Capsid (CA) structural protein
	p17	Matrix (MA) protein, myristoylated
	p9	RNA-binding protein (?)
	p6	RNA-binding protein (?); helps in virus budding
Polymerase (Pol)	p55, p63	RT, RNase H (inside core)
Protease (PR)	p15	Posttranslation processing of viral proteins
Integrase (IN)	p11	Viral cDNA integration
Envelope	gp120	Envelope surface (SU) protein
	gp41 (gp36)	Envelope transmembrane (TM) protein
Tat[b]	p14	Transactivation
Rev[b]	p19	Regulates viral mRNA expression
Nef[b]	p27	Pleiotropic, including virus suppression; myristoylated
Vif[b]	p23	Increases virus infectivity and perhaps cell-cell transmission; cysteine protease (?)
Vpr[b]	p18	Helps in virus replication; transactivation (?)
Vpu[c]	p15	Helps in virus release
Vpx[d]	p15	Helps in infectivity
Tev[b]	p26	Tat and Rev activators

[a] See Fig. 15 for the location of the viral genes on the HIV genome.
[b] Not found associated with the virion; Vpx, not certain.
[c] Only present with HIV-1. Expression appears regulated by Vpr.
[d] Only encoded by HIV-2. May be a duplication of Vpr.

Another viral regulatory protein, Rev (regulator of viral protein expression), interacts with a *cis*-acting RNA loop structure called the Rev responsive element, located in the viral envelope mRNA. This interaction involves cellular proteins and multimers of the Rev protein and permits unspliced mRNA to enter the cytoplasm from the nucleus and give rise to full-length viral proteins needed for progeny production. Thus, Tat and Rev are RNA-binding proteins that interact with cellular factors for optimal activity.

Another protein, Nef (negative factor), appears to have a variety of potential functions including some alleles that down-regulate viral expression (see Section XIII B). Its site of activity is not clear, but it could involve the viral LTR or anti-Rev effects (see Section XIII). In addition, the accessory HIV viral gene products, Vif, Vpr, and Vpu/Vpx, appear to influence events such as assembly and budding, as well as infectivity involved in the production of infectious viruses (Table 3).

As described in reviews on the molecular features of these viral gene products (400, 1205), the regulation of virus expression involves the interplay of many of these viral proteins, which leads to either high or low production of HIV or even the establishment of a latent state. For example, production of Rev in the later phases of the viral replicative cycle can down-regulate its own expression as

TABLE 4. Isolation of HIV from body fluids

Fluid	No. with virus isolation/total no.	Estimated quantity of HIV[a]
Free virus in fluid		
Plasma	33/33	1–5,000[b]
Tears	2/5	<1
Ear secretions	1/8	5–10
Saliva	3/55	<1
Sweat	0/2	—[c]
Feces	0/2	—
Urine	1/5	<1
Vaginal and cervical	5/16	<1
Semen	5/15	10–50
Milk	1/5	<1
Cerebrospinal fluid	21/40	10–10,000
Infected cells in fluid		
PBMC	89/92	0.001–1%[b]
Saliva	4/11	<0.01%
Bronchial fluid	3/24	NK[d]
Vaginal and cervical fluid	7/16	NK
Semen	11/28	0.01–5%

[a] For cell-free fluid, quantities are given as infectious particles per milliliter; for infected cells, quantities are the percentage of total cells infected. Results from studies in the author's laboratory are presented (see Section IV).
[b] High levels associated with symptoms and advanced disease.
[c] —, no virus detected.
[d] NK, not known.

well as that of Tat and Nef (see Section XII A). Virus replication would then be limited.

It is noteworthy that HIV codes for three major enzymes functioning at different times during the replicative cycle. They have, as expected, been prime targets for antiviral approaches (see Section XXIX). The RNA-dependent DNA polymerase (with its RNase H function) acts in the early steps in virus replication to form a double-stranded DNA copy (cDNA) of the virus RNA. The integrase functions inside the cell nucleus to integrate the viral cDNA into the host chromosomal DNA. Finally, as noted above, the protease acts during the maturation of the viral particle either at the cell surface or in the budding virion by processing the Gag and Gag-Pol polyproteins (1205).

IV. HIV IN BODY FLUIDS AND ITS RELATION TO VIRUS TRANSMISSION

The transmission of a virus can be greatly influenced by the amount of infectious virus in a body fluid and the extent of contact with that body fluid. Epidemiological studies conducted during 1981 and 1982 first indicated that the major routes of transmission of AIDS were intimate sexual contact and contaminated blood (514). The syndrome was initially described in homosexual and bisexual men (390, 743, 1097) and intravenous drug users, but its occurrence as a result of heterosexual activity was soon recognized as well (442). Moreover, it became evident that transfusion recipients and hemophiliacs could contract the illness from blood or blood products (142) and that mothers could transfer the causative agent to newborn infants (24). These three principal means of transmission—blood, sexual contact, and mother-to-child—have not changed (105, 1144) and can be explained to a great extent by the relative concentrations of HIV in various body fluids (Table 4).

TABLE 5. Titer of HIV-1 recovered from plasma in relation to $CD4^+$ cell count

No. of $CD4^+$ cells/mm^3	No. of individuals	Mean HIV titer (TCID/ml) and range[a]
≥500	13	114 (1–500)
300–499	8	205 (1–500)
200–299	4	381 (25–500)
<200	8	1,466 (25–5,000)

[a] The trend of finding increased virus titer with lower $CD4^+$ cell counts was statistically significant (Kristal-Wallis test; data from reference 892).

A. Blood

Because of the great concern for the reported transmission of AIDS by blood, major efforts were made early in the study of HIV to quantitate virus in this body fluid. The results indicated that both free infectious virus and infected cells were present in blood, and HIV-infected cells appeared to be more numerous.

For these studies, detection methods had to be established and optimized. The early data suggested that free infectious HIV was present in the blood of about 30 to 50% of infected individuals (290, 782). However, studies with improved virus detection procedures showed that nearly all blood samples contain circulating infectious virus whether the individual is asymptomatic or has AIDS (199, 277, 471, 892, 1021, 1028). HIV is readily found during acute (primary) infection. Titers as high as 5,000 infectious particles (IP) per ml have been reported (179, 217, 339, 676, 892). Subsequently, within weeks, the level of free virus detected in the blood is markedly reduced to sometimes <1 IP per ml (199, 277, 471, 892, 1021). The reason for this decrease in viremia is an important area of study (see Section XXIII). Then, as disease develops with its characteristic loss of $CD4^+$ cells, the concentration of HIV in blood can rise substantially (Table 5), reflecting an increased virus load (199, 273, 471, 875, 892, 1021).

To quantitate optimally the level of free virus in blood, our laboratory found that the plasma must be tested within 3 h after venipuncture. Otherwise, neutralizing antibodies and perhaps yet undefined factors in the plasma of some infected individuals inactivate HIV (892). Other procedures for increasing the detection of HIV in blood have included the measurement of p25 antigen (391) and HIV RNA by polymerase chain reaction (PCR) (480). However, the relation of these data to infectious particles, the potential source of transmission, is not clear. Most recent estimates suggest that up to 100,000 more noninfectious virions than free infectious viruses are present in the plasma of seropositive individuals (649). The noninfectious virus could be detected by the antigen and RNA analyses.

Several studies have indicated that virus-infected cells are more frequent in blood than is free infectious virus. The total amount of infectious free virus present in the blood of asymptomatic individuals averages 100 IP per ml (471, 892). The number of virus-infected cells is about 1 in 1,000 PBMC (45, 99, 441, 492, 953, 1056, 1058) (see Section VI B). With at least 5×10^6 leukocytes per ml of blood, these numbers calculate to around 5,000 infected cells per ml of blood. Thus, the number of infected cells in blood is at least 50-fold larger than the amount of free infectious virus. In addition, each cell could produce several thousand infectious particles daily (670). Moreover, during symptomatic infection, especially AIDS, the number of infectious viruses and infected

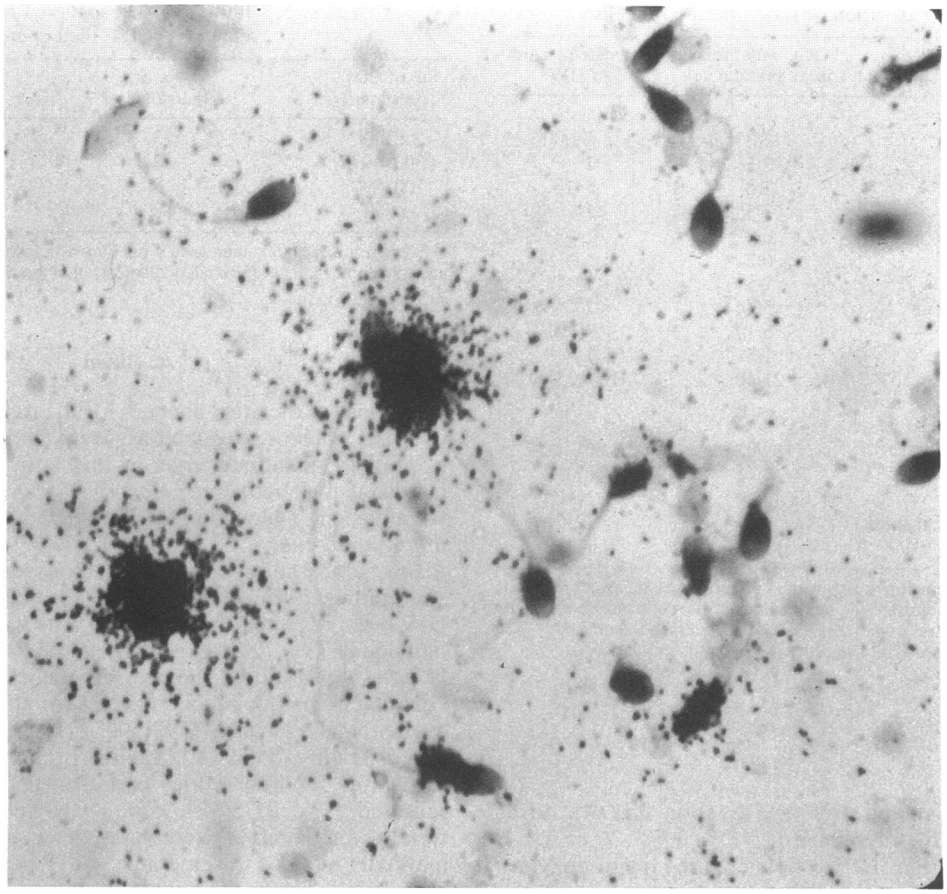


FIG. 3. HIV-infected cells detected in seminal fluid by in situ hybridization. Magnification, ×40. Reprinted from reference 666 with permission.

cells is usually much larger (e.g., 1,000 IP/ml; up to 1:10 $CD4^+$ cells per ml) (45, 362, 492, 1056) (Table 5). The chance of transmitting infection, particularly by HIV-containing cells, could then be even greater.

B. Genital Fluids

The amount of virus in genital fluids is important for sexual transmission. Generally, 10 to 30% of seminal and vaginal fluid specimens have shown the presence of free infectious virus and/or virus-infected cells (28, 85, 456a, 475, 666, 668, 670, 1215, 1223, 1293, 1324) (Fig. 3). Most recently, HIV-1 in male preejaculatory fluid has been reported (953a). However, the levels of free virus detected in these body fluids (10 to 50 IP/ml) from a large number of individuals have not been reported, and the quantity apparently differs considerably (Table 4).

Some studies suggest that the presence of infectious virus in seminal fluid does not correlate with the clinical state (609), although this finding differs when viral RNA is measured (773). In a recent report, recovery was best from men with low $CD4^+$ cell counts (28), but only a small number of subjects was studied. Vaginal fluid only rarely has been found to contain free virus (1293); generally, only infected cells are detected (1223, 1224, 1293). Nevertheless, detection of virus was probably limited in all these reports, since culturing of HIV from genital fluids can be technically difficult because of the cytotoxic effects of these body fluids. Moreover, a delay in assaying the genital as well as other body fluids probably decreases virus detection as noted with plasma samples (see Section IV A).

The prevalence of virus-infected cells appears to be an important variable in genital fluids (668, 1224, 1296) (Table 3). It ranges from 0.01 to 5% in seminal fluid (666) (Fig. 3). Quantities in vaginal fluid have not been reported. Since semen usually has over 10^6 leukocytes per ejaculate (1295), the HIV-infected cells ($>10^4$ in some cases) would be a greater source of transmission than free virus. Moreover, if venereal disease is present, many more inflammatory cells, and thus virus-infected cells, would be present in both seminal and vaginal fluids (see below).

The source of the HIV in seminal fluid is also not well defined. It has been isolated from this body fluid from vasectomized men (29). Thus, the virus and virus-infected cells must come from the prostate and other secretory glands as well as the testes (227, 651). The source in vaginal fluid is not known, but is most probably secretory glands in the vagina or cervix, leukocytes in the uterine cavity, and, in some cases, menstrual blood.

C. Saliva and Other Body Fluids

Although blood and genital fluids can have high levels of infectious virus or infected cells, the results with other body fluids strongly suggest that they are not likely sources of virus transmission (Table 3). Saliva, for example, yields

virus but only on rare occasions (generally <10% of samples) and only in limited amounts (<1.0 IP/ml) (407, 467, 673). Where studied, both free virus and infected cells could be detected (673). This low recovery rate could reflect not only low virus content but also some direct antiviral properties of saliva or the presence of nonspecific inhibitory substances (30, 947, 1147). These substances appear to be fibronectins and glycoproteins (e.g., MG1) which come primarily from gingival and not parotid salivary glands (25, 1147). Like dextran sulfate (2, 43), MG1 blocks HIV infection at the cell surface (25) and could prevent cell-to-cell transfer of virus. The presence of these inhibitory substances provides additional reasons why saliva is not a likely cause of transmission. Nevertheless, whether saliva in children has this antiviral activity needs further study, since HIV has been recovered from the throats of infected children (552).

Urine, sweat, milk, bronchoalveolar lavage fluids, amniotic fluid, synovial fluid, feces, and tears have also been shown to contain none or only low levels of infectious HIV (232, 328, 519, 667, 676, 825, 1107, 1291, 1302, 1313, 1337) (Table 4). Thus, these fluids do not appear to be important sources of virus transmission (328, 687, 1034, 1107, 1179) (Table 4). Nevertheless, transfer of HIV to a newborn via milk has been reported on a few occasions (1212, 1335), particularly when the mother is infected after birth (e.g., by blood transfusion). In this case, the virus content in milk at the time of a primary infection (Section IV A) could be high because of a lack of a substantial maternal antiviral immune response. However, milk has also been reported to contain an antiviral substance (844), perhaps similar to that found in saliva (25, 30).

In contrast to the other body fluids described above, virus has been found in large amounts (e.g., 1,000 IP/ml) in cerebrospinal fluid (CSF), particularly in individuals with neurologic findings (473, 479, 675, 982, 1115) (for a review, see reference 157) (see Section XIX A). CSF, however, would not be a natural source of transmission.

D. Transmission by Blood and Blood Products

In the years before the screening of blood, transfusion recipients and hemophiliacs could be infected by HIV present in blood and blood products such as factors VIII and IX. The screening of blood for anti-HIV antibodies has now reduced the risk of infection by transfusion in the United States to about 1/225,000 units (918). The potential risk of infection of transfusion recipients depends on the virus load, which, as noted above, appears to be greatest as an infected individual (as donor) advances to disease (Table 5). In one study, the chance of infection was reported to rise substantially if the donor developed AIDS in 2 to 3 years after donation (913). Other studies have shown that individuals receiving blood from donors who subsequently develop AIDS within 29 months have a greater chance of progressing to disease than those recipients of infected blood from donors who become symptomatic after this period (1249). This latter finding could reflect the amount of virus present and/or the biologic properties of the virus in the donated blood (e.g., more virulent) (see Sections IV A and XVI D).

In hemophiliacs, this transmission could be caused only by free virus and was associated with receipt of many vials of unheated clotting factors; the chance that an infectious HIV particle was present in the lyophilized product was then increased (285, 287, 379, 591). Nevertheless, evidence of virus particles in old clotting-factor preparations has just recently been substantiated by PCR analysis (1071, 1332), which detected viral RNA. Attempts to isolate infectious HIV from these sources have thus far been unsuccessful (670a). Currently, the procedure of heating factors VIII and IX to high temperatures (>60°C) either before or after lyophilization (680, 681, 756) has virtually prevented further infection of hemophiliacs.

E. Sexual Transmission

AIDS was first identified as a disease that appeared to be transmitted by a sexual route. A high prevalence among homosexual men was initially reported. Subsequent studies indicated spread by heterosexual activity, which now is responsible for the large majority of infections worldwide (855, 1144). As discussed above, the transmission of HIV by genital fluids most probably occurs through virus-infected cells since they can be present in larger numbers than free virus in the body fluids. Moreover, recent studies suggest that these infected cells transfer HIV to epithelial cells best when present in seminal fluid, because cell-cell contact is increased most probably via factors in semen (905) (Fig. 4).

The presence of different levels of infected cells in the genital fluids probably explains the variations in virus transmission among sexual partners. Some individuals do not become infected by HIV despite many unprotected exposures to the genital fluids of infected sexual partners (121, 886, 930). However, as stated above, the concomitant presence of sexually transmitted diseases can increase levels of HIV in genital fluids and thus make transmission more likely (121, 930).

Early epidemiologic data suggested that HIV needed a point of entry in the vagina or the anal canal, and thus abrasions at these sites presumably would increase transmission. This assumption helped explain the high level of heterosexual spread in Africa, where genital ulcers from existing venereal diseases (e.g., *Haemophilus ducreyi* and herpesvirus infections) are associated with increased HIV seroprevalence (121, 463, 930). In this regard, herpes simplex virus and syphilis infections in the United States have also correlated with an increased risk of HIV transmission among heterosexuals (484). Nevertheless, subsequent studies of biopsy tissues have shown that the bowel mucosa and perhaps the cervical epithelium can be directly infected by HIV (453, 679, 744, 843, 937) without the need for ulcerations.

The finding of HIV in the bowel mucosa itself (see Section VI A) provides another reason, besides abrasions, for the high risk of transmission associated with receptive anal-genital contact. Direct contact of the bowel mucosa with HIV-infected cells in semen could be responsible (90, 905, 924) (Fig. 4). Infection could occur following interaction of virus with cellular receptors (1307) (see Section VII G) or attachment of virus-antibody complexes to Fc receptors on the mucosal cells (500) (see Section VIII A). Another possible means of HIV entry could be via intestinal M cells present in the bowel epithelium (21). HIV infection of the mucosa also supports the epidemiological data showing that douching of the anal canal prior to sexual contact increases the risk of infection; cleansing would permit easier contact of infected cells with the mucosal epithelial cells. Douching is a parameter of transmission independent from being the receptive partner in anal-genital contact (1289). Thus, infection via the bowel mucosa could have been the portal of HIV entry for many infected individuals, and the number of sexual contacts with sufficient virus in the genital fluid could

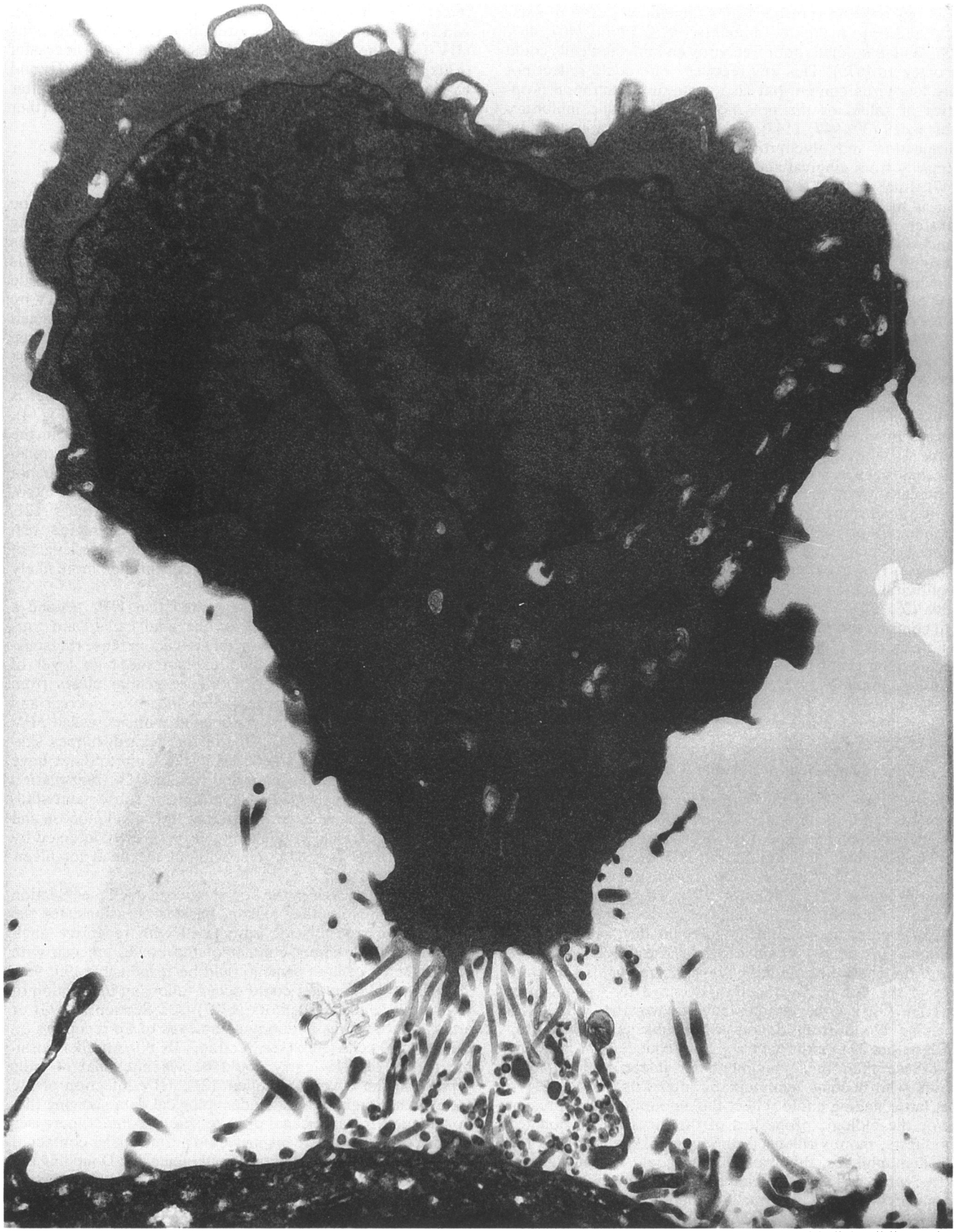


FIG. 4. Transmission electron micrograph of HIV-infected U937 cells 3 h after addition to the I-407 intestinal epithelial cell line. Virus particles can be observed between the monocyte and the epithelial cell surface. Magnification, ×3,600). Photomicrograph courtesy of D. Phillips. Reprinted with permission from reference 90.

be the most important factor in determining sexual transmission.

In vaginal intercourse, the columnar and squamous cell epithelium of the vagina can be a barrier to virus infection, so that ulcerations caused by venereal diseases (see Section IV B) might be required to cause infection at this site. Nevertheless, transmission of HIV has been reported in a chimpanzee inoculated in the vaginal canal with high doses of the virus in culture fluid (330). The factors involved in this infection, however, could be different from those in the natural state (i.e., via semen). In some cases, direct infection of cells in the cervix might occur (937). However, transmission would appear most likely if virus-infected cells in the semen gain entry into the uterus through the cervical os and infect resident lymphocytes, macrophages, and perhaps uterine epithelial cells susceptible to HIV. This risk for HIV infection would be particularly high during menses or shortly thereafter, before the reformation of the mucosal plug (668, 670).

The active, or insertive, partner in sexual contact carries a relatively low risk of infection, although it is not minimal (1289). Transmission could occur through infection of macrophages or lymphocytes in the foreskin or along the urethral canal. A lack of circumcision has correlated in some studies with increased risk of infection of males (121). In this case, the mucosal lining of the foreskin could be susceptible to HIV. Moreover, venereal diseases involving the foreskin might increase the chance of infecting inflammatory cells associated with the foreskin. These possibilities need further study. In macaques, SIV appears to infect the macrophages associated with the foreskin or urethral canal (787a). Finally, oral-genital contact could also lead to infection of either partner, albeit at a low frequency (1289). Obviously in all routes of sexual contact, an increased number of virus-infected cells in the genital fluids (e.g., resulting from venereal disease) would increase both transfer and receipt of the infectious virus.

All these observations emphasize the importance of using barrier techniques during sexual activity. The most common method is the use of condoms, which has been demonstrated in both in vitro and epidemiological studies to be effective in preventing the passage of virus (198, 847). In this regard, the recommendation of using antispermicidal products (e.g., nonoxynol-9) against HIV needs reconsideration. Some studies have demonstrated that the use of certain doses of these compounds is associated with vaginal and cervical irritations that might increase virus transmission (852). Most recently, nonoxynol-9 has not shown efficacy in preventing heterosexual transmission of HIV (608).

F. Transmission from Mother to Child

The transmission of HIV from mother to child appears to occur in 11 to 60% of children born to HIV-positive mothers (7, 77, 206, 207, 271, 501, 641, 700, 845, 883, 889, 1010, 1018, 1049, 1189). This prevalence is based primarily on PCR and virus culture studies; diagnosis by serology is difficult since maternal antibodies are present in infants at birth (for reviews, see references 883 and 1009). The reason for the wide variation in virus transmission rates is not known, and the answer could provide approaches for prevention.

Determining infection in the newborn can be difficult. Serologic evaluation is not possible unless immunoglobulin A (IgA) antibodies are measured (629, 740, 964, 1257). IgA does not pass the placenta and thus does not confer seropositivity to neonates as do other maternal antibodies. IgA production should be specific for HIV infection in the newborn and could be explained in part by the swallowing of infected amniotic fluid by the infant in utero or during birth (740).

Another proposed serologic procedure for detecting an infected newborn is the induction of anti-HIV antibody production in the newborn's PBMC cultures by using a B-cell mitogen (20, 700, 889). Both this evaluation method and the IgA antibody production assay require further study. The most helpful methods for detecting infection in newborns are PCR analysis for viral RNA and virus isolation procedures (244, 271, 610, 845). However, PCR can lack specificity, and virus culture can be time-consuming and difficult to conduct routinely.

The reason for the transfer of virus from the mother to the newborn is not known. This transmission has been reported to correlate with an absence in the mother of antibodies to the viral envelope, especially the third variable region (V3 loop) of gp120 (see Section XIV F). Other indicators include a low $CD4^+$ cell count and the presence of viremia and p25 antigenemia in the mother at the time of delivery (380, 700, 845, 1019, 1049). The latter findings suggest that the level of free infectious virus in the maternal blood could predict the infectious outcome of the newborn. In this regard, the "virulent" nature of the maternal virus (the ability to kill $CD4^+$ cells) could also be a factor (see Section XVI D).

These parameters of transmission need confirmation and are under study. For example, recent reports do not show the association of maternal anti-V3 loop antibodies with protection from HIV transmission to the newborn (7, 427, 900, 1000). However, some of these results reflect studies conducted primarily with peptides representing the principal neutralizing domain (PND) of this portion of the envelope gp120; antibodies (particularly of neutralizing type) to other regions within and outside the V3 loop and to gp41 still appear to correlate with protection (1022a, 1204).

In addition, recent studies suggest that the virus transferred from mother to newborn can be distinguished by molecular and serologic properties (587, 1300). As cited above, the transferred virus could be a more virulent strain. Moreover, in studies in our laboratory, a virus sensitive to enhancing antibodies in the mother's serum (see Section XIV F) has been detected in the cord blood (587). Thus, not only the level of viremia but also specific features of variant HIV strains and antiviral antibodies present in the mother could determine whether transmission occurs.

The source of virus in the newborn is also controversial. It appears that transmission can occur either in utero or during or after delivery (1018). Support for intrauterine transmission comes from the detection of HIV in placentas and fetuses by in situ hybridization, PCR, and immunohistochemical studies (206, 685, 734, 1111); HIV has also been isolated from cord blood, amniotic fluid, and placental and fetal tissues (145, 530, 748, 825, 1018, 1121). Nevertheless, the frequency of HIV infection of tissues in utero has not been well documented. Some investigators have found no virus in fetal tissues (22). Perhaps interferon or female hormones produced by trophoblast cells help prevent this infection (89). Placental cells either expressing or lacking CD4 protein have been infected in vitro by virus or virus-infected cells, but only low-level replication occurs (22, 258, 748, 1318). Whether these findings are relevant to the in vivo situation is not clear.

Observations suggesting a high rate of perinatal or post-delivery infection have received increased attention. HIV is often not isolated from cord blood but is recovered from

virus-infected infants older than 1 month (111, 244, 272, 610). These observations suggest that many infant infections probably occur at birth or shortly thereafter through contact with amniotic fluid, genital secretions, or blood of the mother. This type of HIV transmission at the time of delivery could explain why only one monozygotic twin may be infected (772), as well as the higher risk of infection for the first born of twins (378). In some reports, but not others, cesarean delivery has been associated with decreased HIV transmission (1018). As noted above, in certain cases HIV infection is transmitted via infected milk (464, 1212, 1335), particularly from mothers who acquired HIV postnatally. In general, this route of transmission is considered uncommon (464, 1212).

The factors involved in transfer of HIV from mother to child could be studied in relation to SIV infection. Transmission of this primate virus appears to occur primarily when the animals are sexually active and not during birth (749). Some studies suggesting that SIV is transferred perinatally but remains silent in the infected infant (1219) need further confirmation (329a). SIV transmission to one of three offspring was demonstrated in pigtailed macaques (*Macaca nemestrina*) (865). The consistency of this result, which resembles transmission in humans (i.e., 30%), needs further study. The observation could suggest an HIV transmission model since pigtailed macaques have been found to be sensitive to HIV-1 infection (8).

Information on transmission of the other pathogenic retrovirus, HTLV, might also have relevance to HIV. HTLV is not passed readily in utero (1043). Transfer of this virus occurs primarily via breast milk and genital fluids, most probably in infected cells (462). Moreover, in recent studies on HTLV transmission, approximately 22% of placentas but only 7% of the infants were infected. This observation suggests a defense mechanism at the maternal-fetal interphase (329), which may also be operating in HIV infection.

If the factors influencing maternal transmission of HIV can be well defined, antiviral approaches could be better targeted. Procedures could include monitoring the mother during labor, cleansing the vaginal canal, and rapidly clearing the newborn of amniotic fluid, genital secretions, and maternal blood.

V. ACUTE HIV INFECTION

Clinical manifestations of initial HIV entry into the body might be expected since signs and symptoms commonly accompany acute infections by other viruses. Very early in the studies of AIDS, clinical features of acute HIV infection were recognized and have been described in a number of articles, particularly by Cooper and coworkers (202, 1181, 1183) (Table 6). A recently infected individual can present within 1 to 3 weeks with a viruslike illness. Symptoms consist of headache, retroorbital pain, muscle aches, sore throat, low-grade or high-grade fever, and swollen lymph nodes, as well as a nonpruritic macular erythematous rash involving the trunk and, later, the extremities (Table 6) (202, 764). In some cases, oral candidiasis and ulcerations in the esophagus or anal canal occur (201a, 965), and central nervous system disorders can be seen (e.g., encephalitis) (131). In other acutely infected individuals, pneumonitis, diarrhea, and other gastrointestinal complaints have been reported (1183). These symptoms usually last from 1 to 3 weeks, although lymphadenopathy, lethargy, and malaise can persist for many months. In general, primary HIV-1 infection is followed by an asymptomatic period of many months to years. The presence of this previous viruslike illness can then be elicited only by history.

TABLE 6. Characteristics of primary HIV infection

Clinical[a]
Headache, retroorbital pain, muscle aches, sore throat, low-grade or high-grade fever, swollen lymph nodes
Nonpruritic macular erythematous rash
Oral candidiasis and ulcerations of the esophagus or anal canal
Acute CNS disorders (e.g., encephalitis)
Pneumonitis
Diarrhea and other gastrointestinal complaints
Course
Symptoms last 1–3 weeks
Lymphadenopathy, lethargy, and malaise can persist for many months
Generally followed by an asymptomatic period of months to years
Laboratory findings
First week, lymphopenia and thrombocytopenia
Second week, lymphocyte number rises secondary to an increase in $CD8^+$ cells; CD4/CD8 ratio decreases
Second week, atypical lymphocytes appear in the blood (generally <50%)
HIV antigenemia and viremia detected
Virus might be present in CSF and in seminal fluid
Anti-HIV antibodies first detected within 6–30 days

[a] Some or all of these findings can be present.

It is estimated that about 40% of individuals infected by HIV will give a history of this acute mononucleosislike illness (1181, 1183). Generally, the rash is a valuable diagnostic sign since it can distinguish HIV from other types of infections in the community. The cause of the rash is unknown, but it could be due to antigen-antibody complexes in the skin (764). Recent studies suggest that the occurrence of symptoms during primary HIV infection is associated with faster disease progression (554), but this possibility requires further evaluation.

Laboratory studies conducted on infected individuals during the first week following HIV infection can show lymphopenia and thrombocytopenia (Table 6). In the second week, the number of lymphocytes increases, primarily because of a rise in the quantity of $CD8^+$ cells. $CD4^+$ cells are reduced in number. Thus, during this period, the $CD4^+/CD8^+$ cell ratio becomes inverted. Moreover, atypical lymphocytes can appear in the blood (203, 479) but usually in smaller numbers in primary HIV infection than in EBV, CMV, or other infections that elicit this response (201a, 338). Over the following months, the quantity of $CD8^+$ cells returns to a normal or slightly higher level. This number remains greater than that of $CD4^+$ cells, which increases somewhat; therefore, the inverted ratio is maintained (1181).

During this acute HIV infection, the individual becomes antigenemic and viremic. High levels of infectious virus can be detected in the peripheral blood (179, 217, 337, 1233) (see Section IV A). Moreover, recent studies indicate a fairly rapid production of viral variants as determined by PCR analysis soon after primary infection (894). Thus, heterogeneity of HIV in the host can be recognized quite early in the infection (see Section XIV). Within weeks, as noted above, this viremia becomes markedly reduced, most probably reflecting an active antiviral immune response. Virus has also been isolated from the CSF (473) and semen (1184) during this acute HIV phase. The latter finding indicates the

potential transmission of the virus to sexual contacts during this period.

In acute infection, both cytopathic and noncytopathic strains can be initially isolated. In some reports, the noncytopathic strains are predominantly found and are associated with slow progression to disease (1014). However, this correlation needs further evaluation. Treatment with zidovudine (3'-azido-3'-deoxythymidine [AZT]) in one reported case enhanced progression to disease and delayed seroconversion (1014). My laboratory and others (1182) have noted a similar negative response to AZT when it is used during primary infection. The observations, although made with only a few subjects, raise the question of whether therapy is appropriate during this time when the host's natural immune reaction to the virus is being established (see Sections XXII and XXIII).

Seroconversion can occur within days after infection, but antibodies generally appear after 1 to 4 weeks. In studies performed by Cooper et al. (202) and Gaines et al. (338), antibody was first detected in some subjects as early as 6 days after infection by measurement of the IgM response. Subsequently, usually within 2 weeks, IgG levels could be demonstrated by an indirect-immunofluorescence assay. Recently, by using the present antibody enzyme-linked immunosorbent assay (ELISA) detection kits, which have increased sensitivity and specificity, antibody seroconversion can be detected within a few days, although several months are required for some individuals (339, 1181, 1183).

In some studies, HIV-specific helper T-cell responses have been detected shortly after acute infection before seroconversion takes place (185). Conceivably, other cellular immune responses are present before humoral immunity is evident (184). We have documented $CD8^+$-cell anti-HIV activity in one individual before seroconversion (725a) (see Section XXIII D). Whether an individual can be antibody negative for longer than 6 months is still controversial (see Section XIII C). In my opinion, it is rare for there to be a long period before seroconversion; the sera of most individuals will show antibodies within 3 months after the initial infection.

VI. CELLS AND TISSUES INFECTED BY HIV

A. Cellular Host Range

HIV has been found in several tissues, albeit at a very low level in some (Table 7). The virus can be detected by recently improved techniques of cell culture, in situ hybridization procedures, immunohistochemistry, electron microscopy, and, recently, PCR. Moreover, cell culture studies have shown a wide variety of human cells susceptible to HIV, but the extent of infection varies and can depend on the particular virus strain used (see below). In general, $CD4^+$ cells replicate HIV to the highest titers. The in vitro studies indicate that successful virus infection is determined both by the efficiency of viral entry into the cell and by postpenetration processes influenced by the intracellular milieu (see Section XII). Clinically, direct infection of the brain, bowel, heart, kidneys, joints, and perhaps other tissues could be responsible for some of the pathogenic findings observed in HIV-infected individuals (see Sections XIX, XX, and XXI).

In the hematopoietic system, studies conducted soon after the initial recovery of HIV demonstrated that $CD4^+$ helper T lymphocytes were the major targets for HIV infection (582). However, other cells were then found to be susceptible to the virus, particularly macrophages (354, 472, 682, 848), the target cells for other lentiviruses (419). In macrophage infection, often only low-level virus production occurs and HIV can be found sequestered in intracellular vacuoles (359). The hematopoietic cells now known to be infectable range from stem cells to monocytes, macrophages, B lymphocytes, megakaryocytes, natural killer (NK) cells, eosinophils, thymic epithelial cells, and dendritic cells (135, 152, 327, 860, 902, 1030, 1339) (Table 7). Dendritic cells in the blood have been shown to produce high levels of the virus after infection in vitro (633).

B cells (including B lymphocytes) can be infected in cell culture, but appear most susceptible if EBV is present (219, 455, 798, 800). $CD8^+$ cells have been infected in vitro (243,

TABLE 7. Human cells susceptible to HIV[a]

Hematopoietic
T lymphocytes
B lymphocytes
Macrophages
NK cells
Megakaryocytes
Dendritic cells
Promyelocytes
Stem cells
Thymic epithelium
Follicular dendritic cells
Brain
Capillary endothelial cells
Astrocytes
Macrophages (microglia)
Oligodendrocytes
Choroid plexus
Ganglia
Neuroblastoma cells
Glioma cell lines
Neurons (?)
Skin
Langerhans cells (?)
Fibroblasts
Bowel
Columnar and goblet cells
Enterochromaffin cells
Colon carcinoma cells
Other
Myocardium
Renal tubular cells
Synovial membrane
Hepatic sinusoid epithelium
Hepatic carcinoma cells
Kupffer cells
Pulmonary fibroblasts
Fetal adrenal cells
Adrenal carcinoma cells
Retina
Cervix (? epithelium)
Prostate
Testes
Osteosarcoma cells
Rhabdomyosarcoma cells
Fetal chorionic villi
Placental trophoblast cells

[a] Susceptibility to HIV was determined by in vitro or in vivo studies. See Section VI for details and references.

1197), particularly after prior infection with HTLV-I (243, 1244a). $CD8^+$ cell infection has also been reported during contact with infected $CD4^+$ cells (240). Whether HIV contamination of the assays occurred in these latter studies needs further evaluation; using PCR assays, we have not detected infection of $CD8^+$ cells recovered in vivo. Moreover, although recently some $CD34^+$ bone marrow cells have been found to be infected in certain seropositive individuals (1126), conclusive evidence for a major infection of $CD34^+$ stem cells, B cells, $CD8^+$ cells, and dendritic cells in vivo requires further confirmation (228, 796, 1231). Most recently, for example, dendritic cells in vivo were not found infected but were considered to play a role in pathogenesis by carrying bound virus to activated $CD4^+$ lymphocytes, causing infection and cell death (122). In summary, within the hematopoietic system, $CD4^+$ lymphocytes are the most visibly infected cell type since they can replicate high levels of virus. Macrophages are also frequently found to be infected by HIV, but this infection may go undetected because of low virus production (see Section XIV B).

HIV has also been detected in follicular dendritic cells and the synovial membrane in the joints of AIDS patients (278, 498, 1120, 1124, 1168). In the skin, fibroblasts and possibly Langerhans cells can be infected by the virus, as shown particularly by in situ hybridization, immunohistochemistry, PCR analysis, and in vitro cell culture studies (178, 504, 770, 971, 1143, 1166, 1196, 1326). Nevertheless, definitive evidence of HIV infection of Langerhans cells in vivo is also lacking. Several reports have not confirmed infection of these cells in the tissues examined (538, 544).

In the brain, resident macrophages and microglia have been the most common cells showing the presence of virus (353, 590, 778, 842, 958, 1083, 1283; for reviews, see references 784 and 950). Whether microglia are actually targets for HIV, however, has been challenged (see also Section XIX). Peudenier et al. (922) were unable to infect microglia from the fetal brain, and they present evidence suggesting that microglia can be confused with peripheral blood macrophages infiltrating the brain. However, these two cell types can be distinguished by specific antigens (915, 922). Reports of infection of other cell types, including astrocytes, oligodendrocytes, capillary endothelial cells, and perhaps neurons (by immunohistochemistry), have appeared in the literature (417, 672, 778, 958, 1283) (Table 7). It is noteworthy that, in contrast to observations with brain-derived (813) and liver-derived (1130) endothelial cells, endothelial cells from umbilical or saphenous veins do not appear susceptible to HIV (622, 814). The consistency of these findings and the prevalence of cells infected also need further evaluation.

The presence of HIV in mucosal cells in the bowel has been detected by cell culture, in situ hybridization, and PCR studies of all regions of the gastrointestinal tract (371, 453, 600, 744, 843). The cell types considered infected include goblet and columnar epithelial cells and enterochromaffin cells (454, 679, 843). The enterochromaffin cells are hormone-producing cells that regulate cell motility and digestion (932). Macrophages, and presumably $CD4^+$ lymphocytes in the lamina propria of intestinal tissues, infected by HIV naturally or after in vitro infection, have also been reported (305, 321, 600, 843) (see also Section XX). Moreover, the virus can infect cultured bowel explants and transformed bowel carcinoma cell lines (5, 48, 291, 292, 305, 821).

Finally, HIV infection of other cells and tissues from organs such as the thymus, liver, kidneys, heart, lungs, salivary glands, eyes, prostate, testes, and adrenals has been described (Table 7) (47, 126, 127, 151, 192, 227, 254, 397, 406, 651, 703, 770, 860, 929, 938, 954, 1034, 1054, 1130). HIV antigen has been identified in muscle macrophages of a patient with myopathy (143), and infection of placenta and fetal tissues has been discussed in Section IV F. In the tissues studied, the cells infected could lack the CD4 molecule as well as express it (see Section VII E). In several instances, confirmation of the infection is needed. Nevertheless, the studies of HIV infection of human cells indicate continually that this agent is polytropic and not solely T lymphotropic.

B. Number of $CD4^+$ Cells Infected by HIV

In the early period of research on the AIDS virus, in situ hybridization data suggested that only 1 in 10^4 to 1 in 10^5 peripheral leukocytes of an individual were infected by HIV (441). The major target cell was the $CD4^+$ lymphocyte. These results questioned the viral pathogenic pathway, since $CD4^+$ cell destruction, characteristic of AIDS, could not be easily explained by direct viral infection.

Subsequently, by using quantitative PCR, the number of virus-infected $CD4^+$ cells has been reported to be as frequent as 1 in 10 in some AIDS patients and up to 1 in 10^3 in some asymptomatic individuals (99, 492, 953, 1056, 1058). Most recently, in situ PCR findings have demonstrated infection of 1 in 10 PBMC in symptomatic patients (45). This quantity then greatly increases the target cell number considered infected by the virus and might explain the $CD4^+$ cell loss (see Section XVII). Nevertheless, the number of cells actively replicating the virus (as revealed by in situ hybridization studies measuring viral RNA) could be quite small—only 10% of all cells containing the HIV genome (1100). Some believe that this observation might explain the long incubation period observed in this infection (274a). The finding would not support direct infection by HIV as a major cause of $CD4^+$ cell destruction.

It is important to remember as well that $CD4^+$ cells include macrophages, which are not readily killed by HIV (359). Moreover, the relation of the number of infected $CD4^+$ cells in the blood to the quantity of cells carrying HIV in the body (e.g., in lymphoid tissue) is not clear. Studies have shown HIV DNA in most lymph nodes from infected individuals (898, 1087). Since the PBMC represent only 1 to 3% of total lymphocytes (1274), this parameter could be misleading. In this regard, we have monitored patients with very low $CD4^+$ cell counts (<10 $CD4^+$ cells per ml) for 1 to 3 years and have found that they remain relatively asymptomatic (665). They probably have many more $CD4^+$ cells in their lymph nodes, as has been suggested in the HIV and SIV systems (322, 898, 1016). In these latter studies, it was observed that when these cells in the lymph node disappeared, AIDS quickly developed.

VII. STEPS INVOLVED IN HIV INFECTION OF CELLS

A. CD4 Receptor: Virus Attachment Site

One of the first breakthroughs in studies of HIV was the discovery of its major cellular receptor, the CD4 molecule. The reason for preferential growth of HIV in $CD4^+$ lymphocytes was then explained by its attachment to the CD4 protein on the cell surface (221, 581, 582). Subsequent studies have indicated that, for virus binding, the V1 region

of the CD4 molecule (particularly involving the Phe-43 amino acid in the CDR2 domain) interacts with a CD4-binding region (amino acids 413 to 447) in the fourth conserved portion near the C-terminal end of the HIV envelope gp120 (33, 91, 102, 182, 515, 626, 640, 794, 861, 936, 986, 1044; for reviews, see references 129, 919, 1045, 1046, and 1152).

Nevertheless, since the conformation of gp120 is important for CD4 binding (754; see also Section XXII A), other noncontiguous regions of gp120 probably also interact with the CDR2 domain of the CD4 molecule. Among these could be two hydrophobic domains in the conserved C2 and C4 regions of gp120, as well as hydrophilic domains in the C3 and C4 regions (605, 869, 943; for review, see reference 1132). A second CD4-binding region at the N-terminal portion of the envelope gp120 has also been proposed (986, 1154) but has not been supported by other studies (869). In this regard, several studies indicate that small changes in various regions of the HIV envelope can affect virus binding to the CD4 molecule and tropism (204, 205, 869) (see Section XV A).

With the crystal structure of CD4 now known (1027, 1248), the gp120-binding site has been located on a protuberant ridge along one face of the V1 domain. Initially, the viral attachment site appeared to be separate from the major histocompatibility complex (MHC)-binding site of CD4 (308, 623), but recently the location has been delineated further by using viral mutants and high-resolution CD4 atomic structure (795). These studies indicate that the class II MHC-binding site appears to include the same CD4 region (795). Thus, this overlap might affect the use of inhibitors of the CD4-gp120 interaction.

Further sites on CD4 could still be involved in HIV binding and/or fusion, such as the CDR3 domain of the V1 region (41, 203a, 697). Observations suggesting a role for this region include the blocking of CD4-gp120 interaction by CDR3-related peptides (697) and the decreased fusogenic activity of a virus with a mutation in this region (120). However, these observations have not been confirmed, since point mutations in this region do not affect binding (35, 102), fusion (101a) or infectivity (887a).

The CD4 molecule could also have a role in viral infection aside from its envelope binding (120, 448, 1195). For example, conformational changes in CD4 as a result of virus attachment could help in HIV entry (for reviews, see references 735 and 755) (see below). Its participation in virus-cell fusion has been suggested (944). Furthermore, certain regions of CD4 could be selectively involved in cell-cell fusion (532, 697, 944) (see Section IX).

Biologic studies with soluble forms of CD4 (sCD4), produced by molecular procedures in mammalian cells, have revealed some potentially important findings on the gp120-CD4 attachment process, with differences noted among HIV isolates. The studies suggest that the particular HIV envelope and its conformational changes are important factors determining the result of this interaction. After mixing with sCD4, most HIV-1 strains are inactivated to various extents (1264) (see below), whereas some HIV-2 strains, and especially the SIV_{agm} isolates, are increased in their infectivity, particularly when low sCD4 concentrations are used (17, 177, 1272). Although the reason for these diverse observations is not clear, a possible explanation is differing affinities of sCD4 for the various gp120s. With HIV inactivation, the sCD4 molecule apparently attaches to the viral envelope region and causes its removal from the virus. Thus, gp120 shedding leads to loss of infectivity (446, 805, 806) (see Sections VII B and XXII C). Conceivably, with certain HIV-2 strains and SIV_{agm}, sCD4 binds at low affinities and gp120 remains on the virion. However, the conformation of the viral envelope is altered by this association, and the fusion domain on gp41 (see below) becomes exposed and can now interact with the cell. Infection subsequently takes place and might even be enhanced. A similar event could occur during natural infection after HIV binds to the cell surface CD4 (1045). A conformational change in the envelope takes place, permitting virus fusion and entry. During this process, a cleavage of the envelope V3 loop has been proposed to occur and increase the rate of infection (see Sections VII B and G).

In perhaps related observations, some freshly isolated HIV strains have shown reduced susceptibility to sCD4 (35, 217) and more sCD4 is needed to block infection of some monocyte-tropic strains (384). The reason for these differences is not well defined. They could reflect less efficient binding of virus to sCD4 or lack of gp120 shedding following the interaction with sCD4. A similar suggestion has been made to explain the relative effectiveness of antibody neutralization and enhancement (see Section XXII C). The particular conformation of the viral envelope could influence the extent of CD4 binding and gp120 shedding. However, recent studies do not link the resistance to sCD4 inactivation of primary HIV-1 isolates to a low affinity of viral gp120 for CD4 (1200).

This resistance of some HIV-1 strains to sCD4 has been mapped to the V3 region of the virus envelope (863). Since this portion of gp120 does not bind to CD4, envelope conformation again seems involved. Nevertheless, mutations in gp120, including some within the V3 region that impair cell-cell fusion by some strains, do not affect HIV gp120 shedding induced by sCD4 (62, 1176). Moreover, with other HIV-1 strains, sCD4 resistance is not associated with the V3 loop (1270a). All these observations question the value of conclusions obtained by using sCD4 to mimic the cell surface CD4 molecule. Shedding of gp120 induced by sCD4 cannot be a common indication of conformational changes in the HIV-1 envelope proteins needed for virus infection or syncytium formation. Moreover, gp120 shedding is not a general explanation for sCD4 inactivation (1176).

Another potential factor in the CD4-gp120 interaction is the glycosylation pattern (689a, 747, 809), which can affect envelope conformation as well. Nonglycosylated envelope gp120 does not bind CD4 (689a, 1132). In this regard, the relative resistance of monocyte-tropic viruses to the neutralizing effects of sCD4, in contrast to T-cell-line-adapted viruses, may involve the increased density of carbohydrates on the surface of monocyte-tropic viruses (1045).

Another possible explanation for the differential effects of sCD4 might be a greater avidity of the primary virus strains for the cell surface CD4 receptors than for sCD4 (35, 98, 216, 510, 804). Conceivably, the culture of strains in vitro leads to the emergence of viruses with increased affinity for sCD4. Most importantly, in all studies of this phenomenon, the affinity for the CD4 protein should be measured with the entire envelope of the virus and not soluble gp120 (203a, 487, 489), since the conformation of gp120 (monomer) can be quite different from that of the gp120/gp41 oligomer on the virus or infected cell surface. In this regard, binding of gp120 oligomers (and not monomers) to CD4 molecules simultaneously occurs, and this event could be important in the initial phases of the infection process (269).

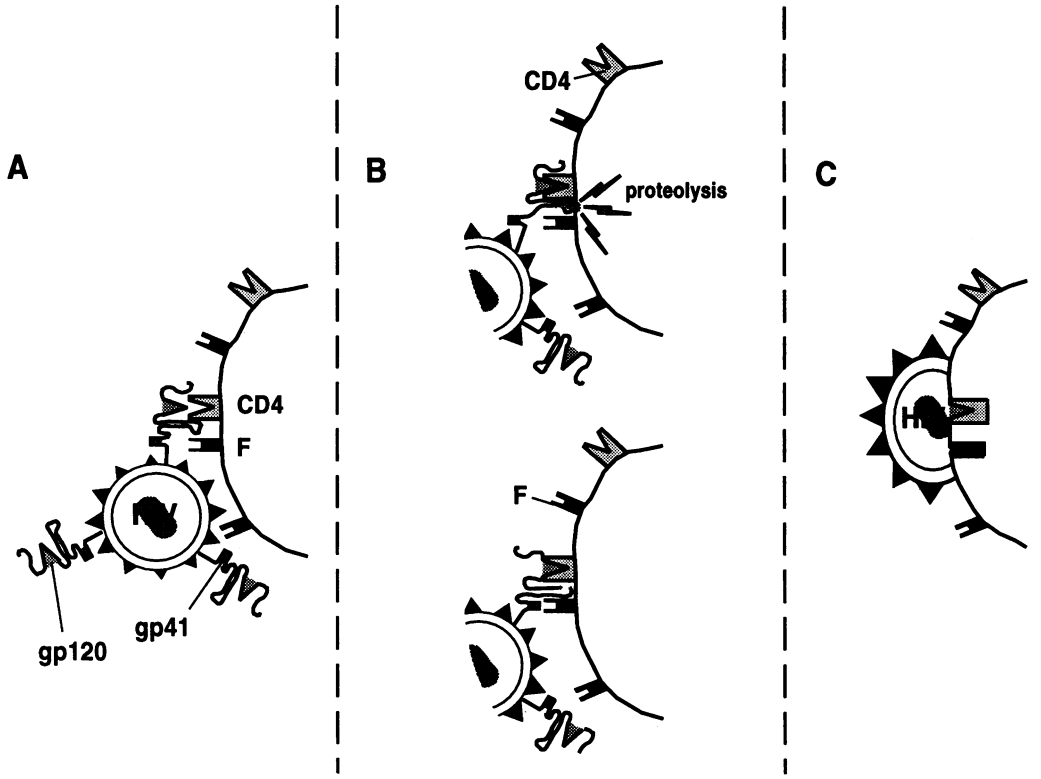


FIG. 5. Proposed steps involved in HIV entry into cells. (A) HIV approaching a cell; a region on the viral surface envelope protein, gp120, interacts with a domain on a cell surface receptor (e.g., CD4). (B) The upper diagram shows that the interaction causes a conformational change in the gp120 (and perhaps CD4), resulting in a potentially proteolytic cleavage of the gp120, most probably in the V3 loop. The lower diagram shows that this process results in an interaction of the external portion of gp41 (fusion domain) with a proposed fusion receptor on the cell surface. (C) HIV fuses with the cell. Alternatively, the interaction of gp120 with CD4 could lead to removal of gp120, with subsequent exposure of gp41 to the cell surface (see Section VII C).

B. Postbinding Steps in Virus Entry

(i) Envelope shedding. The HIV envelope can be involved in steps other than binding during virus infection of a cell. Some reports have suggested, as noted above, that after attachment to the CD4 molecule, the gp120 is displaced, leading to the uncovering of domains on the envelope gp41 that are needed for virus-cell fusion (see below) (1045). Recent analyses suggest that this displacement results from a dissociation of a knob-and-socket-like structure involving the carboxy-terminal region of gp120 and the central portion of gp41 (1064). Multimeric CD4 binding may be important for this dissociation (269), which can be demonstrated with sCD4 (see Section VI A) and is related to specific CD4 binding to gp120 (61, 446, 805). Whether a complete release of gp120 from gp41 takes place during HIV infection is not clear. Shedding does not appear to occur (251) or to be necessary as long as the fusion domain on gp41 is exposed (1045). In this regard, the sCD4-induced shedding of gp120 from viruses, observed in vitro, has not correlated well with virus entry or the viral envelope syncytial properties (62, 1176). Perhaps cell tropisms are determined only in part by the relative extent of gp120 displacement resulting from the virus interactions with cellular CD4 (see below). This phenomenon requires further study.

(ii) Envelope cleavage. Another possible event involving the HIV envelope that influences HIV entry into cells is cleavage of gp120. Certain studies of gp120 have revealed sites within the V3 loop that could be sensitive to selected cellular proteases (450, 567, 595, 827). These protease-sensitive sites resemble sequences for trypsin inhibitors. Moreover, HIV-1 has been found to bind to a TL2-trypsin-like protease (566). A concept has been proposed that these enzymes, when present in the cell, cleave the gp120 in the V3 region after CD4 binding. This event facilitates a conformational change in the envelope so that a viral region (e.g., on gp41) can subsequently fuse with the cell membrane (1045) (see below) (Fig. 5). Thus, the $CD4^+$ cells that cannot be infected by certain HIV strains might lack the necessary cellular proteolytic enzymes for that particular viral V3 region when it is exposed.

The hypothesis of envelope cleavage has gained some support from evidence demonstrating gp120 digestion by proteases (183). Moreover, recent studies have shown that exposure of HIV to sCD4 leads to evidence of cleavage of gp120 by proteolytic activity (805, 1271). This phenomenon can be blocked by monoclonal antibodies (MAbs) to certain regions of the V3 loop. The explanation given for this observation is that an initial conformational change in gp120 (and perhaps CD4) takes place after CD4 attachment, and this event exposes the V3 loop to the enzymatic activity (1271). Support for this conclusion comes from studies demonstrating that certain V3 MAbs can neutralize HIV-1 only in the presence of sCD4; the V3 epitope is exposed by this gp120-CD4 interaction (761). The importance of the process in virus entry remains to be further clarified.

C. Virus-Cell Fusion

Enveloped viruses, such as HIV, enter cells following fusion with the cell membrane. The mechanism for this process in HIV infection is not known. In early studies, computer analysis of the N-terminal external portion of the gp41 of the HIV envelope demonstrated its similarity to fusion domains on paramyxoviruses, such as the Sendai and Newcastle disease viruses (340, 387; for a review, see reference 1278). This observation suggested that HIV entry might involve viral gp120-CD4 receptor attachment and then fusion via gp41 with another cell surface receptor (see Section VII E). This role of gp41 in fusion has been supported by recent studies showing syncytium formation induced by gp41 expressed by both $CD4^+$ and $CD4^-$ cells (912).

The fusion step could follow a conformational change in the CD4 as well as dissociation of the envelope gp120 or exposure of its V3 loop to cleavage (see Sections VII A and B). This fusion process can be measured by membrane fluorescence dequenching (1102). Some studies have suggested the presence of a gp41 cell surface receptor protein that could be involved (963, 1280). This finding merits further evaluation.

The kinetics of this fusion reaction suggest continued attachment of the virus to CD4 while the fusion takes place (251). Thus, complete gp120 shedding most probably does not occur (see above), although some displacement, as described above, might be involved. The V3 loop, as well as gp41, could be important in this membrane fusion event (62, 65, 888, 1131). Mutational studies with gp41 as well as with the V3 loop have suggested that cell-cell fusion and infectivity are linked, since in many cases both are affected by the same amino acid changes (see Section IX). Infectivity presumably reflects the virus-cell fusion (65, 237, 324, 326, 403). Nevertheless, the fusogenic property of a virus may not be as important for infectivity as it is for syncytium formation (1131). Thus, virus-cell and cell-cell fusion could involve different processes (see below).

Some observations suggest that the CD4 molecule, in addition to binding, could be required for the fusion of the viral envelope with the cell surface. Elimination of the proximal region of CD4 through molecular techniques reduces viral infection. It also eliminates the ability of the cell to fuse with infected cells (944). Moreover, some MAbs to CD4 block cell-cell fusion but not HIV binding and vice versa (39, 141, 452, 532, 1195, 1284). Nevertheless, in all these approaches, whether virus-cell fusion and cell-cell fusion do involve the same processes is still not answered. Finally, the nature of the putative cellular fusion receptor(s) is unknown, although a glycolipid that mediates HIV infection has been identified on $CD4^-$ brain-derived and bowel-derived cells (438, 1307) (see Section VII E).

D. pH-Independent Entry

Experiments examining the mechanism of virus entry into cells have also evaluated the effect of changes in the relative acidity of the cytoplasmic endosomes. Enveloped viruses enter by either a pH-dependent or -independent process. If a low pH is needed, virus fusion most probably occurs in endocytotic vesicles. With the retroviruses that have been examined and with several other enveloped viruses, an acidic environment in the cell is generally not needed for virus entry (252, 369, 1278). Chloroquine and NH_4Cl, which raise the pH in cellular components, do not affect HIV infection (750, 1135). Thus, HIV entry is also pH independent. This observation has suggested that the HIV envelope, after attachment to and subsequent interactions with the cell surface, can fuse directly with the cell membrane and not necessarily within endocytotic vesicles (Fig. 5). Nevertheless, whereas virus can enter by fusing directly with the plasma membrane, phagocytosis may also lead to infection in some cells (389, 904).

TABLE 8. Factors involved in modulation of CD4 protein expression

Factor	Reference
Masking of viral receptor by gp120	754, 1044
Block in transcription of CD4 mRNA	1037, 1142
Arrest in translation of the CD4 protein	488, 1317
Complexing of CD4 with envelope gp160 within the cell	208, 209, 511, 594
Removal of CD4 from cell surface by replicating virions	769

E. Other Possible Virus-Cell Surface Interactions Involved in Entry

A role of other factors involved in HIV infection of a cell has been suggested by some studies. Investigators have shown that after attachment to CD4, a delay in viral entry at the cell surface can occur and can influence HIV spread and the extent of virus production (571). Different rates and efficiencies of entry are most probably linked to variations in the envelope (300, 1092) (see Section XV A). Recent studies suggest that the cytoplasmic domain of gp41 might be partly involved in entry through a role in virus uncoating or penetration (336). The phenomenon of delayed entry has been associated in some studies with the absence of the V3 and V4 regions of the CD4 molecule (944). These observations suggest that the CD4 protein could play a role not only in the binding and fusion but also in the penetration of the virion from the cell surface into the cytoplasm of the cell. The virus might remain attached to CD4 (possibly beneath the cellular membrane within endosomes or cytoplasmic vesicles) for a time without release of its viral core into the cytoplasm. Alternatively, the nucleocapsid might be kept beneath the cell membrane bilayer without release of the viral genome. In this regard, recent data suggest that attachment, fusion, and nucleocapsid entry are three independent but sequential steps required in virus infection (1124b). Only after penetration and uncoating of the virus core would reverse transcription and the steps leading to viral production take place. These possibilities merit further evaluation.

F. Down-Modulation of the CD4 Protein

Another early observation made with HIV-1 replication in human T cells was the concomitant disappearance of the CD4 protein from the cell surface (488, 582, 1142). The extent and time of the down-modulation depend on the level of virus production (944, 1142, 1317, 1325). Generally, in vitro a loss in CD4 expression occurs several days after HIV infection of cells when sufficient progeny virions are produced. Thus, a reduction in chronic HIV-1 production by a T-cell line, as was achieved with a Tat antagonist, restored CD4 expression (1075).

The mechanism for the altered expression of this cell surface receptor is still not clear (Table 8). With some HIV

TABLE 9. Evidence suggesting another cellular receptor for HIV

Evidence	Reference
$CD4^+$ lymphocyte cell lines can be resistant to infection by HIV	568
Animal cells expressing human CD4 are noninfectable by HIV	729
$CD4^-$ cells can be infected by HIV (see Sections VI A and VII G)	
Some viruses incubated with soluble CD4 or antibodies to CD4 are not blocked from infecting certain $CD4^+$ and $CD4^-$ cell lines (see Section VII E)	983
The glycolipid GalC, has been detected as an alternative receptor on $CD4^-$ brain-derived and bowel-derived human cells	438, 1307

strains, infection with high levels of virus production does not affect CD4 expression (see Sections XIV A and C). Differences in specific regions of the envelope gp120 could be involved. By using interviral recombinants involving these strains, this CD4 down-modulation has been linked to the envelope region (1314). The CD4 receptor does not internalize with HIV during infection, and CD4-related signal transduction events are not needed for virus entry (872).

Some reports indicate that down-modulation involves an arrest of CD4 mRNA transcription (1037, 1142) or CD4 translation (488, 1317); others demonstrate the complexing of the CD4 with the envelope gp160 within the cell (208, 209, 511, 594). A few studies suggest a masking of the CD4 by the envelope gp120 attached to the cell surface (754, 1044). The latter phenomenon can be demonstrated by using an antibody to a different region of the CD4 molecule located outside of the gp120 binding site. With a MAb such as OKT4 (not OKT4A or Leu 3a), the continual presence of the CD4 protein on infected presumed $CD4^-$ cells can be shown. Finally, some investigators suggest that the CD4 molecule is removed by budding virions (769) (Table 8). The relative effect of each of these processes on CD4 expression again most probably depends on the virus and the cells infected. The relevance to pathogenesis is unclear since some viruses do not modulate expression of CD4 (see Section XIV A). The removal of this HIV-binding site, however, does prevent superinfection of the cells with other HIV strains (see Section VIII C).

G. Possible Presence of Another Cellular Receptor: Infection of $CD4^-$ Cells

Several studies examining the role of this CD4-virus attachment have indicated that this cell receptor interaction alone is not sufficient and is not the sole means for viral entry (Table 9). Some human cells expressing high levels of the CD4 protein are not productively infected by HIV (281, 568). Some animal cells, induced by molecular or somatic hybrid techniques to express human CD4 on the cell surface, cannot be infected (176, 729, 1173). Studies with somatic cell hybrids involving human $CD4^+$ rodent cells suggest that a cell surface factor on human cells is needed for HIV entry (see Section XII B). Moreover, certain cells expressing various constructs of CD4 have shown that the V1 region alone does not appear to be the only portion of CD4 involved in the process (944). In addition, antibodies to CD4 have not blocked infection of some $CD4^+$ cells by certain HIV strains (983).

As cited above (see Section VI A), many types of $CD4^-$ cells can be infected by HIV (Table 10). These include human skin fibroblasts, muscle and bone-derived fibroblastoid cell lines, human trophoblast cells, follicular dendritic cells, brain-derived glial cells, brain capillary endothelial cells, fetal adrenal cells, and human liver carcinoma cell lines (47, 128, 161, 178, 439, 687, 902, 1124, 1165, 1318). Evidence for the absence of a role of the CD4 receptor in virus entry into these cells comes from studies with MAbs to CD4, incubation of virus with sCD4, and lack of detectable CD4 mRNA in the cells (Table 11).

TABLE 10. $CD4^-$ human cells susceptible to HIV infection

In vitro[a]
Fetal astrocytes
Neuroblastoma cell lines (e.g., SK-N-Mc)
Brain-derived capillary endothelial cells
Brain microglia
Osteosarcoma cell line (HOS)
Rhabdomyosarcoma cell line (e.g., RD)
Primary skin fibroblast cells
Fetal adrenal cells
Follicular dendritic cells
Hepatic carcinoma cell line
Bowel adenocarcinoma cell lines
Trophoblast cell lines
In vivo[b]
Bowel epithelium
Renal epithelium
Brain astrocytes, oligodendrocytes

[a] In vitro studies involve cell culture with virus replication detected by reverse transcriptase, p25 antigen, and PCR assay procedures.
[b] In vivo studies include immunohistochemical and in situ hybridization methods (see Section VII G for references).

The extent of virus replication is generally low in the $CD4^-$ cells, and HIV has been shown to enter the cells as well in a pH-independent manner (1165) (see Section VI D). The limited extent of virus production is most probably due to inefficient viral entry; usually fewer than 1% of cells become infected (93, 770). Transfection experiments with DNA molecular clones of HIV suggest that once infection is established, substantial virus replication can occur (671). To detect HIV production in these $CD4^-$ cells, cocultivation of the cells with other sensitive target cells, such as PBMC, has been required (1165). Recent studies suggest that cytokines produced by the PBMC can enhance HIV production in the CD4-negative cells, in particular those of brain origin (1153, 1188).

The nature of the cell surface molecule(s) responsible for viral entry into the $CD4^-$ cells is not known, but entry conceivably could involve a fusion receptor (1165) (see Section VII C). A portion of the viral envelope different from

TABLE 11. Evidence for lack of CD4 protein expression in cells

CD4 protein is not detected on the cell surface by MAbs to the molecule
CD4 protein is not noted in the cells by serologic and immunohistochemical procedures
CD4 mRNA is not detected in cells by Southern blot and PCR procedures
HIV infection is not blocked by pretreating cells with antibodies to the CD4 molecule, e.g., Leu 3a
Infection of the cells is not inhibited by mixing HIV with soluble CD4 protein

that used for $CD4^+$ cell entry seems to be involved since antibodies to HIV differ in their ability to neutralize HIV infection of lymphocytes and $CD4^-$ fibroblasts (1165). This route of entry, however, as noted above, is quite limited when compared with the CD4-mediated process. One conclusion could be that for $CD4^+$ cells, the attachment to CD4 enhances the interaction of the viral envelope with the cellular fusion receptor (see below). Cells lacking the CD4 molecule would use the same means of entry (i.e., a universal one involving fusion), but it would be much less efficient. Likewise, if the cell fusion receptor were absent, infection of $CD4^+$ cells might not occur, as observed with some T-cell lines (568) and fully quiescent $CD4^+$ lymphocytes (see Section XI).

Recently, as noted above, a potential fusion receptor on brain-derived cells has been identified by using rabbit polyclonal antibodies to galactosyl ceramide (GalC) (438). This cell surface product, or a related one, appears to be the receptor for virus entry (71). It binds to a different domain on gp120 (e.g., the V3 loop) from that for CD4 (71). Thus, similar to perhaps a possible cellular fusion domain for paramyxoviruses (738, 1278), a glycolipid could be involved in HIV infection of some $CD4^-$ cells. Most recently, the same receptor has been linked to infection of bowel-derived cells (1307). Whether the GalC mechanism for HIV entry of $CD4^-$ cells is common is not known, but not all brain cells express this glycolipid. Furthermore, antibodies to GalC do not block HIV infection of $CD4^-$ fibroblasts and fetal adrenal cells (47a).

For virus infection, the potential presence of cellular attachment sites for regions of gp41 (963, 1280) needs further evaluation. Moreover, the gp120-binding protein that is a membrane-associated mannose-binding lectin on $CD4^-$ placental cells could be a prototype of other receptors for HIV (213). Recently, a protein receptor of approximately 180 kDa, distinct from GalC, has been demonstrated on $CD4^-$ glioma cells. Binding of recombinant gp120 to this receptor appears to induce tyrosine-specific protein kinase activity in the cells (1055). Its role in virus entry merits attention.

Finally, work demonstrating the lymphocyte function-associated antigen 1 (LFA-1) adhesion molecule as a participant in HIV infection offers another alternative mechanism for viral entry, although its role appears primarily to be in cell-cell fusion (434, 460, 539, 896, 1207) (see Section IX). Perhaps adhesion molecules are important in the cell-to-cell transfer of virus.

H. Cell-to-Cell Transfer of Virus

Besides entering a cell as a free infectious particle, HIV might be passed during cell-to-cell contact. In this regard, evidence that HIV can spread from one cell to another rapidly without forming fully formed particles has been presented (1042). Conceivably, the transfer of nucleocapsids is involved, with subsequent de novo reverse transcription (688). In other studies, macrophage-to-lymphocyte transfer of virus in the presence of neutralizing antibodies has been demonstrated (412). Moreover, HIV can be transmitted from monocytes or lymphocytes to epithelial cells during such close contact that neutralizing antibodies do not block the transfer (924). In these studies, electron micrographs show that complete virus particles are transferred and that they are present at the site of cell-cell contact (Fig. 4). In one recent report, time-lapse photography showed one infected lymphocyte transferring virus particles to several different epithelial cells during short intervals of contact (905). Thus, HIV spread in the host could result from cell-to-cell transfer (via cores or virions) as well as from circulating free virus. During cell-to-cell contact, neutralizing antibodies might not prevent this means of infection.

I. Conclusions

In summary, the leading concept on early events in HIV infection is that attachment of HIV to the CD4 molecule most probably leads to some conformational changes in gp120 and perhaps CD4. The initial attachment appears to be at one site on CD4 (i.e., the CDR2 domain). It most probably involves nonlinear epitopes of gp120 that come into contact with the CD4 site through a specific conformational structure. Subsequent displacement of gp120 or cleavage of the envelope protein (most probably in the V3 loop) by cellular enzymes causes another change in the viral envelope, permitting the interaction of gp41 with the target cell membrane, possibly involving another cell surface receptor; virus-cell fusion subsequently occurs (1045) (Fig. 5) (see Section VII C). Without CD4 expression, fusion of viral gp41 with the cell membrane to bring about infection might take place but might be greatly limited. This pH-independent process could explain infection of $CD4^-$ cells. In some cells, that cell fusion receptor could be GalC (438). Moreover, the roles of the recently described gp41 cell membrane protein (963, 1280) or other cell surface molecules interacting with gp120 (see above) merit further evaluation.

How efficiently the virus core enters the cell to begin reverse transcription might be determined by the specific features of the virus and the CD4 molecule or other cell membrane proteins involved in virus-cell interactions (1124b). Subsequently, the early molecular events following virus nucleocapsid entry can determine the extent of virus replication by the acutely infected cell (see Section XII). Once infection takes place, expression of the CD4 molecule is generally reduced if virus replication occurs, but exceptions have been observed with some strains (see Sections XIV A and C). Finally, HIV spread in the host results from production of infectious progeny and also most probably by cell-to-cell transfer (a summary of events is given in Table 12).

VIII. OTHER POTENTIAL MECHANISMS INVOLVED IN HIV ENTRY INTO CELLS

A. Fc and Complement Receptors

Besides entering cells via the interaction of the virus envelope with cell surface receptors, HIV can infect cells by other mechanisms. For example, during the course of studies on the humoral response to HIV-1 infection, the phenomenon of antibody-dependent enhancement (ADE) of HIV infection was discovered. It involves the binding of the Fab portion of nonneutralizing antibodies to presumably the surface of the virion and transferring the virus into a cell through the complement or Fc receptor (Fig. 6) (482, 646, 980, 1007, 1160, 1191). The former has been shown with fresh serum or plasma from infected individuals or by the addition of complement to heat-inactivated serum (1005, 1007). Fc-mediated ADE has been observed with heated (56°C for 30 min) decomplemented HIV-1-seropositive serum (482, 483, 1160).

In some T-cell and monocyte cell lines and, in one study, primary macrophages, the CD4 molecule was reported to participate in this entry via Fc or complement receptors

TABLE 12. Steps involved in HIV infection of a cell[a]

Attachment of viral envelope to cell surface receptor (e.g., CD4) or alternative receptor
Conformational change in gp120 and perhaps CD4 (i.e., the cell receptor) following attachment
Displacement of gp120
Proteolytic cleavage of the V3 loop or its envelope counterpart (i.e., for HIV-2)
Interaction of the fusion domain of HIV (e.g., gp41) with a fusion receptor on the cell surface (conceivably a glycolipid)
pH-independent viral fusion with the cell membrane
Entry of viral RNA associated with core and polymerase proteins into the cytoplasm
Production of viral DNA copy (cDNA) from viral RNA and duplication into a double-stranded DNA structure. Generation of covalently bound circles and noncovalently bound circular forms
Transport of cDNA to the nucleus, followed by integration of the noncovalently-bound forms into chromosomal DNA
Production of viral mRNA and viral genomic RNA from the integrated proviral DNA. The extent of production depends on relative expression of HIV regulatory genes (e.g., *tat*, *rev*, *nef*) (see Section XI)
Production of viral proteins from full-length and spliced mRNA
Incorporation of viral genomic RNA into the capsid forming at the cell membrane
Processing of Gag and Gag-Pol polyproteins at the cell surface or in budding virions
Budding of the viral capsid through the cell membrane with incorporation of the processed viral envelope glycoproteins present on the cell surface (can depend on the viral *vif* gene product)

[a] Summarized from discussions in Sections VII and XI.

(914, 1007, 1159, 1331). The proposed process is that these alternative cellular receptors bring the virus closer to the CD4 molecule for subsequent entry. However, from other studies with peripheral blood macrophages, T lymphocytes, and CD4$^-$ human fibroblasts, the CD4 protein did not appear to be required for entry (482, 763). Thus, the complement and Fc receptors could serve as alternative sites for virus infection although the mechanism of entry is still not defined.

Fc-mediated infection by HIV highlights a potential role of

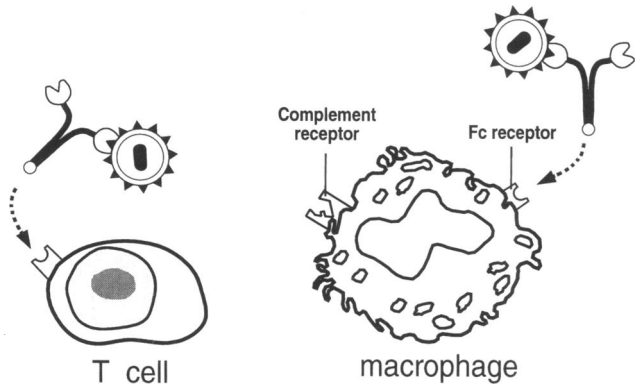


FIG. 6. Mechanism of antibody-dependent enhancement of HIV infection. The antiviral antibody binds to the viral envelope glycoprotein. This virus-antibody complex can then enter cells (T cells and macrophages shown here) through an interaction of the Fc portion of the antibody with either the cellular Fc or complement receptor (after complexing with complement). Reprinted from reference 669 with permission.

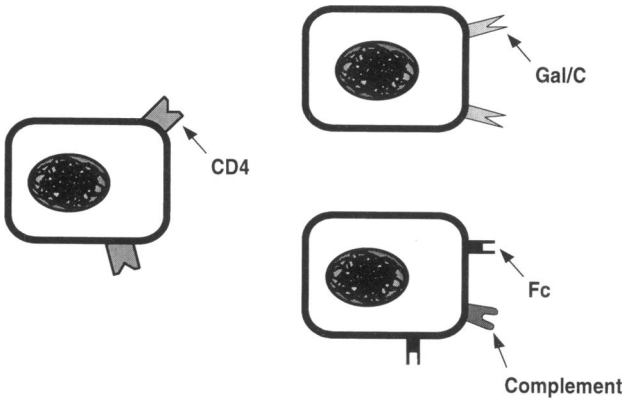


FIG. 7. Four different cellular receptors that can be used by HIV to enter cells.

herpesviruses as cofactors in HIV infection. These viruses can induce Fc receptors on the surface of infected cells (53, 557, 967, 1277) that can then serve as potential target cells for HIV. Studies with CMV infection of CD4$^-$ fibroblasts have demonstrated the appearance of Fc receptors on the cell surface. Subsequently, the CMV-infected cells were susceptible to HIV infection through antibody-virus complexes (763). Fc receptors have also been detected on rectal mucosal cells (500). Thus, conceivably, infection could take place in the anal canal via antibody-virus complexes in seminal fluid. In summary, at least four different cellular receptors could be involved in HIV infection (Fig. 7).

Further serologic studies with individuals infected with HIV are needed to answer the question of the clinical relevance of ADE. This phenomenon has been well described in other viral systems (428, 910). In dengue virus and perhaps in other lentivirus infections (e.g., caprine arthritis-encephalitis virus and equine infectious anemia virus), the process has been associated with a more severe clinical course (428, 508, 586, 759) (see Section XXII C).

B. Phenotypic Mixing: Pseudotype Virion Formation

Another mechanism for HIV entry into cells is phenotypic mixing (81, 496, 1225). By this process, a viral genome can be within the envelope of a different virus and thus have the host range of that virus. Phenotypic mixing between HIV-1 and HIV-2 strains has been described (655). Moreover, cells coinfected by HIV and murine retroviruses have demonstrated pseudotype virion formation in which the HIV genome can be found within the envelope of different mouse retroviruses (123, 167, 168, 723, 1119). Subsequently, HIV could infect a wide variety of cells susceptible to these animal retroviruses (Fig. 8). In addition, HIV pseudotypes have been produced in vitro with herpesviruses and rhabdoviruses (e.g., vesicular stomatitis virus) (1265, 1334).

The vesicular stomatitis virus pseudotypes have been helpful in defining the cellular restrictions to HIV entry (1265, 1266). Cells exposed to a virus containing the vesicular stomatitis virus genome within the HIV envelope show vesicular stomatitis virus-induced lysis only if they are susceptible to HIV infection. Finally, in vitro phenotypic mixing among different human retrovirus groups (e.g., HTLV and HIV) has also been described (168, 625, 655, 1334). In preliminary studies, however, we have not observed this process occurring during coinfection of cells with HIV and the human spumavirus (670a). In summary, viruses

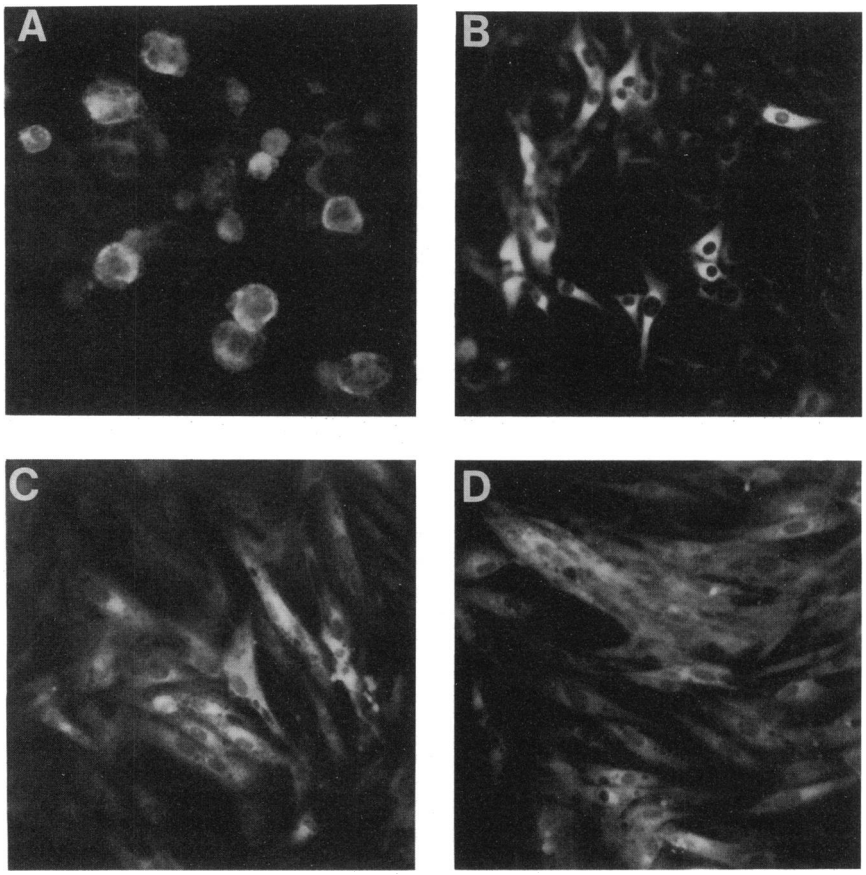


FIG. 8. Coinfection of a human T-lymphocyte line with HIV-1 and the murine xenotropic retrovirus led to virus preparations that contained phenotypically mixed particles. Thus, the HIV-1 genome enveloped in a xenotropic virus coat could infect a wide variety of animal cell lines previously resistant to HIV-1 infection. Infection by HIV is demonstrated by indirect immunofluorescent antibody staining. (A) HUT 78 human T cells; (B) mink lung cells; (C) horse dermis cells; (D) goat esophagus cells. Magnification, ×40. Reprinted from reference 123 with permission.

that can undergo phenotypic mixing with HIV-1 are listed below.

- HIV-2
- HTLV-I
- Murine xenotropic, amphotropic, and polytropic type C retroviruses
- Vesicular stomatitis virus
- Herpesvirus

Whether pseudotype virus formation occurs in nature is unknown. Although not recognized in vivo, HIV-infected individuals coinfected with herpesviruses or with HTLV-I could have virus populations representing phenotypic mixtures with these two agents (625, 1334). Moreover, as noted above, infection in vivo by HIV-1 and HIV-2 might, under some circumstances, lead to phenotypic mixing of the two virus subtypes (655). The consequences of these events could include increased pathogenesis. The observations in vitro have also suggested that the use of animal models for studying HIV infection must recognize that phenotypic mixing with an endogenous virus in the animal (e.g., mouse) (540, 815, 816, 836) could compromise the study objectives. Thus far, a problem with this phenomenon in mice with severe combined immunodeficiency (SCID) has not been observed (814).

Finally, whether recombination could occur between the genomes of two different viruses infecting the same cell must be considered, particularly if heterotypic viruses form (495) (i.e., the two RNA species within a virion core come from different viruses). This event could produce new viruses with different biologic and pathogenic properties.

C. Interference and Superinfection

(i) Cellular level. With most retroviruses, the cell after infection becomes resistant to superinfection by a similar virus. The mechanism for this interference appears to be the elimination or covering of the cell surface receptor needed for viral entry (1129, 1226). This conclusion is supported in the HIV system in which superinfection cannot occur if the CD4 molecule is down-modulated (168, 444, 655). Yet the previously infected cells can replicate a different HIV-1 strain if its DNA molecular clone is transfected into the already infected cells (655). The block to superinfection is primarily at the cell surface and is not intracellular.

The lack of viral interference has been proposed as one cause of the cytopathology of HIV strains. Before cells down-modulate CD4, continual infection of these cells by the progeny HIV can take place. This superinfection can lead to an accumulation of unintegrated viral DNA that is associated with cell death (see Section X) (70, 903, 1001, 1325). However, cells infected by the relatively noncyto-

pathic HIV-2_{UC1} strain continually express CD4, produce high titers of virus, and remain viable (282, 655). Whether these cells lack accumulation of extrachromosomal viral DNA copies is not known.

These observations suggest that the relatively slow decrease or lack of elimination of the major viral receptor could lead to cells that are superinfected by the same or related HIV strains. Recently, the potential role of the CDR3 domain of the CD4 molecule in superinfection has been suggested, if it is still expressed after the initial infection when the major CD4 receptor site for HIV-1 (e.g., OKT4A) is absent (866). The phenomenon of superinfection would appear possible in vivo since $CD4^+$ cells infected with HIV but not producing the virus have been recovered from separated PBMC from infected individuals (953, 1246). Conceivably, these represent relatively nonactivated cells that carry virus for a short period (see Section XI) or virus in a latent state. These cells might be superinfected before the initial virus infection is aborted. The resulting progeny virions then could consist of phenotypically mixed particles and even recombinant viruses. Nevertheless, in limited studies of individuals infected with both HIV-1 and HIV-2, one cell producing both viruses has not been detected (283).

(ii) Within the host. The term "superinfection" is also used to denote infection of an individual by more than one HIV strain. In this regard, individuals with both HIV-1 and HIV-2 infection have been documented (283, 976), although this event is most probably uncommon. Moreover, chimpanzees can be simultaneously infected by more than one HIV-1 strain (136, 332). In both these cases, recovery of two distinct viral strains from the same cell has not been reported.

The prevalence in vivo of infection by multiple strains is unknown but is also probably rare. Early and late in infection, viruses studied by PCR procedures seem related to a dominant strain (765). Even if the initial infection potentially involved several viral isolates (e.g., recipients of many factor VIII units or multiple blood transfusions) a predominant HIV-1 strain seems to emerge; others, if present, are presumably suppressed or eliminated by the dominant strain and/or the host immune response. Moreover, with subsequent exposure to a new virus strain, the relative number of incoming virus particles could be quite small compared with the quantity of virus already present in the blood and lymph nodes of the individual. Thus, the chance of establishing an infection with another strain would seem unlikely (670). Furthermore, as discussed later (Section XXIII D), $CD8^+$ cells could establish a relative state of resistance in the PBMC so that superinfection of the host would be limited (546). Moreover, as shown in cell culture studies with PBMC, superinfection might be prevented by the antiviral antibodies produced by B cells (1192).

IX. HIV INDUCTION OF CELL FUSION: CYTOPATHOLOGY

An important biologic feature of HIV infection is the formation of multinucleated cells in culture (and perhaps in the host), resulting from the fusion of infected cells with uninfected $CD4^+$ cells (Fig. 9; see also Fig. 13A) (694, 695, 698). Syncytium formation is often the first sign of HIV infection in culture and can appear within 2 to 3 days; accompanying this cytopathic effect is balloon degeneration of the cells, most probably resulting from membrane permeability changes (see Section XVII A) (Fig. 9). This cell-cell fusion does not require DNA, RNA, or protein synthesis (288, 435, 1163).

Whether this process is directly related to virus-cell fusion is not clear. The cell fusion event, as shown by specific antibodies, also involves the CD4 molecule and both the HIV gp120 and the gp41 envelope proteins (304, 324, 435, 604, 694–696, 698, 747, 1024, 1109, 1138). Moreover, it could be influenced by the pattern of viral envelope glycosylation (296), as well as by the extent of proteolytic cleavage of gp160 within the cell (86).

Regions of CD4 and gp120 different from those used for viral attachment can also play a role in the cell-cell fusion (120, 697, 944). As cited above (see Section VII C), certain MAbs to CD4 will not block virus binding but prevent cell fusion and infection (39, 141, 452, 1195, 1284). Interviral recombinants have demonstrated that syncytium formation is linked to specific regions in the gp120 (160, 1314) and, in some mutational studies, the V3 loop (237, 325, 326, 888, 1190). The latter was suggested by earlier work in which cell-cell fusion was blocked by the RP135 (amino acids 307 to 330) peptide of HIV-1 gp120 (1024). In other studies with both HIV-1 and HIV-2, gp41 was noted to contain an important determinant for this process (304, 324, 325, 912, 1131). However, it is still not clear which viral epitopes are directly involved versus those that influence this biologic event.

Moreover, the role of cellular membrane proteins such as the adherin LFA-1 in cell-cell fusion has been emphasized (460) (see Section VII C). MAbs to this cell surface protein block cell aggregation and syncytium formation but not virus infection (896). In addition, the absence of fusogenic activity of murine cells that express the human CD4 molecule when mixed with HIV-infected cells appears to reflect the lack of a human cell surface factor (260, 1173). Its relation to a fusion domain for gp41 proposed as a means for HIV entry has yet to be determined. Nevertheless, events involved in cell-cell fusion may be distinguishable from those mediating virus-cell fusion (see Section VII C).

The process of cell fusion has been linked to viral cytopathicity (see below) and cell death (694). Some investigators believe that this phenomenon is important in $CD4^+$ cell depletion in the infected host (for reviews, see references 349 and 447), but evidence of multinucleated cells in vivo, except in the brain (668, 893, 1077, 1078) is lacking. Moreover, in other retroviral systems, multinucleated cells can remain viable for long periods (662).

X. VIRAL EXTRACHROMOSOMAL DNA ACCUMULATION AND CELL DEATH

Besides cell-cell fusion, the cytopathology and cell death occurring during acute HIV infection in vitro are often associated with an accumulation of viral cDNA in the cytoplasm of the cells (676, 1082). Whether this process occurs during virus infection in vivo is not known. In the brain, neurologic damage has been found associated with large amounts of unintegrated HIV DNA in the cells (893). The possible role of superinfection in this process is discussed in Section VIII C. Similar observations have been made with infected T cells arrested in division (1164). In this case, continued production of the unintegrated cDNA could be the cause of cell death since viral progeny are not produced. The same phenomenon linked to cytopathology has been previously reported with in vitro infection by the avian spleen necrosis virus (562, 1269).

These observations support the conclusion that high levels

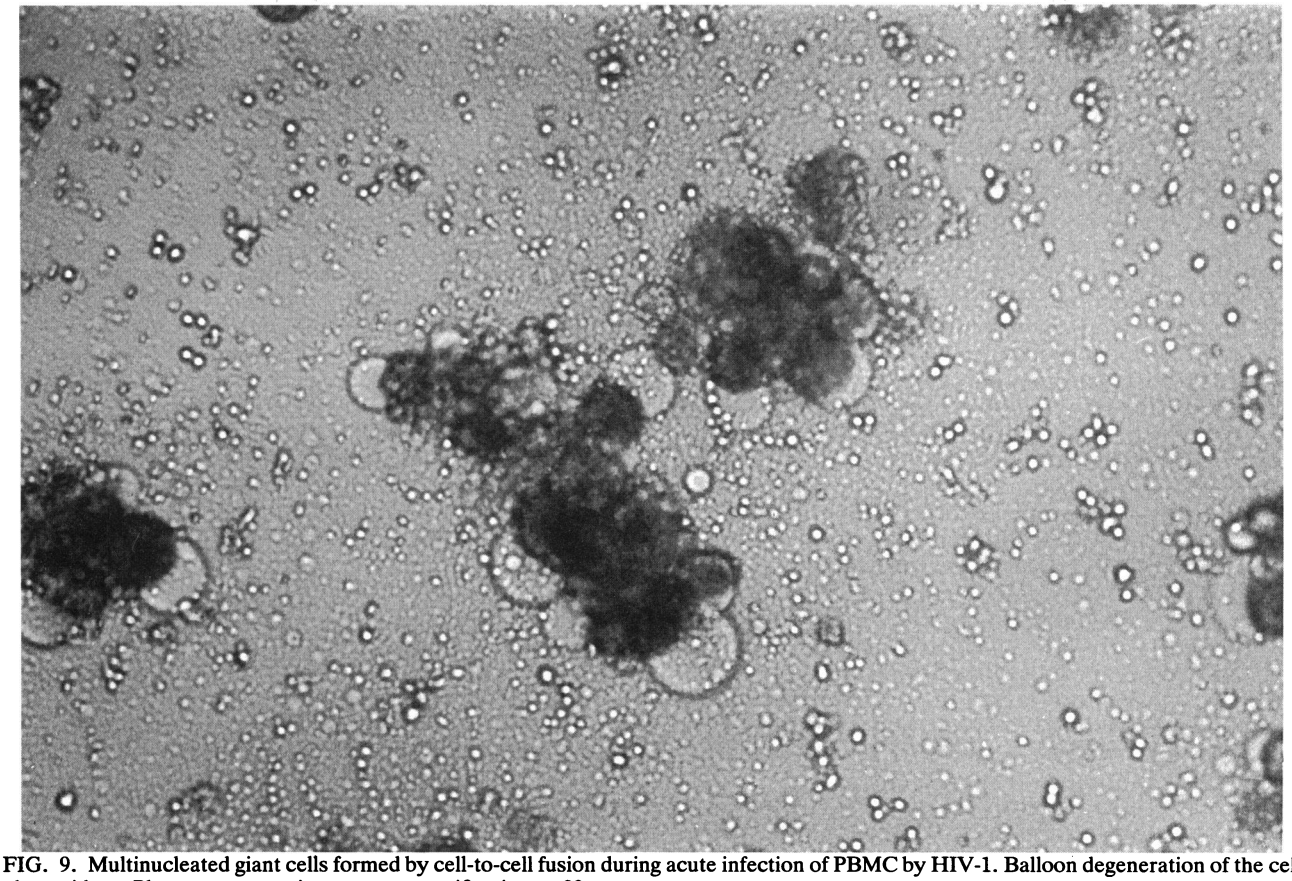


FIG. 9. Multinucleated giant cells formed by cell-to-cell fusion during acute infection of PBMC by HIV-1. Balloon degeneration of the cells is also evident. Phase-contrast microscopy; magnification, ×80.

of intracellular viral DNA can be toxic to the cell and, in the early events of infection, could contribute to the initial cell killing observed (676, 1083). Nevertheless, single-cell killing is not always associated with accumulation of viral DNA in the cytoplasm (64, 1112) (see Sections IX and XVIII A). Moreover, accumulation of extrachromosomal viral DNA sequences has been reported during a latent HIV infection of a monocyte cell line, although in this case the DNA was methylated (1103). Finally, as discussed above and in other sections of this review, a variety of processes can be involved in cell death, reflecting the cellular toxicity of viral proteins and cellular products (see Sections IX and XVIII A). Thus far, the focus has been on cell-cell fusion and intracellular accumulation of viral DNA that might occur early in HIV infection.

XI. VIRUS INFECTION OF QUIESCENT CELLS

A. $CD4^+$ Lymphocytes

Steps leading to productive viral infection and the consequences of that infection have been discussed. What happens when HIV encounters a resting lymphocyte is another important question. The initial experiments with HIV infection of lymphocytes indicated that virus replication occurred best with antigen- or mitogen-induced activation (50, 736). Studies with nondividing peripheral blood $CD4^+$ T cells have provided other information on the potential initial events involved in efficient virus infection and progeny production. The results indicate that the level of cell activation can influence the extent of viral reverse transcription and infectious virus release from the cell (Table 13).

Cells completely blocked in DNA synthesis and kept inactivated (at G_0) (e.g., no human leukocyte antigen-DR [HLA-DR] and low CD25 expression) cannot be infected by HIV (393, 1163a). These cells, despite the expression of CD4, show no evidence of viral entry by subsequent cell activation procedures that can induce infectious virus production in culture. The reason for this cell resistance is not known but could be related to expression of a viral fusion receptor only on activated $HLA\text{-}DR^+$ $CD4^+$ cells. In this regard, the DR molecule is not directly involved since antibodies to it do not block HIV infection (1163a).

In contrast to the above observations on nondividing cells, some investigators have reported that resting $CD4^+$ lymphocytes can be infected in vitro but that virus replication is

TABLE 13. Studies of quiescent cells

Characteristic	Reference
Virus replication is blocked at virus entry	393, 1163a
Virus enters but is blocked in reverse transcription[a]	1320
Virus enters and is reverse transcribed but is blocked at viral integration[a]	1141
Virus enters and integrates into a resting cell (e.g., epithelial cell), with subsequent virus replication	684

[a] HIV can be produced after activation of the cell (see Section XI for a discussion).

arrested. Unintegrated viral cDNA forms can be detected by PCR in T cells from a few days to 2 weeks after the initial infection (1141, 1320). Upon activation, these cells can be induced to release infectious progeny viruses. These studies have suggested that HIV enters the quiescent cells but that in some cases, only limited portions of the viral gene are transcribed (1319, 1320); no viral proteins are produced. In certain cases, if these cells are not fully activated within 3 to 5 days, the infection is aborted (1320). In other situations, more extensive cDNA viral forms are made within the cell and this unproductive viral infection can last for 2 to 4 weeks (1141, 1163a). Most recent studies suggest that following infection, this preintegration complex is rapidly transported to the nucleus by a process requiring ATP but not cell division or a functional viral integrase (108).

These observations in vitro, using purified quiescent $CD4^+$ cells, have also been applied to clinical specimens. Purified $CD4^+$ cells from asymptomatic individuals were found to consist of a large percentage of resting cells that contain primarily unintegrated viral DNA forms (109). These cells were reported to lack DR expression, but a low level of DR^+ cells (0.3%) was present in the cell population (109). In our studies, this amount of contaminating DR cells is sufficient to permit HIV infection in vitro. In individuals with AIDS, the recovered $CD4^+$ cells were primarily DR^+ and had integrated HIV with expression of viral RNA. These in vivo observations mirror in part those already obtained by using PCR analysis on PBMC specimens; asymptomatic individuals show very little expression of viral RNA (1100) (see Section VI B).

These findings support the conclusion that in many $CD4^+$ cells of asymptomatic individuals, HIV can be present in an unintegrated noninfectious form for perhaps many more days than appreciated by studies in cell culture. Whether it can code for certain viral proteins (e.g., Gag), as has been reported with integrase-deficient HIV strains (1139), should be examined. It will be interesting to determine whether the $CD8^+$ cell factor that suppresses virus replication and prevents virus superinfection (546, 725) could contribute to this arrest in viral replication in the quiescent cell in vivo (see Section XXIII D). Moreover, conceivably the free virus in the plasma (see Section IV A) could be the source of repeated infection of quiescent cells that, unless activated, eventually lose the viral cDNA forms. If virus replication does not occur, CD4 expression would remain intact, so reinfection would be possible (see Section VIII C). Thus, cycles of virus infection and virus removal could characterize a dynamic situation in cells within an infected individual.

These observations in vitro and in vivo on limited reverse transcription of HIV in quiescent cells require further study. For example, heterogeneous viral DNA has been found within the HIV virions (716, 1193). Whether this DNA is responsible for the low-level DNA detected by PCR in the resting-cell experiments (1320) has yet to be determined. The partial reverse transcripts might be those associated with viruses bound to the cell and not internalized or those failing to continue their replicative cycle. Moreover, the intracellular factors that might influence the extent of virus production have not yet been identified. Most probably they involve cellular DNA-binding proteins (e.g., NF-κB) (see Section XII B).

The difficulty in resolving these different findings with resting cells revolves around the definition of quiescence. If a small number of DR^+ cells are present in the inoculated cell population in vitro, they could misleadingly indicate, by the PCR analysis used, successful virus entry into all cells. In our experiments, this possibility was well controlled by the elimination of all DR^+ cells. Moreover, in the experiments of Zack et al. (1320) and Stevenson et al. (1141), removal of macrophages was not rigorously performed. These nondividing cells can be infected (see below). Nevertheless, full-level virus replication was not achieved, even in the relatively pure quiescent cells described in these studies. Thus, the findings do suggest that virus entry and expression appear to be influenced by the state of cell activation. The length of time a cell could carry the unintegrated viral DNA must also reflect the level of its activation (109, 1141, 1320).

Finally, how quiescent $CD4^+$ cells lacking DR expression become infected in vivo is also unknown (109), since their infection in vitro does not appear possible (1163a). Whether a DR^+ $CD4^+$ lymphocyte can, after infection, return to a quiescent DR^- state must be determined. Preliminary evidence in our laboratory suggests that this is possible (1163a). Alternatively, as noted above, the few quiescent $CD4^+$ cells found infected in vivo (109) could be the few DR^+ cells present in the resting-cell population (0.3%).

B. Monocytes

Studies of peripheral blood monocytes also suggest that intracellular as well as cell surface events are needed to permit productive infection. Monocytes found in the blood are not very susceptible to HIV infection, despite >90% expression of the activation marker, HLA-DR (984, 1062, 1164, 1208); differentiation into macrophages is required. Perhaps specific cell surface receptors are involved, but, interestingly, nondifferentiated monocytes have more CD4 expression than differentiated macrophages (197, 552a). Although in one study, proliferation of the macrophages was needed for infection (1062), most studies indicate that HIV can infect a nondividing differentiated macrophage (1163a, 1259). Integration probably takes place but has not been definitively demonstrated (274b). In our experiments, purified peripheral blood $CD4^+$ monocytes were inoculated with HIV in suspension, washed, and maintained for several days without attachment to plastic dishes. Virus production was very low even after the cells differentiated into macrophages. Unless the cells were permitted to attach and differentiate in culture before infection, efficient HIV infection did not take place (1163a). At the time of differentiation, cell division had stopped but productive infection took place. Nevertheless, terminally differentiated macrophages are also not very susceptible to HIV infection (670a, 1208).

These observations place further emphasis on tissue macrophages as the primary site of virus replication. In some studies, monocytes in the blood have been found by PCR techniques to be infected (531), but this observation has also only been reported in a few studies and for a small number of cells (757). HIV could at times infect but remain quiescent in a nondifferentiated circulating monocyte, but infection most probably occurs best after differentiation in the tissues. Perhaps the lymphadenopathy accompanying acute HIV infection (202) (see Section V) reflects virus present initially in the lymph nodes.

Following HIV infection, these tissue macrophages in turn could pass the virus to T cells but only after they are activated. Resting $CD4^+$ cells in the G_0 phase and lacking HLA-DR expression cannot be infected when cocultured with virus-releasing macrophages (1163a). Essentially, the macrophage in the tissues, particularly lymphoid organs, can

be a major reservoir for production and spread of HIV in the host.

C. Other Cells

Recently, Lewis et al. (684) have demonstrated that nondividing human epithelial cells expressing the human CD4 molecule can be infected by HIV; virus integration into the cell chromosome takes place (Table 13). The murine type C retroviruses that can infect human cells do not show this biologic activity; no infection occurs. The reason for the productive infection of these nondividing epithelial cells by HIV is not known, but it does not appear to involve any of the viral regulatory or accessory genes. Conceivably, a portion of the viral polymerase or the integrase gene is responsible. The observation further demonstrates differences in the ability of HIV, and conceivably lentiviruses, to infect resting or nondividing cells and offers some direction for obtaining vectors that might be useful in gene therapy of resting stem cells. Nevertheless, observations on resting T cells cited above suggest that productive infection of quiescent cells could be cell type specific (Table 13).

XII. INTRACELLULAR CONTROL OF HIV REPLICATION

A. Early Intracellular Events

Once the virus has entered the cells as a ribonucleocapsid, several intracellular events take place that lead to the integration of a proviral form into the cell chromosome. The viral RNA, still associated with core proteins, undergoes reverse transcription, using its RNA-dependent DNA polymerase and RNase H activities, and eventually forms double-stranded DNA (for reviews, see references 400 and 1205). These DNA copies (cDNA) of the viral RNA then migrate to the nucleus, where, as circular but noncovalently bound molecules, they integrate into the cell chromosome. This integration of the provirus appears to be random and is essential for the cells to produce progeny virions. Whether HIV can be produced without integration of the provirus is still not known. This phenomenon has been described for the visna lentivirus (443), although it has not been confirmed.

Recent observations, described above (see Section XI), on the early events in viral infection have revealed noteworthy features of HIV replication. In T cells arrested in division, virus infection is abortive, whereas in nondividing macrophages or epithelial cells, progeny production takes place. In permissive activated T cells, HIV undergoes integration and replication within 24 h (571). In macrophages, the process is similar but progeny production appears to occur after 48 h (826). The earliest mRNA species made in the infected cell have a low molecular weight, representing the viral LTR and other major regulatory genes, particularly *tat*, *rev*, and *nef* (398, 400, 569). It appears that Tat is made first and upregulates the subsequent production of Rev. The interactions of these regulatory genes have been discussed previously (for reviews, see references 398, 400, and 1205). Presumably, the predominance of one of these viral gene products can determine whether HIV infection will lead to a productive or latent state (see Sections III B and XII B). The presence of Tat at high levels will stimulate substantial virus production (231, 303). Expression of Nef could induce a latent state (717) (see Section XIII B).

The Rev protein appears to provide a balance in expression of Tat and Nef and encourage the production of large unspliced mRNA species responsible for the other essential viral gene products giving rise to infectious viruses (294, 1109, 1110) (for reviews, see references 400 and 1205). In the late stages of the virus replicative cycle, Rev could downregulate its own production and cause decreased progeny virus formation and perhaps latency. In cells not fully permissive to HIV replication, the relative expression of these regulatory proteins can differ, leading to abortive infection, low persistence, or a latent state (44, 939) (see Sections XI and XIII).

B. Differences in Virus Production: Role of Intracellular Factors

(i) Biologic studies. How the state of T-cell activation and monocyte differentiation can influence the extent of viral expression has been discussed. These observations emphasize the role of intracellular factors as well as cell surface proteins in the HIV replicative cycle. Although the HIV LTR can be its own promoter, early mRNA transcription appears to rely primarily on the binding to the LTR by cellular transcription factors such as nuclear factor kappa β (NF-κB), NFAT, AP-1, SP-1, and the Tat-binding proteins (for reviews, see references 356 and 1186). Thus, the intracellular milieu can determine the relative dominance of viral regulatory proteins in an infected cell (see Section XII A).

Further evidence of this intracellular control is provided by biologic studies showing variations in replication of HIV strains in different cell lines, macrophages, and PBMC from various donors (134, 135, 188, 281, 682, 867a, 1228). Variations in infectibility of macrophages from different sites in the body have also been reported (867a). Viral binding and entry can be similar, but the postpenetration events differ, so that titers of progeny viruses produced vary widely. The data for HIV infection of PBMC are most dramatic, and the various intracellular factors responsible could influence virus spread and pathogenesis in the host (669).

These differences in intracellular replication of HIV can be studied post entry by transfecting molecular cDNA clones of HIV-1 into cells. The results again show variations depending on cell type. In general, human cells replicate HIV to higher levels than do cells of other animal species, particularly murine cells (671). Similar observations are made with phenotypically mixed particles that introduce the HIV genome into heterologous cells via a different viral envelope (123) (see Section VIII B). After undergoing reverse transcription from their own RNA genome, the respective viruses replicate in cells to various degrees. These observations demonstrating intracellular control of virus replication have been made with other retroviruses (662). They suggest the presence of a cellular inhibitory factor or the relative lack of a cellular product needed for viral replication.

In this regard, some studies with human-animal cell hybrids have suggested the dominance of the permissive state for virus replication. Thus, the absence of a particular cellular protein appears to limit viral production. Human-hamster and human-mouse cell hybrids have implicated human chromosome 12 in coding for a permissive factor that enhances Tat activity (19, 445, 846). Its identity is not yet clear, but a 36-kDa human cellular protein that binds to Tat has been reported. On microinjection, it was found to increase the efficiency of Tat transactivation in murine cells (245). This observation needs confirmation.

Other cellular proteins that could influence virus replication are those reported to increase Tat binding to the TAR (19). Recent experiments suggest that two related cellular

Tat-binding proteins might compete to up-regulate (e.g., MSSI) or down-regulate (e.g., Tat-binding protein 1) Tat activity and thereby affect HIV production (840, 1089). Their mechanisms of action need further elucidation. In other experiments, resistance of a cell to HIV infection has been dominant, and a factor in murine cells that acts against the *rev* gene has been described (1194). The potential for using these observations with Tat and Rev for antiviral therapy merits further evaluation.

(ii) Effect of T-cell activation. The processes involved in T-cell activation are not fully defined but are involved in HIV replication via the interaction of intracellular factors with regions in the viral LTR (323, 346, 528, 551, 834, 1303; for a review, see reference 356). This activation is part of a signal transduction process by which the binding of antigens or mitogens to the surface T-cell receptor (CD3) and CD28 molecules affects gene expression within the cell. The activation is mirrored by an increase in the concentration of intracellular free calcium and depends on the subsequent activation of calcium-dependent protein kinase C (PKC) and other phosphorylation events (356, 507, 574, 1187, 1262).

Following these events in T-cell stimulation, cellular proteins are released, most likely from intracellular inhibitors (e.g., NF-κB from its inhibitor, IκB) (856), probably via phosphorylation by PKC. They enter the nucleus, where binding to other cellular proteins and, in the case of HIV, attachment to viral DNA sequences take place. The interaction of these cellular transcriptional factors with viral LTR regions can up-regulate viral replication. Identification of all the cellular factors involved is an ongoing endeavor, but many of them have been recognized (for a review, see reference 356). Certain cytokines, as well as transactivating proteins encoded by other viruses, can also increase HIV production via these intracellular events (574) (see Section XII C).

With HIV infection, a displacement of the Src-family tyrosine kinase, $p56^{lck}$, from the CD4 molecule could be involved with subsequent activation of PKC, thereby leading to increased virus production (356, 1187). Since $p56^{lck}$ appears to have a variety of intracellular targets such as the interleukin-2 (IL-2) receptor (449), it could either directly or indirectly affect the activity of cellular factors binding to the HIV LTR. In some reports, attachment of native gp120 to CD4 alone has activated the $CD4^+$ lymphocytes as measured by an increase in intracellular inositol triphosphate and calcium levels, as well as an induction of the IL-2 receptor expression (301, 598). This observation, however, has not been confirmed by others, who have shown no effect of HIV binding on cellular or CD4 phosphorylation patterns, CD4-associated $p56^{lck}$ kinase activity, or calcium influx (871, 1235). Furthermore, the calcium channel inhibitor verapamil has shown no effect on HIV entry (871). Thus, a role for calcium influx in the initial events in HIV infection of T cells is not established. Nevertheless, as discussed in Section XIX, gp120 can induce calcium influx in certain neural cell lines by a mechanism blocked by verapamil; however, this process does not involve the CD4 protein (262). In brief, signaling via CD4 does not seem important in HIV production.

Cytokines (particularly tumor necrosis factor alpha [TNF-α]) and other external stimuli have also shown various effects on HIV expression via interaction with the viral LTR, usually depending on their influence on intracellular transactivating factors, particularly NF-κB (140, 266, 436, 574, 607, 874, 934, 1125, 1210; for reviews, see references 745, 933, 1016, and 1234). For example, TNF-α increases HIV production (see Sections XIV B and XVIII G). Moreover, some viruses, such as CMV and herpes simplex virus, can enhance HIV production through activation of the viral LTR—a process that, in some cases, is mediated by a cytokine (812, 920) (see Section C below).

Finally, the viral *tat* gene product, after interacting with cellular factors, binds to the TAR of the viral LTR in conjunction with cellular RNA-binding proteins (1186, 1205, 1304) that may be phosphorylated (432). Up-regulation of viral expression takes place (see Section XII A). The induction of TNF-α production in T cells by HIV Tat could also be involved in increasing virus production (110). A role of cellular factors in increasing subsequent Tat function is also under consideration. The Nef protein could also suppress virus replication through an interaction with cellular proteins (159) (see Section XIII B). All these observations reflect how both viral and cellular factors, working together, can affect HIV replication.

C. Effect of Other Viruses on HIV Replication

As cited above, some viruses can enhance HIV production via induction of cytokines. Other experiments have shown that coinfection of cells with certain viruses, including herpesviruses, papovaviruses, hepatitis viruses, and retroviruses, can increase the expression and production of HIV-1 by another mechanism. Generally, these studies have demonstrated that transactivating factors produced by the infecting virus, usually early-gene products, interact directly or via intracellular factors with the HIV LTR, usually at the κB region. As examples, CMV, human herpesvirus 6 (HHV-6), and EBV have been shown to activate the HIV LTR as measured in cell culture by the chloramphenicol acetyltransferase (CAT) assay (13, 230, 361, 372, 486, 545, 556, 968, 1096, 1222; for reviews, see references 642 and 841) (see Section XXV). Some studies, however, indicate that this activation of HIV replication by DNA viruses can involve regions of the viral LTR independent of the normal cellular activation pathways (835; for a review, see reference 356).

These molecular studies, showing increased expression of the HIV LTR induced by other viruses, have been supported by some observations in vitro with dually infected cells. HIV production is increased (133, 381, 455, 722, 1108). However, in other studies with coinfected cells, CMV, HHV-6, and EBV were found to inhibit HIV replication (132, 602, 677). The differences observed probably reflect the cell types, the viral strains used, or both.

Moreover, some biologic assays involving HTLV-I and other animal retroviruses have demonstrated an increased production of HIV after coinfection (123, 437). Similarly, some B-cell lines already transformed by EBV appear to replicate virus best, perhaps resulting from a postinfection process (218, 798, 799). Even mouse fibroblasts infected with murine retroviruses replicate HIV to higher levels after transfection than do the murine cells alone (945a). The mechanism(s) for this enhanced expression of HIV in the coinfected cells is unknown but again could reflect a cross-reaction with the HIV LTR by induced cellular factors.

XIII. LATENCY

A. Cellular Latency

The discussion of HIV infection indicated that some nonactivated cells can harbor the HIV genome in an unintegrated state for several days without evidence of virus

replication (see Section XI). This type of silent infection in cells differs from the classic state of viral latency, in which the full viral genome is in the cell but expression is suppressed. For retroviruses, no viral RNA or protein would be expressed from the integrated provirus in the cell chromosome (212, 310, 663). Subsequently, conditions within the cell would alter its state so that HIV replication and spread and cell death occur. Although cellular latency is demonstrable to some extent in vitro, it is not known to what extent it exists in vivo. Nevertheless, PCR and in situ PCR studies suggest that, in the host, HIV-infected $CD4^+$ lymphocytes and macrophages that do not express viral RNA and protein are frequently present (274a, 1100). Moreover, infected lymphocytes can be recovered from the PBMC of infected individuals, and these cells express CD4 conceivably because they are not producing progeny virus (1058, 1246). Thus, a reservoir of latently infected cells in the host could be a common phenomenon in HIV infection.

In one of the first in vitro studies of HIV cellular latency, Hoxie et al. (491) reported long-term culture of naturally infected human $CD4^+$ lymphocytes that did not express much virus until several weeks after culture. Then, high levels of HIV were spontaneously produced, and this was followed by cell death. Recently, clones of $CD4^+$ lymphocytes isolated from seronegative donors have been shown after infection in vitro to harbor virus in a latent state (148). This cell culture system, if confirmed, should lend itself to future studies of silent infections in vivo.

Fauci and coworkers have used established cell lines such as the infected U-1 and ACH-2 cell lines to study cellular latency; these cells produce relatively low levels of HIV (309, 312, 934). The lines were derived from established monocyte (U-1) or T-cell (ACH-2) lines chronically infected with $HIV\text{-}1_{LAV}$ and generally show only 2-kb mRNA (781, 939). Thus, they appear to lack production of Rev (1015, 1110, 1205) and to some extent, resemble certain Nef-expressing cells (see Section XIII B). A possible effect of low Tat expression should also be considered. When the cell lines are activated, for example by treatment with a variety of cytokines (e.g., TNF-α, IL-1, phorbol esters, and granulocyte colony-stimulating factor), viral RNA and infectious-virus production is markedly increased. This response is often in association with activation of the cellular NF-κB protein that binds to the viral LTR (for reviews, see references 266, 310, 311, 436, 834, 835, 874, 934, 1016, and 1186). During this activation process, a shift in mRNA patterns occurs, with a reduction in spliced mRNA and an increase in unspliced mRNA (781). Thus, expression of Rev does appear to be involved.

Moreover, silent infection of monocytes has been reported with mutant HIV-1 strains lacking *vpu* or *vpr* functions (1275). Virus can be recovered by cocultivation with uninfected PBMC. A similar observation on this amplification of HIV release by adding PBMC to the cultures has been made with established cell lines and HIV-infected macrophages (281, 310, 1060, 1206). Thus, this "latent" state in monocytes could reflect arrest in virus release rather than earlier events involved in virus infection. The mechanism has not been elucidated.

In other studies, halogenated pyrimidines, UV irradiation, and heat shock have led to virus activation (140, 672, 1125, 1134), perhaps secondary to DNA damage (1210) (Fig. 10). As noted above, other viral infections can reactivate a latent HIV infection in vitro, most probably also via effects on the viral LTR (812) (see Section XII C). Again, the molecular events in this process are not well characterized.

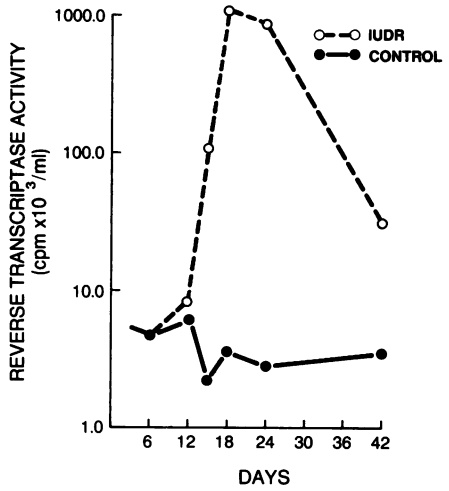


FIG. 10. Latent HIV infection of an established T-cell line. The $HIV\text{-}1_{SF247}$ strain, obtained from a patient of E. Koenig in the Dominican Republic, was used to infected the Jurkat T-cell line. After 6 days in culture, very little virus replication was detected in the culture fluid by the reverse transcriptase assay. After the addition on day 6 of 50 μg of iododeoxyuridine (IUDR) per ml, HIV-1 was released to high levels as measured by particle-associated reverse transcriptase activity. Within 2 weeks, virus replication decreased to almost a latent state. Reproduced from reference 672 with permission.

Recently, a cell line that oscillates between a latent $CD4^+$ and a virus-productive $CD4^-$ state has been described by Butera et al. (113). Derived from the HL60 promonocytic cell line, this model of latency seems more typical of classical viral latency; little if any viral RNA and protein are made unless virus activation is induced. TNF-α predominantly influences the state of virus expression in this cell line.

Persistent nonproductive HIV infection of EBV-transformed B lymphocytes has also been described (219). Clones from these cells, however, showed many intracytoplasmic viral particles. This result indicated that although virus latency seemed to be present, the state reflected the effect of cellular and not viral factors: HIV was not released by the particular B-cell clone. Once produced, it replicated like the parental virus in PBMC. Finally, in a recent report, latency in the U937 monocyte cell lines was associated with methylation of high levels of extrachromosomal viral DNA copies (1103).

It is important to recognize that all these past in vitro studies of cellular latency have used established cell lines with integrated HIV genomes and not infected normal lymphocytes that would be more relevant to the in vivo situation. Unfortunately, aside from the recent report cited above (148), $CD4^+$ lymphocytes after infection cannot usually be maintained in culture without spontaneous activation (670b). Moreover, whether observations on cells producing low levels of virus (e.g., U-1 and ACH-2) mirror conditions occurring within cells in a completely latent state (in which relatively no viral RNA is produced) is still not clear.

B. Mechanism of Cellular Latency

Several hypotheses have been presented to explain the mechanism of cellular latency with HIV (Table 14) (for a review, see reference 310). It could be caused by methyla-

TABLE 14. Possible mechanisms of HIV latency[a]

Mechanism	Reference
Methylation of viral DNA	56
Lack of sufficient viral Tat expression	298, 445
Expression of viral Nef protein	717
Lack of expression of Rev	939, 1194
Lack of viral Vpu and Vpr expression	1275
Inhibition of intracellular factors that interact with the NF-κB protein or other regions on the viral LTR	356, 834
Inhibition of virus expression by $CD8^+$ cell factor	1244

[a] See Sections XII A and XIII B for other references and discussion.

tion of certain portions of the integrated viral LTR needed for induction of the replicative process (56) or, as described above, by methylation of extrachromosomal viral DNA sequences (1103). It could result from an inactivation of the *tat* or *rev* gene (37, 159, 264, 298, 310, 445, 939, 1066, 1194) (see Section XII). Other studies have suggested that the virus itself produces a protein, such as Nef, that interacts with cellular factors and establishes the silent infection (10, 156, 159, 717, 851). Suppression of *vpu* or *vpr* function could be responsible (1275). In all these processes, certain cellular proteins appear to be involved (551). Finally, cellular latency could be induced by $CD8^+$ cell anti-HIV-suppressing activity, perhaps via a cytokine (546, 1244) (see Section XXIII D).

The role of the *nef* gene in latency was proposed because deletion of this viral gene from the molecular clone of the HIV-1_{SF2} strain produced a variant that replicated to high titer and was more cytopathic than the original SF2 isolate (717). Work with other HIV isolates and SIV have supported the conclusion that the *nef* gene can down-regulate virus replication in T cells and monocytes (10, 72, 850, 851, 1174, 1199).

Subsequent findings have also suggested an association of *nef* with latency. The HIV-1_{SF2} *nef* gene (linked to the viral LTR or the simian virus 40 promoter) transfected in T cells suppressed virus replication (156). Most noteworthy was the observation that highly cytopathic strains (e.g., HIV-1_{SF33} or strains recovered from individuals with disease) replicated in the Nef-expressing cells without any visible effect of the viral protein on HIV production (156). These observations on viral heterogeneity could explain in part why some investigators have not found a silencing effect of Nef on HIV expression (431, 570). The results also suggest that HIV virulence in the host could depend on the sensitivity of the particular virus to the effects of the viral Nef protein (see Section XVI D).

How Nef suppresses HIV replication is not clear. Some investigators have proposed that the viral LTR is affected (10, 415, 730, 808, 1315). Other data suggest alternative mechanisms (44, 159, 431). Recently, an inhibition by Nef of NF-κB induction in T cells has been reported (849). Our studies with interviral recombinants have suggested that Nef has an anti-Rev-like effect (159). Sensitive HIV strains infecting Nef-expressing cells were found to make very little viral protein and only small spliced mRNA species (e.g., 2 kb and 4 kb), as is observed in cells infected with *rev*-deleted mutant viruses (1015, 1110, 1205). Moreover, with interviral recombinants resistant or sensitive to Nef, resistance was mapped to a region encompassing the second exon of Rev (159). Observations on the effect of Rev on Nef expression also support these conclusions (9). Most probably, Nef functions through an interaction with cellular proteins, probably via phosphorylation events (414, 415, 647, 945, 1294) that have yet to be defined.

Most studies indicate, however, that the function of Nef can be pleiotropic. The sequences in the Nef region are highly heterogeneous (239), and differences in activity can be found among various alleles and in different cell lines. For example, the Nef protein from certain viruses down-modulates CD4 in some cells (347, 414), but the Nef protein from others does not (156). Moreover, Nef expression affects IL-2 induction in some cells (720). Studies in our laboratory have demonstrated that Nef proteins from some viruses have no effect or can even enhance replication kinetics (154a). Others have also shown that some *nef* mutants can replicate better in macrophages than in T cells (1175). Recent studies suggest that the *nef* allele of some strains is associated with acceleration in virus replication in $CD4^+$ lymphocytes and T-cell lines (242, 1329). Nevertheless, a mutant from another strain (HIV-1_{SF2}), not expressing Nef, replicates faster and to higher levels in PBMC than the parental virus does (717).

Some animal experiments have also not supported a virus-suppressing role of Nef. In experiments with rhesus macaques, the *nef*-deleted viral mutant appeared to be less pathogenic than the wild-type virus counterpart (564). This latter observation may indicate differences in function of the SIV and HIV Nef proteins. Alternatively, a *nef* mutant might be expressed to such high levels in vivo that the host immune system recognizes it more readily and thus suppresses its pathogenesis. These possibilities require further study.

In summary, the mechanisms involved in induction of a state of HIV latency have not yet been fully defined, and it is not known why certain viral strains can enter latency more readily than others (see Section XIV E). Moreover, whether the in vitro studies of viral latency have relevance to an in vivo situation has yet to be determined. Nevertheless, the HIV regulatory proteins, *tat*, *rev*, and *nef*, and intracellular factors certainly appear to be involved.

C. Clinical Latency

The interval between infection and clinical disease in an individual has also often been called latency. This state is quite different from the latent state within the cell. The factors influencing this clinical condition not only are cellular but also, most importantly, involve the immunologic response of the host against the virus (see Sections XXII and XXIII). Evidence today suggests that clinical latency, defined as an absence of symptoms, can be present at a time when virus replication is active in the host (see Section VI B). Thus, the interrelationship between cellular and clinical latency has not been well defined.

A clinical reflection of cellular latency in the host was suspected when infected but antibody-negative and viremia-negative individuals were identified. In their blood, non-virus-producing HIV-containing cells were detected by PCR or other techniques (293, 505, 520, 880, 969, 1299). In some cases, PBMC from such individuals were induced in vitro to produce anti-HIV antibodies (521, 1218), but this observation needs further confirmation. The existence of this cellular HIV latency in nature is controversial since most studies now indicate a short seronegative interval in HIV-infected individuals (367, 485, 693, 737, 892). In most if not all of those infected, virus expression is continually taking place. Thus, seronegative infected individuals most probably reflect a delay in response of the immune system rather than the presence in vivo of a latent cellular state. Nevertheless, non-virus-producing HIV-infected cells are probably also

present in some tissues in the host throughout the course of infection (Section XIII A). In summary, in terms of cellular latency existing in vivo, probably all infected individuals will have some cells replicating virus. Most people will seroconvert within 1 to 3 months of infection, and all will seroconvert by 1 year. Rarely, newborn infants infected in utero become seronegative after elimination of maternal antibodies, but they show evidence of productive virus infection (271).

XIV. HETEROGENEITY OF HIV STRAINS

Several studies conducted after many HIV strains were recovered indicated quite early in AIDS research that the virus responsible was highly heterogeneous in a variety of biologic, serologic, and molecular features.

- Cellular tropism
- Replication kinetics
- Level of virus production
- Cytopathicity
- Plaque- or syncytium-forming ability
- Latency and inducibility
- Sensitivity to neutralizing/enhancing antibodies
- Genetic structure

Moreover, two subtypes could be distinguished. These characteristics of HIV are discussed in this section. How they could influence disease is considered in Sections XVI D, XIX, and XX.

A. HIV-2 Subtype

Shortly after the discovery of HIV-1, a second subtype of the AIDS virus was recovered in Portugal from patients with AIDS who had arrived from West Africa, particularly the Cape Verde Islands and Senegal (180). Cloning and sequence analysis showed that this new virus differed by more than 55% from the previous HIV-1 strains isolated and thus it was designated a subtype of HIV (180, 189, 416). Other HIV-2 strains were subsequently isolated from individuals from Guinea Bissau, The Gambia, and the Ivory Coast (11, 134, 283, 596, 612, 1063). The major serologic difference between HIV-2 and HIV-1 resides in their envelope glycoproteins (Fig. 11). Antibodies to HIV-2 generally cross-react with the Gag and Pol proteins of HIV-1 but might not detect HIV-1 envelope proteins, and vice versa (181, 376). For this reason, blood banks are now mandated to use ELISAs consisting of both HIV-1 and HIV-2 proteins (862). Sera from some individuals from Africa have reacted with both HIV-1 and HIV-2 proteins, suggesting cross-reactivity or dual infection. In certain cases, this infection by both subtypes has been documented, but the prevalence of this event is not clear (283, 364, 909, 976).

HIV-2 glycoproteins appear to cross-react readily with strains of SIV (181) (Fig. 11), a complex group of primate lentiviruses. Some SIV isolates can give rise to an AIDS-like disease in certain primate species (rhesus macaque) or are relatively nonpathogenic in their species of origin (e.g., SIV_{agm} in African green monkeys) (348). Since antibodies to SIV and HIV-2 cross-react and the sequences of these two lentiviruses are similar, some investigators believe that HIV-2 was derived from SIV sometime in the near-distant past (274, 466, 742, 1088).

One hypothesis on the origin of HIV links all human and simian viral sequences back to 600 to 1,200 years ago,

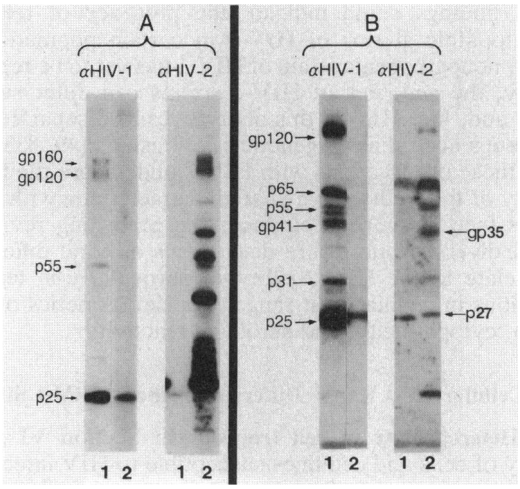


FIG. 11. Immunoblot analyses showing antibody reactions with HIV-1, HIV-2, and SIV proteins. (A) Serum from an African patient with HIV-1 and HIV-2 infections was tested for reactivity against electrophoretically separated cell lysates containing HIV-1 (lane 1) and SIV_{mac} (lane 2). Note the differential detection of the envelope gp160 and gp120 proteins. (B) Proteins from purified HIV-1 (lane 1) and HIV-2 (lane 2) isolates were reacted with serum from an HIV-1- or HIV-2-infected individual. Reprinted from reference 282 with permission.

although continued transfers between the species could be taking place (832, 833). Evidence in support of this latter possibility is the recent detection of an SIV-like HIV-2 strain from a human in Liberia (344). Nevertheless, the genomic heterogeneity among SIV and HIV-2 strains, which continues to be appreciated as more viruses are isolated and sequenced, questions the conclusion that HIV came from the nonhuman primate lentiviruses (315, 823, 1198). Along with the lentiviruses from other animal species (Table 1), the simian and human viruses could have evolved independently from a progenitor lentivirus that entered the animal kingdom many thousands of years ago. In this regard, a primate counterpart to HIV-1 has not been identified, except perhaps for recent isolates from chimpanzees (SIV_{CPZ}) (497, 908). The relation of the SIV_{CPZ} to the transmission of HIV-1, however, is not clear, and the two viral types do differ substantially (497).

HIV-2 strains have now been recovered from patients in several parts of Africa, primarily in the western region. They have also been detected in individuals in Europe, South America, and the United States (862, 1267). In this country, 13 of 17 identified infected individuals have been West African (862). The spread of this virus throughout the world has therefore not been as extensive as that of HIV-1. Some investigators believe that the transmissibility and pathogenic potential of HIV-2 strains are lower than those of HIV-1 (27, 911, 946). Nevertheless, individuals infected solely with HIV-2 have developed AIDS. These patients often present with gastrointestinal abnormalities and central nervous system (CNS) disorders as well as immune deficiency (134, 280, 283). A possible particular tissue tropism of this subtype merits further attention.

Another potentially relevant observation with a few HIV-2 strains has been their reduced cytopathic properties in cell culture and absence of CD4 antigen modulation (see Sections XIV C and D) (134, 282, 596, 615). Moreover, several HIV-2-infected patients have normal $CD4^+$ cell counts (134).

These findings could indicate the presence of relatively noncytopathic strains of HIV-2 in certain populations. A similar nonpathogenic strain of HIV-1 has yet to be reported. Finally, the genomes of HIV-2 strains can differ substantially, and, like HIV-1, this subtype can be separated into subgroups according to genetic relationships (49, 833).

All these observations with HIV-2 underscore the heterogeneity of this subtype—a shared characteristic with HIV-1 strains (see above). In essence, the preceding review on HIV-1 diversity and future discussions on viral differences also relate to the HIV-2 subtype, particularly in terms of variations in cellular host range (tropism), kinetics of replication, cytopathicity, and serologic reactivity.

B. Cellular Host Range Differences among HIV-1 Strains

(i) Heterogeneity in cell tropism. In Section VI A, the variety of cells and cell lines susceptible to HIV infection in vitro was reviewed. Ongoing studies continually demonstrate the wide and varied cellular host range of HIV strains. When HIV-1 was initially recovered, it was grown in mitogen-stimulated normal PBMC (50, 674, 941). Because the cells died with time, fresh PBMC had to be added on a regular basis. Within a few months of study, however, the virus was shown to infect and grow persistently in established lines of T and B cells that were not killed by the virus. These lines were useful in growing large quantities of HIV through cell culture procedures (674, 682, 800, 941). Established cell lines soon became the source of screening tests used for detecting antibodies to HIV (57, 541).

(a) Cellular host range. One early observation on HIV heterogeneity was that many HIV-1 strains could not be propagated in the established human T-cell lines (38, 281, 672). Subsequent studies with several independent HIV-1 isolates have since demonstrated that some can grow in certain established human T-cell, B-cell, and monocyte lines and that others cannot (38, 135, 188, 298, 314, 682, 1031, 1066). Certain strains replicate well in primary macrophages, whereas others can replicate efficiently only in peripheral blood $CD4^+$ T cells (359, 360, 1066, 1228) (see below). Some HIV strains can infect B-cell lines and even B lymphocytes in culture, particularly if EBV is present (218, 455, 800). Likewise, viruses can be distinguished by their ability to grow in bowel- and brain-derived cell lines as well as in primary cells from fetal and adult organs (47, 155, 298, 1031, 1066) (see also Section VI A). Some investigators have used these and other properties to classify HIV strains into subgroups (38, 298, 1228) or to designate their degree of virulence (38, 163, 298, 668, 1170, 1172) (Table 15).

Even in the highly sensitive target cell for HIV, the $CD4^+$ lymphocyte, variations in virus production can be observed. An HIV-1 or HIV-2 strain might grow to high titers in the PBMC of only certain individuals (135, 136, 188, 281). In some cases, up to 1,000-fold differences can be demonstrated (188). No HIV strain that grows well in PBMC from all individuals has been found; likewise, PBMC from one individual have not shown an equal susceptibility to infection by all HIV isolates (Fig. 12). Similar differences in infection of peripheral blood macrophages can be demonstrated (210). Thus, it is conceivable that one virus infecting two individuals could have a different pathogenic pathway depending on its ability to grow and spread in the peripheral leukocytes of each individual. The susceptibility to virus replication appears to be determined by the genetic makeup of the host cell (e.g., cell surface and intracellular factors) (see Section XII).

TABLE 15. Classification of HIV strains by host range and replicative properties

Subtypes
Virulent versus avirulent strains (see Table 19) (163)
SI versus NSI strains (1172)
Rapid/high versus slow/low strains (298)
Groups a to d (for lymphocytes) or α to γ (for macrophages)[a] (1228)
Phenotype considered
Host range defined by replication in primary $CD4^+$ lymphocytes versus macrophages, as well as relative growth in established human T-cell, B-cell, and monocyte cell lines
Replication defined by how soon virus is released from the cell (kinetics, e.g., rapid versus slow) and to what levels it is produced at peak virus replication (titer, e.g., high versus low)
Cytopathology defined by cell killing as well as induction of syncytia via cell-to-cell fusion

[a] Kinetics not a parameter.

(b) Macrophage tropism. At the time of this writing, evidence for a purely macrophage-tropic virus is limited. Some investigators report that viral strains that grow primarily or only in macrophages can be initially isolated from macrophages of infected individuals (627, 940, 1061). Then, after cocultivation of these macrophages with T cells, a virus with a dual host range can be recognized (166). Fresh isolates from PBMC may be initially dual-tropic but then change after growth in cell culture into T-cell-tropic strains. Other investigators have reported that some HIV strains will show substantial differences in their ability to grow in macrophages and T cells (359, 360, 1061). In both cell types, the CD4 protein on the cell surface appears to be the major receptor for entry (197, 210).

In general, HIV-1 strains that preferentially infect T cells can be identified (T-cell-tropic strains), but macrophage-tropic viruses are dual-tropic (359). Nevertheless, some HIV-1 strains grow to high titers in macrophages and are very cytopathic in these cells (163, 848, 1262a). Usually, differentiation of monocytes to macrophages is needed for efficient infection (984, 1062, 1208) and macrophages from different tissues can vary in sensitivity to HIV infection (867a) (see Section XI B). However, macrophages are much less susceptible to HIV once terminal differentiation has occurred (670a, 1208). Finally, low-level virus replication in infected macrophages appears to be common with HIV-1 strains considered non-macrophage-tropic (1206); after cocultivation with T cells, virus can be readily recovered (1060).

(c) Conclusions. Most HIV strains can infect both T cells and macrophages but with great differences in efficiency. For instance, all of the non-macrophage-tropic strains in our laboratory can be detected in macrophages after inoculation, if PCR or cocultivation with PBMC is conducted (670a). Also, recent studies suggest that strains that are poorly tropic for macrophages enter and undergo reverse transcription but have greatly reduced progeny production (1053). The reason for this observation is not known. The continuous passage of HIV strains in vitro conceivably selects strains with T-cell tropism. Moreover, fresh isolates, particularly from plasma, might not readily infect cultured PBMC (see Section XVI C), perhaps because of a reduced relative affinity for the $CD4^+$ lymphocyte in culture.

For these reasons, some investigators warn about artifacts introduced by in vitro techniques (619, 779). Nevertheless, studies in which the same approaches to isolation and comparison among strains are used should help control for

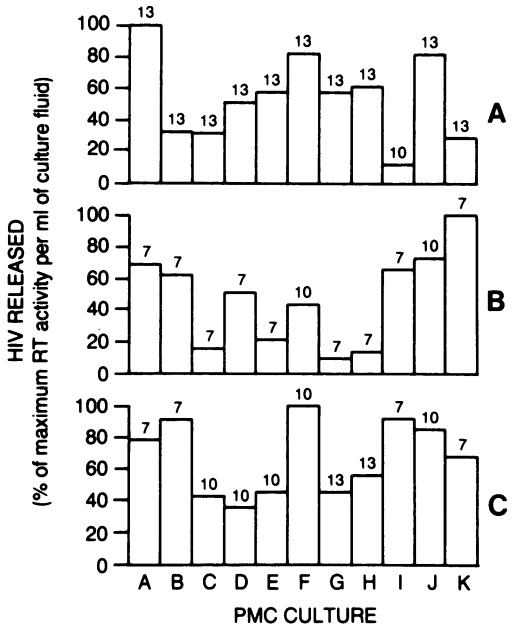


FIG. 12. Variation in HIV replication in PBMC (PMC). The cells from 10 different Caucasian, Asian, and black donors were infected with three different strains of HIV-1. Reproducible differences in replication and time of virus release (number above bar) were observed. Modified from reference 281 with permission.

this variable. Moreover, evaluation of viral strains directly in tissues (e.g., by PCR) carries the risk of studying defective virions. Recent measurements indicate up to 1,000 more noninfectious particles than infectious particles in HIV preparations (573) and up to 100,000 more noninfectious viruses than infectious ones in the plasma of seropositive individuals (649).

These differences in host range among HIV strains appear to be determined primarily by the initial steps involved in virus entry (see Section XV A). Subsequently, intracellular factors affect the extent of virus replication (see Section XII).

(ii) Cellular host range and glycosylation. Two reports (162, 906) demonstrated that HIV strains passed through a variety of cell types were modified in their host range properties. Whereas selection of a variant could be involved, posttranscriptional modification of the infecting virus strain should be considered. For example, some HIV-1 isolates grown in the HUT 78 T-cell line, in contrast to PBMC, take on biologic features permitting infection of a variety of other established T-cell and macrophage lines. When the virus is passed back in PBMC, this expanded host range disappears. The only viral proteins that appear changed during this transfer of HIV are the envelope glycoproteins. On exposure to tunicamycin, the nonglycosylated envelope proteins of all the viruses studied have the same size (162); it is the extent of glycosylation that differs.

In further support of intracellular modification of the HIV strain are observations with an infectious molecular clone of HIV-1_{SF2}. When this strain was passed through different cell lines or PBMC from different individuals, variations in replicating ability in PBMC and established T-cell lines were noted (162). The results strongly suggest that the glycosylation pattern of the envelope protein determined by events within the cell (297) can affect the host range of the progeny virions. One hypothesis considers that carbohydrate-binding proteins on the cell surface or a macrophage endocytosis receptor interacting with oligosaccharides on the virus could affect infectivity and cellular host range (296). Recent studies, however, suggest that only some N-linked glycosylation sites might be important for infectivity (653). Nevertheless, this posttranscriptional alteration is another example of the influence that intracellular factors could have on HIV infection and spread. Therefore, glycosylation differences could be added to the general features of HIV that might determine pathogenesis in individuals infected by the same HIV strain (see Section XVI). Glycosylation could also affect the sensitivity of certain HIV strains to antiviral antibodies (58) (see Section XXII A).

(iii) Kinetics and level of virus replication. The difference in ability of HIV strains to infect cells is reflected not only in virus entry, as discussed above, but also in the rate of virus replication (kinetics) and the extent of viral progeny production (titer) in various cell types. Moreover, in part, the virus titer over short periods can reflect the extent to which a strain of HIV can spread among inoculated cells. The relative abilities to replicate in cells have been used by some investigators to categorize HIV into "rapid/high" and "slow/low" strains (38, 298) (Table 15). The rapid/high strains are associated with disease in the infected individuals. In general, these distinctions in kinetics and titer fit most isolates; however, some low-titer viruses have been found to replicate rapidly and certain slow-replicating viruses can eventually grow to high titers after a prolonged period in culture (670a, 1228).

These biologic features of an HIV strain reflect factors already discussed (Section VII), such as the affinity of virus attachment, virus-cell fusion, the rate of virus nucleocapsid entry into the cell, and the influence of the intracellular milieu. How the particular viral envelope interacts with the cell and how the viral LTR responds to viral (e.g., Tat), and cellular factors depend on the basic molecular features of the individual HIV strain.

Differences in virus replication can also result from external stimuli (e.g., cytokines) acting on intracellular factors that influence the expression of particular HIV strains (see Section XII). For example, TNF-α, and IL-1, via PKC activation, appear to induce the attachment of the NF-κB protein to a promoter region of the viral LTR and enhance virus replication (266, 574, 607, 745, 876, 1234). These cytokines are produced by activated macrophages and T cells and by HIV-infected cells of the immune system (see Section XVIII G). Likewise, by transfection with the *tat* gene, $CD4^+$ T cells can be modified into targets in which HIV strains that previously did not grow well in these cells can replicate to high levels (298). Moreover, as described above, certain cellular factors could interact with Tat to increase virus replication. Furthermore, infection of the cells by other viruses can result in enhanced HIV replication (see Sections XII B and C). Finally, expression of a viral Nef protein might "dampen" the level of viral replication via interaction with cellular factors, and/or viral regulatory proteins.

All these findings, as well as those on virus tropism and intracellular milieu (see Section XII), emphasize the influence of both external and internal cellular factors interacting with viral gene products in determining the extent of HIV infection and replication (Table 16).

TABLE 16. Factors influencing HIV infection and replication: host range[a]

Presence and number of cellular receptor(s) for HIV
Virus envelope (structure, conformation, charge)
Extent of viral envelope glycosylation
Number of envelope spikes: extent of shedding
Cellular proteases
Interaction of intracellular factors with the viral LTR
Extent of expression of viral regulatory and accessory genes (e.g., *tat*, *rev*, *nef*, *vif*, *vpu*, *vpr*)

[a] Summarized from discussions in Sections VII, VIII, IX, and XV.

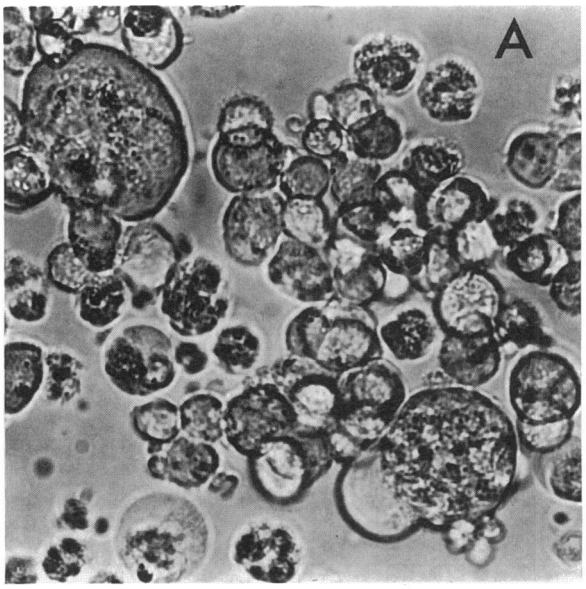
C. Modulation of CD4 Protein Expression

In the course of studies of HIV-1 and HIV-2 strains, some viruses that did not down-modulate the CD4 molecule were found (see Section VII F). One HIV-2 strain (UC1) (282) that is also relatively noncytopathic replicated to high titer in $CD4^+$ lymphocytes without disturbing the expression or number of CD4 molecules on the cell surface. This observation was made with both $CD4^+$ lymphocytes and established T-cell lines. Another HIV-2 strain (ST) (596) has also been shown to have minimal effects on CD4 protein expression. This variation in extent of CD4 modulation can also be seen with diverse HIV-1 strains (672) and is one distinguishing property of viruses recovered from the brain (158, 165) (see Section XVI A). Whether this feature, which varies among viral strains, has any role in the pathogenic pathway is still unknown.

D. Cytopathology

In addition to the relative ability of HIV strains to infect and replicate in cells and to modulate CD4 expression, the extent of cytopathology produced by a variety of HIV-1 and HIV-2 strains can differ substantially (26, 163, 1138, 1166). As mentioned above, some HIV-2 strains have been recovered that replicate to high titer in PBMC but do not induce any cytopathology as defined by syncytium formation and reduction in cell viability. Some HIV-1 strains also have limited cytopathic properties, but thus far all those described cause cell-cell fusion. With cytopathic HIV-1 and HIV-2 strains, however, the relative extent of cell killing of $CD4^+$ lymphocytes as well as macrophages can vary dramatically (134, 282, 1165, 1262a). Using established T-cell lines, syncytium-inducing (SI) and non-syncytium-inducing (NSI) strains have been described (1170), and differences in plaque-forming ability of HIV-1 strains have been reported (1166).

The plaque assay (437) is very useful in detecting highly cytopathic HIV strains. It is performed with cells from the HTLV-I-infected T-cell line MT-4, attached to the surface of plastic dishes with poly-L-lysine. The highly cytopathic strains will replicate well in these cells and will produce a plaque reflecting syncytium formation and cell death (1166) (Fig. 13). Most noteworthy have been the variations in induction of cytopathic effect and plaque formation observed in viral isolates recovered from the same infected individual over time. The later isolates are the most cytopathic (163). Likewise, they are high-SI agents (1170, 1172). A similar observation on heterogeneity in HIV-1 cytopathicity has recently been made by using the MT-2 cell line (597). As noted above, the host range, replicative abilities, and cytopathic properties of HIV-1 strains have been used to classify strains into separate biologic subtypes (Table 15).



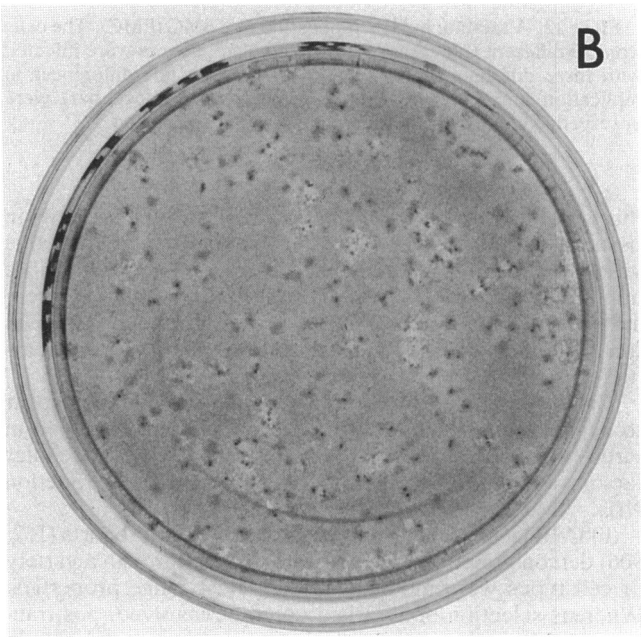


FIG. 13. Plaques formed in the MT4 cell line by cytopathic strains of HIV-1. (A) Cytopathology induced in PBMC by HIV-1_{SF33}. Magnification, ×65. (B) HIV-1_{SF33}-induced foci of syncytia and cell death detected by staining as plaques in the MT-4 cell monolayer. Magnification, ×40. Photomicrographs courtesy of C. Cheng-Mayer.

E. Latency

Just as other virologic properties show heterogeneity, so does the induction of latent infection in cultured cells (see Section XIII). Some HIV isolates enter into a latent or silent state in vitro much more rapidly than others do. Again, this biologic feature depends on the cell type as well as the viral strain. For example, the HIV-1_{SF247} strain recovered from a patient in the Dominican Republic induces a latent state in the established Jurkat T-cell line but replicates well in PBMC (672) (Fig. 10). Sometimes, the early isolates from an asymp-

tomatic individual will enter a latent state in established T-cell lines, whereas later isolates from the same person with AIDS replicate efficiently in the cells (159a). Certain HIV-1 strains studied in our laboratory (e.g., HIV-1_{SF33}) have never induced a latent infection in T cells in vitro. If this consideration of latency also includes low virus production (i.e., viral persistence), similar variations among HIV strains in different cell types (e.g., macrophages versus T cells) can be appreciated (113, 310) (see Section XIV B). The observations on latency have therefore emphasized the dependence of this state both on the genetic differences in viral genes (e.g., *tat*, *rev*, and *nef*) and on their varying interactions with intracellular factors. The mechanisms are probably diverse and require continued study (see Section XII).

F. Serologic Properties

(i) Sensitivity to antibodies mediating neutralization and ADCC. Differences in the susceptibility of various HIV strains to serum neutralization have also been demonstrated. Initially, evidence for neutralizing antibodies against HIV was limited, most probably because of the viral assays used. Subsequently, a number of laboratories demonstrated that sera from HIV-infected individuals from many parts of the world could neutralize HIV-1 and HIV-2 strains to various extents (136, 155, 469, 474, 746, 1265, 1266). Some viruses, such as HIV-1_{SF2}, are easily neutralized by many sera, particularly from patients in the United States. Often, high titers of serum-neutralizing antibodies can be detected by using this isolate (483, 1265). One explanation for these observations is that this virus is a North America-predominant strain with envelope properties shared by many isolates (see below). The HIV-1_{MN} strain is a similar antigenic type (518, 639). Besides antibody recognition, other possible reasons for the high sensitivity of these strains to neutralization could be the increased release of their envelope gp120 from the virion, the reduced number of gp120-bearing knobs on the virion surface, or both (760).

Examining several HIV-1 strains isolated in San Francisco, Cheng-Mayer et al. (155) demonstrated that the HIV isolates could be placed into at least four subgroups (A to D) depending on their sensitivity to neutralization by three different sera (Table 17). Viruses recovered from the brain, in contrast to those from the blood, were not very susceptible to neutralization (group C). This observation is one characteristic of brain-derived strains (see Section XVI A). Notably, an isolate from Africa (SF170) was resistant to neutralization by these sera as well as many other North American sera. However, it can be neutralized by African sera. These early studies were undertaken to derive serotype sera that could distinguish viruses by their sensitivity to neutralization. Work with MAbs should eventually permit this type of serologic classification.

As reviewed in Section XXII, the viral envelope gp120 appears to contain the major regions susceptible to neutralization. These include the CD4-binding domain (1133, 1150) and the third variable (V3) loop (403, 517, 518, 639, 1340). Other portions of gp120 (469) and gp41 (146), and perhaps p17 (1040), could also be important. Polyclonal antibodies and MAbs to the V3 loop are type specific but cross-react with several strains (69, 265, 425). This response occurs since this cysteine-bound V3 region has a central portion with certain amino acid sequences (e.g., GPGRAF), now termed the principal neutralizing domain (PND), that are shared by many HIV isolates (e.g., HIV-1_{SF2}) (Fig. 14).

TABLE 17. Neutralization of HIV-1 infectivity by anti-HIV-1 sera[a]

Proposed subtype	HIV-1_{SF}	Source	Neutralization by serum[b]:		
			1	2	3
A	SF2	PBMC	≥1,000	100	10
	SF4	PBMC	≥1,000	100	100
	SF13	PBMC	≥1,000	100	10
	SF33	PBMC	≥1,000	100	10
	SF66	PBMC	≥1,000	100	10
	SF113	PBMC	≥1,000	100	100
	SF117	PBMC	≥1,000	100	10
	SF301A	CNS	≥1,000	100	100
	SF315	PBMC	100	10	10
B	SF97	PBMC	80	20	–
	SF171	PBMC	20	10	–
C	SF98	CNS	20	–	–
	SF128A	CNS	20	–	–
	SF161B	CNS	100	–	–
	SF162	CNS	100	–	–
	SF178	CNS	20	–	–
	SF185	CNS	20	–	–
	SF153	PBMC	20	–	–
	SF247	PBMC	100	–	–
D	SF170[c]	PBMC	–	–	–

[a] Taken from reference 155, with permission.
[b] Tenfold and twofold dilutions of anti-HIV-1 sera (sera 1, 2, and 3) were tested for their ability to neutralize the infection of PBMC by 20 different HIV-1 isolates from individuals in the United States except for SF247 (Dominican Republic) and SF170 and SF171 (Africa). Figures represent the reciprocal of the highest serum dilution, causing a reduction greater than or equal to 67% in RT activity in the culture fluid. A negative (–) indicates no virus neutralization at a 1:10 serum dilution.
[c] Rarely neutralized by sera from individuals outside of Africa.

Unrelated strains with different sequences in the PND are resistant to neutralization by the same MAbs (265).

Since neutralizing responses following immunization with an envelope-based HIV vaccine can result primarily from anti-V3 antibodies, the issue of variability in this region can pose problems for vaccines in different parts of the world. Thus, the extent of serologic heterogeneity has been studied in part by analyzing the V3 (and particularly the PND) regions. The results suggest that the amino acid sequence of the V3 loop can be used to identify strains from Africa, Asia, and the Caribbean (169, 537, 880). How these variations will relate to antigenic differences among HIV-1 isolates worldwide is not yet known. If the viruses share some common neutralization epitopes, a candidate V3 vaccine would be feasible. In general, however, successful approaches to identifying different HIV serotypes will also have to consider amino acid sequences outside the V3 region that could influence neutralization (762, 981), as well as other portions of the viral envelope (see Section XXII A).

With HIV-2 strains, specific neutralizing domains of the viral envelope, such as a PND, have not yet been conclusively identified, although their presence is suggested by recent studies (75, 80, 248). Neutralization studies, moreover, have also demonstrated heterogeneity in responses among HIV-2 isolates (134, 1266).

Variations in sensitivity to neutralizing antibodies have been found as well with viruses recovered from the same individual over time. Most noteworthy has been the observation that sera from infected individuals generally do not

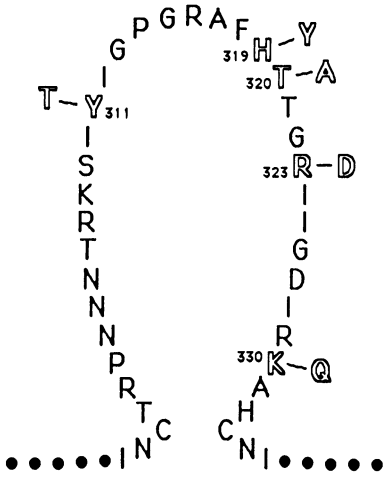


FIG. 14. Comparison of the amino acid sequence of the V3 regions of the HIV-1_{SF2} and HIV-1_{SF162} strains. The complete V3 sequence of HIV-1_{SF2} is shown, and the five amino acid residues that differ in HIV-1_{SF162} are designated. The positions of amino acid residues are relative to the HIV-1_{SF2} genome referenced in the Los Alamos AIDS and Human Retroviruses database. Reprinted from reference 1092 with permission.

neutralize the homologous virus (that strain replicating in the person at the time of serum collection) as effectively as they neutralize previous autologous strains or other heterologous HIV strains, especially those grown in the laboratory (481, 1229) (see below). This finding, particularly in symptomatic patients, has suggested that the virus within the individual changes to "escape" immune surveillance (762, 981) (see Section XXII A). It further emphasizes the serologic diversity of isolates even within the same individual.

The generation of viruses that have escaped sensitivity to serum antibodies has also been demonstrated by cell culture studies. HIV-1 strains cultured in the presence of neutralizing MAbs mutate so that they are no longer sensitive to neutralization (762, 981, 997). In these studies, an alteration outside of the region identified by the MAb may bring about this resistance (1287, 1288). These observations emphasize the influence of other envelope domains on the overall conformation of the viral envelope that can determine effective antibody binding. This conclusion has also been reached by studies of separated antibody species (1133) (see Section XXII A).

Other nongenetic factors associated with the virus can also reveal differences in serologic responses. Viruses cultivated in one cell line in a laboratory, for example, can become more or less sensitive to neutralization by specific sera. In some instances, the serologic effect could be due to reactivity with cell surface proteins (490), carbohydrate moieties, or differences in virus envelope stability. For example, antibody to the blood group A antigen has been reported to neutralize HIV produced only by lymphocytes from blood group A donors (32). In other cases, glycosylation patterns could differ and affect antibody binding (229, 296, 355) (see Section XIV B). In addition, the age of the virus preparation can affect antibody sensitivity. With time in culture, the envelope region of the virion becomes less stable and detaches early; neutralization becomes more effective (650, 760). Thus, it has been recommended that viruses for serologic study be grown in PBMC, preferably of the individual being evaluated, and culture fluids 2 days old or less be used.

Finally, as reviewed in Section XXII B, anti-envelope antibodies mediating antibody-directed cellular cytotoxicity (ADCC) also reflect the serologic heterogeneity of HIV strains. They can be distinguished in some cases from neutralizing antibodies (87). The relative binding of the antibodies to the viral antigen on the surface of cells infected by a variety of isolates can differ depending on the specific gp120 and gp41 proteins expressed (601, 707). Thus, certain viruses can be distinguished by their sensitivity to ADCC following infection of target cells.

(ii) Sensitivity to enhancing antibodies. Enhancing antibodies were recognized during evaluation of sera for neutralizing activity against HIV. Robinson et al. (1005) noted that HIV-seropositive sera in the presence of complement could enhance the infection of the MT-2 T-cell line by certain HIV-1 strains. Homsy et al. (483), in studies of guinea pigs immunized with various HIV-1 strains, noted that instead of inducing a neutralizing antibody, the immunization produced sera that enhanced HIV infection. Virus replication in $CD4^+$ lymphocytes as well as macrophages doubled or tripled after exposure of the HIV inoculum to serum or purified immunoglobulins from the immunized animals. Chimpanzees infected with HIV and sera from HIV-infected individuals showed similar results. Depending on the viral strain used and the serum selected, either neutralization or enhancement of virus infection could be demonstrated. Others reported comparable results for decomplemented sera (1160). Most notable have been the observations that a viral strain within the same individual can change from sensitivity to neutralization to sensitivity to enhancement (482) (Fig. 15). Generally, this modification in HIV is associated with progression to disease (see Section XVI D). Recent studies suggest that small substitutions in the V3 loop can bring about this alteration in the serologic sensitivity of the virus (see Section XXII C).

In the laboratory, certain HIV-1 strains that are more sensitive to neutralization than others (e.g., SF2) can be grown. Likewise, other strains are found most susceptible to enhancing antibodies (e.g., SF128A, a brain isolate, or SF170, a strain isolated from a patient from Rwanda). The reason for these differences is not known but appears to be related to specific regions on the viral envelope (see Section XXII). The variation could also result from distribution of the viral gp120 on the virion surface and its stability (see above). Enhancement of infection by some HIV-2 strains has also recently been noted with certain sera (585a). Thus, this immunologic phenomenon that also reflects viral heterogeneity could have relevance for pathogenesis by either HIV subtype.

G. Sensitivity to Cell-Mediated Immune Responses

Another property that could differ among HIV strains is the relative ability to be recognized by the cellular immune system with subsequent killing of the infected cells or the suppression of HIV replication in the cell (see Section XXIII). In one study in which PBMC cultures were used, virus strains that were not eliminated by antigen-specific $CD8^+$ cytotoxic T lymphocytes (CTL) were detected by PCR, but no consistent strain of virus could be identified (780). In another report, the escape in vivo of a specific virus strain from the effect of $CD8^+$ CTL was described (925). That finding supports the in vitro studies showing that a single amino acid mutation in the viral gp41 can eliminate cell killing by $CD8^+$ CTL (220). The observations need further confirmation.

Work in our laboratory has suggested that slow, less

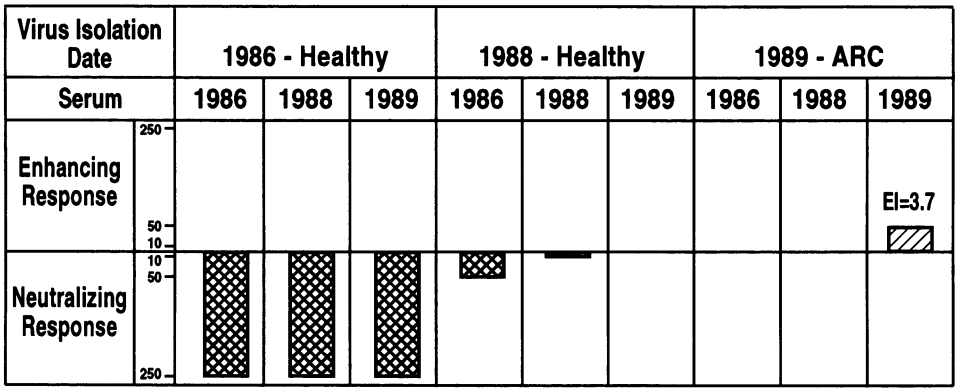


FIG. 15. Neutralization or enhancement of infection by sequential homotypic HIV-1 isolates. HIV-1 strains recovered from the same individual were tested for enhancement or neutralization by the corresponding sera obtained early or late in the infection. The sera were evaluated at fivefold dilutions (1:10 to 1:1,250). Normal control serum was used at similar dilutions. The clinical status of the individual at the different time points is indicated. The extent of neutralization is shown below the bar; the enhancement index (EI) is shown above the bar and defined as the ratio of the viral RT activity in supernatants of cultures receiving virus preincubated with homotypic serum to the activity in virus preincubated with control serum. Modified from reference 481.

virulent HIV strains are somewhat more sensitive to the inhibition of virus replication shown by antiviral $CD8^+$ lymphocytes (725, 1247). However, this difference most probably reflects the relative extent of virus replication and spread rather than the specific recognition of an HIV strain for suppression by the cell-mediated response. Finally, recent studies suggest that HIV strains within one individual might show different sensitivities to the suppressing effects of $CD8^+$ cells (see Section XXIII D). Two seemingly different strains of HIV were recovered from the same individual when the $CD4^+$ cells alone (depleted of $CD8^+$ cells) and when all the PBMC were grown in culture (1167). This finding requires further evaluation.

H. Molecular Features

The above discussions describe the extensive biologic and serologic heterogeneity of HIV strains. These differences are mirrored in the genetic sequences of the viruses. How these diverse strains of HIV arise is not clear, but the viral reverse transcriptase is very error prone and thus appears to give rise readily to changes in the genome (949, 998, 1162). Fidelity is severalfold higher with RNA than with DNA, suggesting that most mutations occur with the DNA template-DNA primer (92). Estimates of up to 10 base changes in the HIV genome per replicative cycle can be made. Molecular techniques have helped define the variations in the viral genome associated with HIV heterogeneity (see Section XV).

One of the first differences recognized among HIV-1 strains was the variation in sensitivity of the cloned, proviral genome to digestion by restriction enzymes. When the restriction enzyme patterns of two prototype isolates, IIIB and LAV, were examined, they were virtually identical (16, 422), but that of a third, ARV-2 ($HIV\text{-}1_{SF2}$), showed marked differences (106, 718). The latter observation became the rule as highly divergent strains were recognized by their different restriction enzyme patterns.

Viruses recovered from one individual appear to conserve several restriction enzyme sites and thus can be identified as coming from the same and not a different person (59, 163, 423). Similarly, viruses from a mother and child (1300), individuals receiving a blood transfusion or clotting factor from the same source, or two sexual partners could show their close relationship by having similar restriction enzyme patterns (see below).

When complete sequence data were available on the initial HIV-1 strains, it became clear again that IIIB and LAV were virtually (and now proven to be) the same strain, whereas SF2 and subsequently other strains could be differentiated by their viral genomic sequence (822, 974, 1039, 1239). At least 6% of the viral genome can differ among strains. Some isolates can vary widely. The greatest sequence heterogeneity is observed in the genes of the regulatory and envelope proteins (741, 779, 833), where with some stains over 40% differences in amino acid sequences occur (Fig. 16) (831, 833). A major current focus of research is correlating these sequence

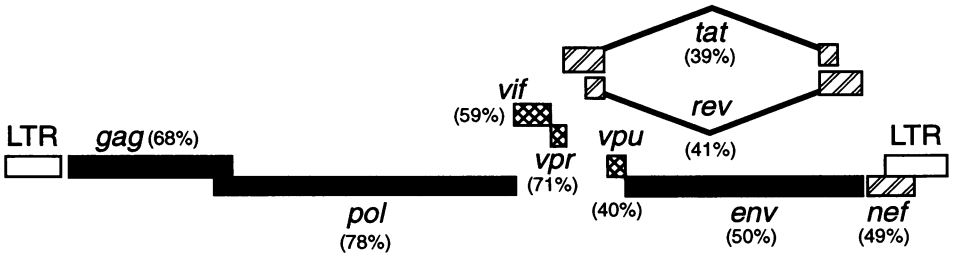


FIG. 16. Estimated similarities in amino acids for the different HIV-1 gene products. Figure drawn from data in reference 831, analyzing several HIV-1 strains worldwide.

differences with functional variations among HIV strains (see Section XV).

The PCR technique combined with DNA sequencing, as discussed above, has been particularly helpful in conducting rapid comparisons of different sequences among HIV-1 and HIV-2 strains (537, 620, 741, 753, 880), particularly the V3 region. This procedure has revealed extreme envelope diversity as well as certain similarities among strains (see Section XIV F). By studying several hundred virus isolates from about 20 countries, at least five major HIV-1 genotypic subtypes (called clades) which differ by 30 to 35% in their *env* and *gag* gene sequences have been identified; only one virus clade has been reported in the United States (831a). PCR sequencing has been useful in demonstrating transmission of one HIV strain to other individuals in the recent past (112, 766, 1297) and from mothers to infants (1300). In most cases, a selected transfer of one or a limited number of variants was shown (1297). In recipients of the same clotting-factor preparation, PCR sequencing revealed a lack of substantial change (175, 585). This technique was also helpful in demonstrating that a dentist infected five of his patients during surgical procedures, most probably through the use of unsterilized instruments (879).

Finally molecular approaches have suggested HIV diversity in infected hosts that is not appreciated after isolation of virus in vitro (619, 779). Whether selection in culture influences conclusions made about HIV heterogeneity and pathogenesis remains to be determined (see Section XIV B).

XV. IDENTIFICATION OF THE VIRAL REGIONS DETERMINING THE BIOLOGIC FEATURES OF HIV-1

The initial molecular studies of the HIV genome defined the relative importance of various viral genes in general for infection and replication. These approaches led to the recognition of regulatory genes influencing virus production (for reviews, see references 400 and 1205). Subsequent studies have emphasized the identification of specific viral regions responsible for certain biologic properties such as cell tropism, kinetics of replication and cytopathicity. These results are discussed in this section. The regions mediating sensitivity to immune responses are considered in Section XXII.

A. Envelope Region and Cell Tropism

Attempts to find limited alterations (perhaps only one amino acid change) associated with a particular viral feature such as cell tropism have focused on the generation of interviral recombinants. Advantage is taken of restriction enzyme sites shared among diverse HIV strains or the introduction of such sites by PCR techniques. Selected regions of a virus are removed by the restriction enzymes and reinserted into the backbone of another cloned virus. In some studies, two biologically active molecular clones have been used. In others, a noninfectious molecular clone has been used to donate regions to, or exchange regions with, a biologically active clone. Subsequently, site-directed mutagenesis has been useful to further define the genetic sequences involved.

Several reports initially demonstrated that the envelope region contains the primary genetic sequences responsible for T-cell line and macrophage tropism, cytopathology, CD4 protein modulation, and neutralization (125, 160, 168, 706, 864, 1314). However, it is important to recognize that in all these studies, differences in the ability to infect established (transformed) T-cell lines does not indicate variations in tropism for $CD4^+$ lymphocytes. Most mutants, except those that lose infectivity in general, maintain the ability to infect PBMC. Furthermore, as noted below, tropism for primary macrophages does not correlate with infection of transformed monocytic cell lines.

In terms of cellular host range, subsequent experiments considerably narrowed the region of the virus responsible for this biologic property. For example, in a study of two unrelated HIV-1 strains (SF2 and SF162), macrophage tropism was found associated with a 159-amino-acid region in the right-hand portion of gp120 (1091). A similar finding was made with two other viral strains (864). Most recently, the involvement of the V3 loop alone (amino acids 304 to 324 of gp120) in macrophage tropism was demonstrated (168, 502, 1092, 1276). In addition, in one study as few as three amino acid changes in the V3 region were found to confer macrophage-tropism on a T-cell line-tropic strain (1092).

The specific sequences associated with infection of T-cell lines were initially noted to be somewhat broader (310 amino acids) than those for macrophages in the study of the SF2 and SF162 strains. However, again no regulatory proteins were involved (1091). More recently, the V3 loop has also been found to be important for this T-cell tropism (124, 502, 1092). Changing of the five amino acid differences to those of SF2 in this region of $HIV\text{-}1_{SF162}$ converts the virus to a T-cell line-tropic strain. In one SF2 mutant, a single amino acid change in the V3 loop eliminated the ability of the virus to infect one particular T-cell line (MT-4) but not others (1092).

In our laboratory, other studies examining structure-function relationships have used $HIV\text{-}1_{SF2}$ and $HIV\text{-}1_{SF13}$, which are closely related but biologically distinct viral isolates recovered over time from the same individual (163, 164). With these two strains, comparison of genetic differences was possible since the two viral isolates differ by less than 3%. Macrophage and T-cell-line tropisms and cytopathicity were found to be associated with 10 or 12 amino acid differences in the envelope gp120 of SF2 and SF13 (Fig. 17).

Most noteworthy in these studies of SF2 and SF13 was the observation that tropism for certain cell lines and cell types was determined by nonoverlapping regions of the HIV gp120. Infection of macrophages, HUT 78, and the MT-4 cell lines was associated with the envelope domain encompassing the V3 loop; tropism for CEM and U937 cells was linked to a separate portion of gp120 containing V4, V5, and the CD4-binding domains (164, 164a) (Fig. 17). A similar selective effect of an amino acid change in the CD4-binding region on tropism for U937 but not a T-cell line was shown by Cordonnier et al. (204). That separate regions controlled entry into primary macrophages and into the U937 cells further indicated that the latter cell line is not an ideal target for examining macrophage tropism. Moreover, these studies again demonstrated that the V3 loop alone does not determine infection of all cell types.

Studies with other HIV-1 isolates (e.g., the GUN strains) have shown that a single amino acid in the V3 loop (amino acid 311) can affect HIV infection of $CD4^+$ brain fibroblasts (1161). Moreover, perhaps as expected, when strains JR-FL and NL4-3 were used, the infection of brain-derived microglia was linked to the same envelope region controlling macrophage tropism (1081). In other studies, the pattern of envelope N-linked glycosylation appeared important for infection (653). Most recently, studies introducing mutations in the crown of the V3 loop (GPGRA) have generally indicated a loss of infectivity and changes in the fusogenic

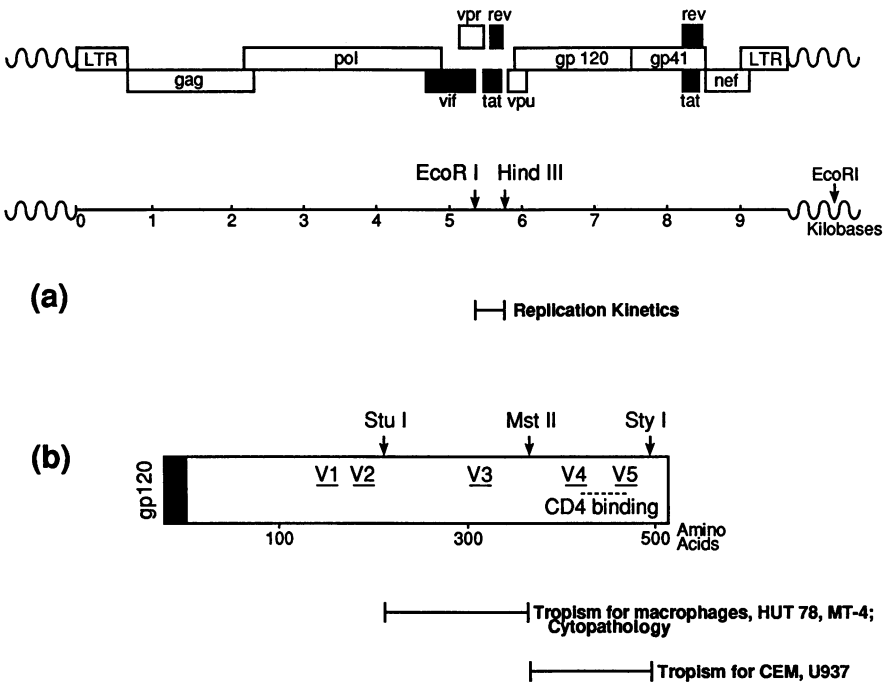


FIG. 17. Structure-function relationship of HIV-1. Results of studies with HIV-1_{SF2} and HIV-1_{SF13} are shown (164, 164a). The regions of HIV-1 needed for cell tropism, cytopathology, and CD4 down-modulation are indicated (b). A region in the first coding exon of *tat* has been found associated with the kinetics of virus replication (a). Reproduced from reference 164a with permission.

potential of the viruses (403, 509, 888) without affecting CD4 binding. Furthermore, in some studies (320, 1092) but not in others (154), the charge in the V3 loop was associated with efficient infection, syncytium formation, and replication. Finally, in some recent experiments with the SF2 and SF13 strains, changes outside the crown, but in the V3 loop, were found to affect infectivity of these HIV strains for PBMC (154).

All the results have indicated that generally more than three amino acid changes are required to affect cell tropism, although in some cases one modification has affected the infection of a single cell line (204, 1092). The findings emphasize that a variety of viral epitopes determined by the conformation of gp120, particularly in the V3 loop, are important for HIV entry. In support of this conclusion, additional regions of the envelope gp120 outside the V3 loop were found to enhance the extent of virus replication in T-cell lines and macrophages, most probably by increasing the efficiency of virus entry (168, 1091, 1276). In this regard, nonlinear epitopes of gp120 could be interacting with a contiguous region of CD4 (see Section VII). Since it seems likely that each viral strain, depending on its amino acid content, will have a different conformational structure, various envelope regions for specific viruses could determine entry into cells.

With these observations on cell tropism, it seems evident that emphasis should now return to studies of the role in infection of the three-dimensional structure of the viral envelope; less attention need be given to individual epitopes. For example, recent studies in our laboratory suggest that certain amino acid changes in the V3 loop of the SF2 and SF13 mutant viruses can increase the extent of gp120 dissociation from gp41. The mutant viruses showing increased gp120 loss are less infectious and not very cytopathic (1124a). In this case, the affinity of gp41 interacting with a region of gp120, not in the V3 loop, has been affected by the V3 loop changes (see Section III A). The V3 region modifications most probably influenced the conformational structure of the viral envelope and caused the increased dissociation of gp120 from the virus envelope and the associated biologic properties.

Only further work with interviral recombinants, using HIV strains from a variety of individuals, will determine whether a common structure or a particular region in a viral envelope correlates with a certain cell tropism. Specific envelope-cell interactions must be examined, and several mechanisms will most probably be found to be involved. With some isolates, the influence of electrical charge should be considered. Finally, the potential role of cellular proteases in virus entry (see Section VII B) can be addressed with these mutant viruses.

B. Regulatory Proteins and Virus Replication

The relative role of HIV regulatory genes in determining the extent of virus replication has also been studied with recombinant viruses. With the interviral SF2 and SF13 recombinants, substantial virus replication in PBMC and the HUT 78 cell line was linked to the first exon coding region of *tat* and reflected only two amino acid differences (164, 164a) (Fig. 17). A change in one of these two amino acid differences and not the other has reduced the kinetics of the fast-replicating SF13 strain to that of the SF2 strain (655a). Thus, very limited modification in the regulatory protein in some isolates could greatly affect virus replication.

In support of these findings are results from additional studies that examined the effect of HIV-1_{SF2}, HIV-1_{SF13}, and HIV-1_{SF33} Tat proteins on their respective LTRs (655a). As discussed above, these viruses isolated in our laboratory

differ in biologic properties; SF2 replicates with slower kinetics and is less cytopathic than its related strain SF13 and the highly cytopathic SF33 isolate. First, it was noted that cell type can influence the effect of Tat. Tat_{SF13} enhanced transactivation via the LTR in human T cells but not in monkey COS cells. The level of transactivation by Tat_{SF2} was at least 10-fold lower. Second, the effect of Tat_{SF2} was most evident on the LTR from the fast-replicating strains (SF13 and SF33) rather than from SF2 itself. Finally, when one amino acid from Tat_{SF13} was changed to that of Tat_{SF2} (noted above), the function of this regulatory protein in the assays resembled that of the Tat_{SF2} protein (655a). Thus, these findings correlated well with the biologic studies indicating the Tat_{SF13} mutant virus replicated less well than the wild-type SF13 virus. They also indicated the influence of both Tat and the LTR on virus production.

As noted previously, introducing the *tat* gene into cells that are relatively nonpermissive for replication of a particular HIV strain can convert them into actively producing cells (37, 298). Also, rodent cells lacking a cellular factor that interacts with the Tat protein are less permissive to HIV replication than cells (e.g., human) that have it (445) (see Section XII B). All these observations indicate the major role of the *tat* gene in promoting virus replication but also reflect its important interplay with the viral LTR. Moreover, some studies suggest that small changes in the *vif* gene, as well as *vpr* and *vpu*, can affect the extent of virus infectivity and replication (974, 1275) (see also Section XIII B). Finally, Rev, Nef, and intracellular factors (e.g., the results discussed above with Tat in COS cells versus T cells) appear to affect HIV production by a variety of mechanisms (356) (see Sections XII B and C and XIII B).

C. Envelope Region and Cytopathicity

Other observations with the interviral recombinants have identified to some extent the specific regions in the viral envelope that determine cytopathicity as measured by syncytium formation and plaque formation in MT4 cells. With the SF2 and SF13 recombinants, this region is the same as that associated with tropism for primary macrophages and HUT 78 and MT-4 cells (Fig. 17). Further studies on smaller portions of this envelope region should distinguish the domains responsible for tropism versus cytopathicity. As noted above, in some studies particular portions of the V3 loop can be involved. In this regard, Stevenson et al. (1138) have reported that only two glycosylation sites in the viral envelope can determine the extent of cell killing resulting from infection. This observation supports the role of glycosylation in this process. Moreover, recently de Jong (236) demonstrated that the introduction of one positively charged amino acid (e.g., arginine) into a specific region of the V3 loop can, in some cases, produce a syncytium-inducing virus. The mechanism(s) by which the viral envelope would bring about this cytopathology is discussed in Sections XIV D and XVII A.

XVI. RELATION OF HIV HETEROGENEITY TO PATHOGENESIS

Several studies have been initiated to determine whether distinct HIV subgroups with specific biologic and serologic features are associated with pathology in certain tissues. The three most discussed are reviewed below, but others could eventually include HIV strains isolated from the heart, kidneys, and endocrine organs.

TABLE 18. Characteristics of HIV-1 strains recovered from different tissues[a]

Characteristic	Extent in virus from[b]:		
	Peripheral blood	Brain	Bowel
Growth in $CD4^+$ lymphocytes	++	++	++
Growth in established human cell lines	++	−	±
Growth in macrophages	±	++	+
Modulation of CD4 antigen expression	++	−	+
Cell killing	+	−	+
Serum neutralization	++	−	+

[a] Reprinted from reference 669 with permission.
[b] Relative extent noted by the number of + signs; −, not evident.

A. Brain Isolates

Studies in our laboratory have demonstrated that HIV-1 strains recovered from the brain or CSF of patients with neurologic symptoms can be distinguished from viruses recovered from the blood of individuals who are asymptomatic or who have a marked reduction in $CD4^+$ cell number (Table 18) (157, 158, 165). In general, the brain-derived isolates, while growing to high titer in $CD4^+$ lymphocytes, are not cytopathic for these cells and do not down-modulate the CD4 protein on the cell surface. These characteristics could explain in part the finding of CNS disease in some individuals with near-normal $CD4^+$ cell numbers (672, 838). Brain-derived strains are also not as sensitive to serum neutralization as blood isolates are. In one report, certain strains from the brain appeared to be more sensitive to CSF antibodies (1114), but this finding has not been confirmed (1230). In addition, the brain-derived isolates grow to higher titer in macrophages than the blood-derived isolates do (157, 590, 606). Moreover, the CNS isolates can rarely be propagated in established lines of T cells, B cells, or monocytes (e.g., U937). These differences can also be appreciated when comparing brain and blood isolates from the same individual (165).

When the relative ability of the HIV isolates to replicate in brain-derived cell lines was examined, other noteworthy observations that could have relevance to neuropathogenesis were made (see Section XIX). In one study, the blood-derived isolates and not the macrophage-tropic, brain-derived isolates grew best in the human glioma cell lines (161). Similarly, a non-macrophage-tropic strain recovered from the CSF, and not a brain-derived macrophage-tropic isolate from the same individual, grew in a glioma explant culture (606).

Other investigators showed that only the macrophage-tropic HIV-1 strains (characteristic of brain isolates) grew well in adult microglial cells in culture (529, 1081, 1253). This observation was not unexpected since microglia are supposedly derived from macrophage precursor cells. Nevertheless, as noted above, Peudenier et al. (922) have challenged the report of infection of microglia, particularly since these latter cells most probably lack CD4 protein expression. The infected cells could have been brain macrophages. This issue is still not resolved but has relevance to any hypothesis on CNS pathogenesis. Finally, the relative ability of HIV strains to infect brain capillary endothelial cells (813) could determine whether they enter the CNS.

The biologic differences between blood and brain isolates have also mirrored variations in restriction enzyme sensitiv-

ities and V3 loop sequences. Whereas strains isolated from the brain and blood of the same individual are related, certain differences exist (276, 421, 689, 895, 1137). The findings suggest that distinct but related viral strains could evolve independently in the infected host.

B. Bowel Isolates

HIV-1 strains have been detected in the bowel mucosa all along the gastrointestinal tract from the esophagus to the rectum (48, 371, 453, 600). Studies similar to those described above with the brain isolates have indicated some differences between the blood and the bowel isolates, but the distinctions were not as great as those defining the brain-derived HIV-1 strains. Nevertheless, the bowel isolates did show substantial macrophage-tropism and less capability of infecting established T- and B-cell lines than the blood isolates did. In contrast to brain isolates, however, they were sensitive to serum neutralization and were cytopathic for $CD4^+$ cells in culture. The existence of bowel-tropic strains was particularly suggested by the extent of these differences observed when closely related blood and bowel isolates from the same individual were evaluated (Table 18) (48). Molecular studies on bowel and blood isolates from the same person have not yet been conducted to determine whether separate evolutionary pathways have taken place within the host, as suggested for the brain-derived isolates.

C. Plasma Virus

Recent studies have indicated that virtually every infected individual has free virus circulating in the blood (199, 471) (see Section IV A). In asymptomatic individuals, it is found in small amounts (1 to 100 IP/ml); in AIDS patients, it can be detected in high quantities (100 to 10,000 IP/ml). In most situations, HIV has been recovered from both blood and cultured PBMC. In others, the virus has been found only in the plasma and not in the PBMC (782). This latter finding may indicate a different source for the plasma virus (e.g., lymph nodes). Alternatively, the lack of recovery of virus from PBMC could be related to the antiviral activity of $CD8^+$ cells (see Section XXIII D).

Studies in our laboratory have indicated that several plasma-derived viruses replicate less efficiently in PBMC than the associated PBMC-derived isolates do. Only low-level p25 antigen production and no RT activity have been detected in culture fluid (892). Conceivably, the plasma virus recovered from the same individual has less affinity for the cultured PBMC since it comes from another source in the host. In this regard, a recent paper has demonstrated that during any one time interval, the predominant plasma virus variant may be antigenically distinct from the virus in the PBMC (1101). This finding may relate to the escape mutants detected by neutralization assays in individuals over time (see Section XXII A). All these observations suggest that the plasma virus might be a better representative of the actively replicating virus in the host than are isolates from cultured PBMC.

D. HIV and Virulence: Changes in Biologic and Serologic Properties of HIV over Time in the Host

One of the first observations linking biologic heterogeneity to disease was the finding that viruses isolated from AIDS patients differed in biologic properties from those isolated from asymptomatic individuals (38, 163, 298, 1170, 1172) (Table 19). Similarly, HIV strains recovered from an individual in the early asymptomatic period were remarkably different from viruses isolated from the same person at later times when disease had developed (163, 1171). The earlier virus replicated in a limited number of cell types (usually not macrophages), grew to relatively low levels, and showed slower kinetics of virus replication than did the later strain associated with disease in the host (163). Moreover, the early virus or the strain in asymptomatic individuals, in contrast to the later one, was not very cytopathic for PBMC. Other distinctions of HIV strains linked to virulence in the host include lack of induction of latency in established cell lines (159a), resistance to the suppressing effect of Nef (156), and sensitivity to enhancing and not neutralizing antibodies (482) (Table 19).

TABLE 19. Characteristics of HIV strains associated with virulence in the host

Enhanced cellular host range
Rapid kinetics of replication
High titers of virus production
Disruption or alteration of cell membrane permeability
Increased syncytium induction
Efficient cell killing
No latent state in vitro
Lack of sensitivity to suppression by the Nef protein[a]
Sensitivity to antibody-mediated enhancement of infection

[a] As assayed with the HIV-1_{SF2} *nef* gene product (156).

Other studies have demonstrated by molecular techniques that viruses isolated from the same individual are related by restriction enzyme sensitivities and sequence analyses (163) but that they differ particularly in certain sequences in the envelope region (163, 164) (see below and Section XV A). Specific genetic changes have correlated with enhanced cytopathicity and escape from the immune response (174, 613, 1298). Thus, the HIV strains after infection appear to change over time and acquire properties associated with virulence in the host (Table 19). The genetic bases for these differences have been further reviewed in Section XV.

In regard to the cell tropism differences, Schuitemaker et al. (1061) have demonstrated that fresh isolates from the blood of asymptomatic individuals as well as some AIDS patients can replicate in macrophages. They concluded that this property presents more efficient transmission of the virus via the macrophage. The finding contrasts with those of others, who previously reported macrophage-tropism associated primarily with symptomatic infection (163, 1170, 1172). Yet, in agreement with the results of Cheng-Mayer et al. (163), these strains from healthy individuals were not highly cytopathic in PBMC, nor could they infect established T-cell lines. Moreover, the later isolates were highly cytopathic and infected T-cell lines but were less able to infect macrophages.

These somewhat conflicting observations must be further examined, but the recent findings suggest that macrophages form a reservoir for relatively noncytopathic strains that can later emerge into more virulent isolates. Most probably, as noted above (Section XIV B), all strains can infect macrophages but the efficiency varies dramatically. In addition, the isolates described in the more recent studies could be HIV strains that have infected the subjects later in the course of this epidemic. They could have already acquired certain biologic properties following replication in previous hosts and could thus differ from HIV strains recovered in the

TABLE 20. Possible mechanisms of cytotoxicity by HIV or its proteins[a]

Syncytium formation
Accumulation of unintegrated viral DNA
Virus release causing changes in membrane integrity
Altered plasma membrane permeability to cations
Decrease in synthesis of membrane lipids
Decrease in "second-messenger" (diacylglycerol) activity
Interference with cellular heteronuclear RNA processing
Competitive inhibition by HIV of normal growth factors (e.g., brain)
Induction of apoptosis[b]
Release of toxic cytokines by infected cells
Destruction by immunologic responses (ADCC, CTL)

[a] Viral proteins gp120, gp41, Tat, Nef, and Vif have been considered potentially responsible for cell death (see Sections XVII and XVIII).
[b] Cytokines might also be involved.

initial periods of viral transmission. This possibility merits further study.

The association with disease of viruses with more "virulent" features, as defined in cell culture, is highly suggestive of causation. However, the way in which these biologic changes reflect a pathogenic property can be evaluated only in animal models. In cats, the induction of immune deficiency by the feline leukemia virus has been linked to its envelope region and its ability to cause cytopathic effects in an established feline T-cell line (881). Work in the SIV system, however, has indicated that other portions of the viral genome (e.g., *nef*) could be responsible for its in vivo pathogenic characteristics (564, 739). In this regard, recent studies with SCID mice reconstituted with human PBMC have shown that macrophage tropism and not cytopathicity by an HIV strain correlates best with $CD4^+$ cell loss (818). The reason for this observation is unknown but might involve relative levels of cytokine production (see Sections XVII and XVIII). Certainly, no conclusions on HIV pathogenesis can be drawn from in vitro studies alone.

XVII. MECHANISMS OF HIV-INDUCED CELL KILLING

An important part of our understanding of the pathogenesis of HIV in the host should come from studying the direct toxic effect of the virus or its proteins on individual cells. As noted above, certain HIV-1 strains, particularly those recovered when the individual is advancing to disease, have a greater capacity for killing the infected cell. Besides syncytium formation and accumulation of intracellular viral DNA, other mechanisms of cytopathicity involving the virus itself are reviewed below (Table 20). Section XVIII considers the direct and indirect effects of HIV infection on the function of the host immune system.

A. Viral Proteins

Several observations have associated cell death with direct toxicity from the virus or viral envelope proteins. The relative quantities of the viral envelope protein produced by the cell can determine cytopathicity (605, 659, 695, 972, 1109, 1140). The use of interviral recombinants has shown that cytopathicity, including cell fusion, may be linked to regions in gp120 (160, 237, 1314). Moreover, the cell fusion that often leads to cell death has been associated with gp120 (164, 695, 696, 1109) (see Section IX).

In one study, just a doubling in the production of gp120 gave rise to cytopathology and cell death following HIV

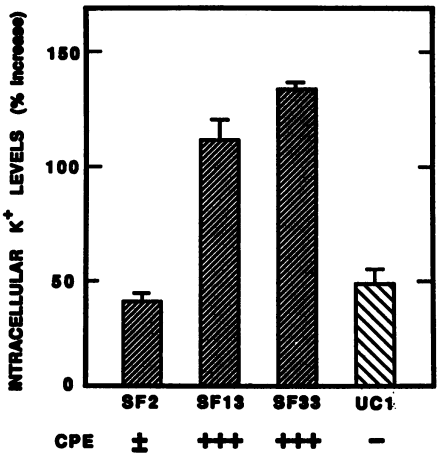
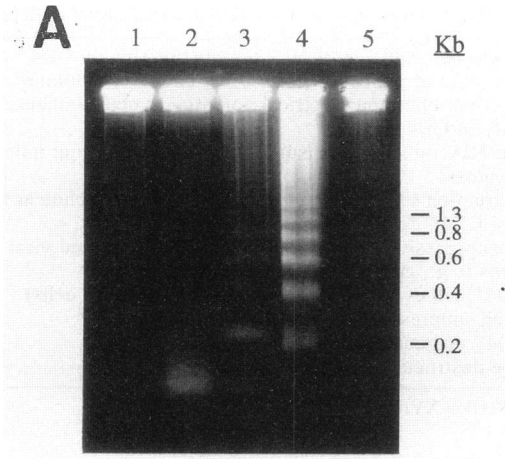


FIG. 18. Membrane permeability changes resulting from HIV infection. PBMC were infected with HIV strains with different cytopathic properties, and the influx of radioactive potassium (K^+) was measured by standard procedures (349). Percent increase compared with results with uninfected cells is shown. A correlation between cytopathology and a greater ingress of K^+ was noted. UC-1 is a relatively noncytopathic HIV-2 strain (282). The experiments were conducted with R. Garry.

infection (1140). In another, two changes in the N-linked glycosylation sequences of gp120 produced a cytopathic strain (1138). In a further report, the accumulation of gp160 without secretion of the processed envelope proteins (gp120 and gp41) led to single-cell death (593). Moreover, addition of gp120 to PBMC or cultured brain cells caused cell killing in a dose-dependent manner (96, 262, 536). Presumably, the cytopathic effect of irradiated HIV (972) also results from the envelope proteins and could reflect the extent and type of glycosylation. gp41 can be also toxic to cells (790); a change in the viral gp41 (304, 604) has modified or produced cytopathic variants. Finally, the *vif* gene has been linked to cytopathology, probably by increasing infectious virus replication (1032).

The mechanisms for this induction of cell death by the viral envelope proteins are not clear. Disturbances in membrane permeability could be involved, as reflected by the balloon degeneration in cells observed in vitro (Fig. 9 and 13A). HIV binding to and entry into cells have shown membrane discontinuities and pores in association with ballooning (299). In this regard, cells infected by and producing cytopathic HIV demonstrate an inability to control the influx of monovalent and divalent cations that accumulate in the cell along with water (187, 349, 413, 724) (Fig. 18). The resulting loss in intracellular ionic strength not only leads to cell death (visualized by balloon cells) when carried to extreme but, at relatively noncytopathic levels, could change the electrical potential of the cell so that normal cell function would be compromised.

This phenomenon of direct damage to the cell membrane has been demonstrated, for example, with cultured brain cells exposed to HIV gp120. A high influx of calcium resulted, concomitant with a disturbance in membrane integrity and cell function (262). The toxic effect of the viral envelope was reversed by the calcium channel antagonist nimopdipine (262). This observation, in fact, has prompted therapeutic trials with nimopdipine to reverse neurologic abnormalities during HIV infection. Conceivably, the glycosylated HIV protein expressed on the cell surface disturbs the membrane permeability, leading to cell death. Alterna-



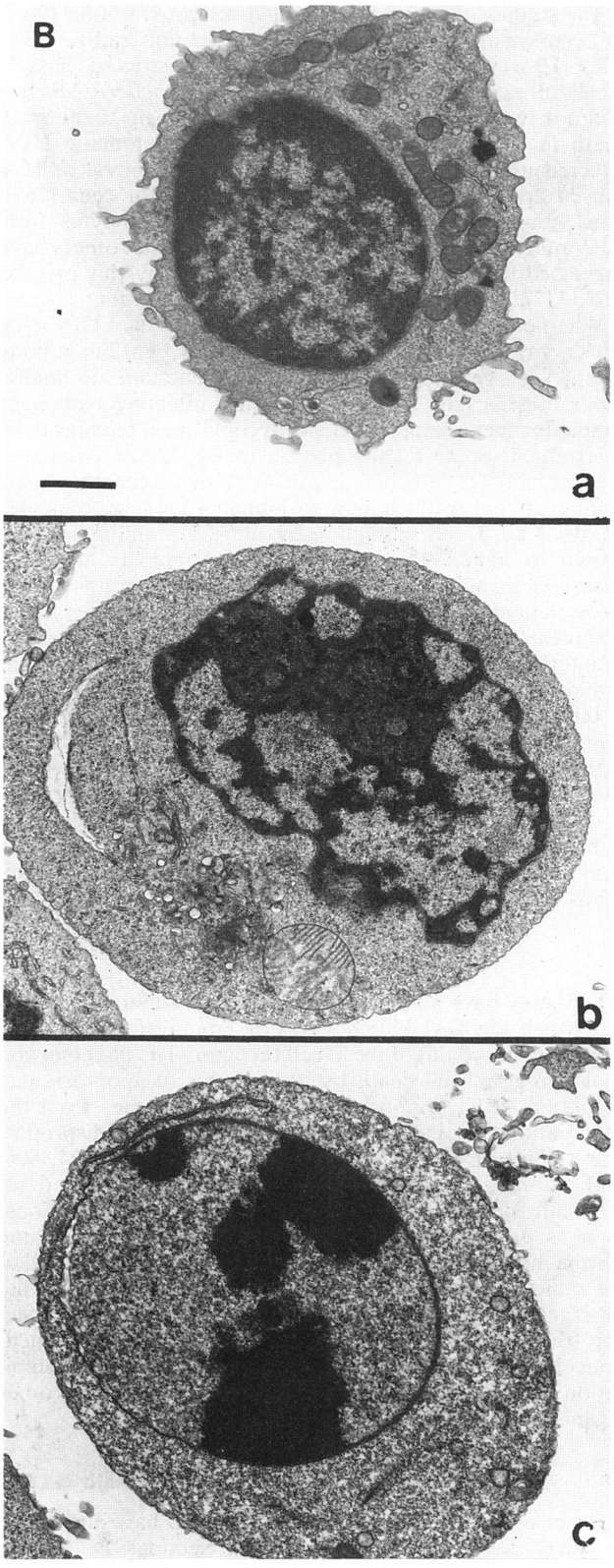


FIG. 19. Activation-induced apoptosis in human CD4+ peripheral blood T lymphocytes following CD4 ligation by anti-CD4 antibody or by anti-gp120. (A) Agarose gel electrophoresis of total DNA after no treatment of cells (lane 1) or treatment with anti-T-cell receptor (anti-TCR) (lane 2), gp120 cross-linked with polyclonal anti-gp120 antibody and then incubated with anti-TCR (lane 3), 500-rad γ-irradiation (lane 4), or gp120 cross-linked with polyclonal anti-gp120 (lane 5). The typical ladder pattern of DNA digestion associated with apoptosis is observed only after γ-irradiation and the cross-linking experiments conducted with anti-gp120 and anti-TCR antibodies (lanes 3 and 4). (B) Ultrastructural morphology of apoptotic T cells induced by ligation of TCR after gp120-CD4 interaction. (a) Untreated CD4+ cells. (b and c) CD4+ T cells treated with the recombinant chimeric protein gp120 plus antibody to gp120 and then incubated with anti-TCR antibodies. No apoptotic cells were seen in the control sample (a). Apoptosis in its early (b) and late (c) stages was observed in the treated samples. Magnification, ×10,140. Bar, 1 μm. Figures courtesy of T. Finkel. Reproduced in part from reference 46, with permission.

tively, it could induce *N*-methyl-D-aspartate (NMDA) receptor-mediated neurotoxicity (705). Changes in the membrane potential of cells have also been shown after exposure to the Nef protein, which has some sequence homology to scorpion toxin (1273). Other regions in the virus (e.g., *tat*, gp41) have also shown similarities to a neurotoxin (351). Moreover, a toxic effect on cells by the C-terminal region of gp41 has also been suggested (790) (see Section XIX E).

The cytopathic effects of HIV have also been linked to a cellular activation process involving gp41 and the CD4 protein, in which tyrosine phosphorylization of a newly recognized 30-kDa protein was detected (193). Inhibition of this phosphorylization led to reduced syncytium formation. Whether approaches to modifying specific intracellular signals would decrease CD4+ cell loss via this mechanism is under study.

B. Apoptosis

Recently, death of CD4+ T cells by apoptosis has been suggested as a cause for CD4+ cell loss in HIV infection (408, 648). The process has been observed in T cells during other viral infections (e.g., with EBV) (1203). This phenomenon involves the inappropriate reemergence of a programmed T-cell loss that is a normal physiological response during thymocyte maturation (191, 195, 365, 561). The process requires cell activation, protein synthesis, and the action of a Ca^{2+}-dependent endogenous endonuclease that produces fragmentation of the cellular DNA into small measurable nucleotide units (Fig. 19). Apparently CD4+ cells do not undergo apoptosis in HIV-infected chimpanzees or SIV-infected monkeys (241). Thus, the lack of disease in these animals could be explained on this basis.

The studies, thus far, indicate that cell proliferation alone, as occurs with phytohemagglutinin, does not lead to apoptosis. However, stimulation with MHC-restricted class II recall antigens (e.g., tetanus toxin, *Staphylococcus* enterotoxin) or with pokeweed mitogen can cause up to 40% cell death in 2 days in $CD4^+$ cells from asymptomatic HIV-infected individuals (408). In one report, removal of IL-2 caused apoptosis in murine cytotoxic effector cells (267). Most studies suggest that only $CD4^+$ lymphocytes from HIV-infected individuals undergo apoptosis, but others have suggested that some $CD8^+$ cells might die by this process (392, 777). This possibility merits further attention.

Whether apoptosis results from direct effects of HIV itself or its viral proteins, antibodies to CD4, gp120-antibody complexes, variations in cytokine production, or finally, superantigens (see below) from other infecting pathogens (staphylococci, streptococci, or mycoplasmas) remains to be determined. Some results suggest that gp120 or virus-antibody complexes can elicit apoptosis (1169). Recently, cross-linking of the gp120 bound to human $CD4^+$ lymphocytes followed by T-cell activation by anti-CD3 antibodies was shown to induce this process (46). Apoptosis has been observed in feline $CD4^+$ cells with certain strains of the feline leukemia retrovirus (1011). Some cytokines (e.g., IL-4) can also increase this process in macrophages by countering the protective effects of other cytokines (TNF-α, gamma interferon [IFN-γ]) on these cells (731). These types of interactions might be involved in HIV infection.

Since unstimulated $CD4^+$ cells removed from the infected individuals do not undergo apoptosis, whether this phenomenon occurs to a substantial extent in vivo (from activation) is uncertain. One report does suggest enhanced cell death from this process even in PBMCs taken directly from the blood of infected individuals (408), but this observation needs confirmation.

C. Role of Superantigens

HIV may have a peptide that acts like a superantigen that can attach to $CD4^+$ lymphocytes by one portion (e.g., beta and not alpha chain) of the T-cell receptor. The phenomenon could program cell death by the process of apoptosis just described (191). Support for this concept comes from the observation that individuals with AIDS show a disproportionate loss of T cells with a certain beta chain (224, 506, 645). Moreover, superantigens have been considered responsible for the loss of T cells in other retrovirus infections, such as with the murine mammary tumor virus and the murine model of AIDS (191, 499, 1301). The nucleocapsid of the rabies virus has recently been reported as a potential superantigen (621). If this process is present in HIV infection, the antigen that is involved has not been determined. Conceivably, as noted above, this mechanism for the elimination of $CD4^+$ cells, if confirmed, might be caused by other organisms or antigens present during HIV infection.

D. Other Causes of HIV-Induced Cell Death

Other events in the viral infection cycle have also been linked to cell death (as discussed in Sections IX and X) (Table 20). The accumulation of unintegrated viral DNA appears to be toxic, and the viral Tat protein can kill brain cells (1029). Moreover, interactions of certain cytokines (e.g., TNF-α) with HIV-infected "fragile" cells might bring about additional damage (745), including apoptosis (see Sections XVII B and XVIII A). Finally, anticellular responses of immune cells could be involved (see Sections XVIII E and F). All mechanisms considered in these processes require further study.

TABLE 21. Factors involved in HIV-induced immune deficiency[a]

Direct cytopathic effects of HIV and its proteins on $CD4^+$ cells: cell destruction; effect on stem cells; effect on cytokine production; effect on electrical potential of cells; enhanced fragility of CD4+ cells
Effect of HIV on signal transduction and cell function; induction of apoptosis
Cell destruction via circulating envelope gp120 attachment to normal $CD4^+$ cells: ADCC, CTL
Immunosuppressive effects of immune complexes and viral proteins (e.g., gp120, gp41, Tat)
Anti-$CD4^+$ cell cytotoxic activity ($CD8^+$ and $CD4^+$ cells)
$CD8^+$ cell suppressor factors
Anti-$CD4^+$ cell autoantibodies
Cytokine destruction of $CD4^+$ cells

[a] See Section XVIII.

XVIII. HIV-INDUCED IMMUNE DEFICIENCY

The mechanism by which HIV causes a loss of immune response is a major mystery of AIDS. Several studies suggest that immune abnormalities can be observed in T cells, B cells, and macrophages early in infection even before the loss of $CD4^+$ cells begins (184, 786, 1084–1086). Several possibilities for the induced immune deficiency, besides the effects of viral proteins and HIV described in the previous section, are discussed below (Table 21).

A. Direct Cytopathic Effects on $CD4^+$ Cells

The first immunologic disorder recognized in patients with AIDS was a loss of $CD4^+$ lymphocytes of the helper (inducer) type (390, 787). Whether this loss reflects direct cell destruction by the virus or its proteins (as discussed in Sections IX and XVII) or a secondary effect of immune dysfunction is still not clear. Four other features of direct HIV-1 infection, however, might contribute to the reduction in $CD4^+$ cells and their function. First, despite the inability to detect HIV-1 in a large number of $CD4^+$ cells, even in healthy individuals (see Sections IV A and VI B), HIV could be present in a latent or silent state and affect the function, long-term viability, and replication of these cells. This possibility is supported by recent studies showing a large number of infected $CD4^+$ cells detected by an in situ PCR method (45).

Second, the virus could infect or suppress the production of the early precursors of $CD4^+$ cells (e.g., stem cells) and reduce the quantity of fresh lymphocytes added regularly from the bone marrow to the peripheral blood. Folks et al. (313) have infected early bone marrow progenitor cells in vitro. Since the circulation of lymphocytes in the blood represents only 1 to 3% of the total population in the body (1274), loss of stem cells could influence the replenishment of the normal $CD4^+$ cells required to maintain a steady state. Nevertheless, PCR analyses have not detected HIV in these early progenitor cells of the hematopoietic system (228). In other investigations, hematopoiesis has been suppressed in vitro in some (256, 1136) but not all (796) studies with HIV. Moreover, an inhibitory effect of gp120 and gp160 on the in vitro growth of $CD34^+$ progenitor cells has been reported by some investigators (1328) but not confined by others (1149).

The relevance of these findings to the in vivo situation is also not known. In addition, some investigators believe that a preferential infection of $CD4^+$ memory T cells selectively causes immune dysfunction (1057). A loss of memory T cells has been reported in asymptomatic HIV-infected individuals (1214). If confirmed, this phenomenon could influence immune function in infected individuals.

Third, the HIV *tat* gene expressed in infected cells might reduce the responses of $CD4^+$ cells to recall antigens (e.g., tetanus) (1220) and contribute to immune deficiency. This latter effect would be most evident via transfer of extracellular Tat to uninfected $CD4^+$ cells (1220). Finally, even if HIV does not replicate to high levels, it might alter the membrane integrity of $CD4^+$ cells sufficiently to affect not only normal function (noted above) but also increase their overall sensitivity to cellular factors (e.g., cytokines) (see Section XVIII G). The interplay of all these processes in cell destruction and function requires further evaluation.

B. Disturbance in Signal Transduction

Besides the direct effects of HIV on $CD4^+$ lymphocytes and macrophages, infection of these cells by HIV could interfere with the normal events in signal transduction. This process, as described above (Section XII B), involves an extracellular signal that affects the activity of sequence-specific transcription factors. A protein kinase cascade and protein phosphorylation are involved in this information transfer. It occurs when natural ligands bind to the CD4 antigen or interact with other membrane surface proteins to bring about T-cell activation and effective immune response (for reviews, see references 356, 398, 400, 413, and 547). The HIV-1 gp120 has been found to form an intracellular complex with CD4 and $p56^{lck}$ in the endoplasmic reticulum (209). The retention of this tyrosine kinase in the cytoplasm could be toxic to the cell or affect its function. Moreover, both HIV and envelope gp120 have been found to inhibit the early steps of lymphocyte activation (478, 701). Thus, the function of these cells could be compromised by HIV even if they are not directly infected.

Moreover, induction of the phosphorylation of a 30-kDa protein, discussed above, has recently been linked to cell death (193). Furthermore, a possible gp120-receptor interaction on $CD4^-$ brain cells with subsequent activation of tyrosine phosphorylation of certain cellular proteins might be involved in neuropathogenesis (1055). Finally, apoptosis could reflect intracellular disturbances that affect normal cell activity and function.

C. Bystander Effect

Another mechanism for $CD4^+$ cell loss is the covering with gp120 of cells carrying the $CD4^+$ molecule. These uninfected cells are then recognized as virus-infected cells by NK effector cells or CTL (636, 1099, 1260, 1261) and subsequently destroyed, even though they are not infected by the virus. This hypothesis requires the detection of circulating gp120 in the blood of individuals or on uninfected cells. Although some gp120 released from cells has been found by in vitro studies (370), this feature has not been well documented in vivo.

D. Effect of Viral Proteins and Immune Complexes

Several investigators have demonstrated, as noted above, that viral envelope proteins (e.g., glycosylated gp120 and gp41) have immunosuppressive effects on the mitogenic responses of T lymphocytes (147, 250, 611, 732, 884, 890, 1236, 1261) or normal NK cell activity (139). In the case of B-cell function, gp120 could interfere with normal T-cell help via a block in contact-dependent interactions (171). Moreover, as cited above, the Tat protein can suppress $CD4^+$ cell responses to recall antigens (1220).

Initial studies with the envelope gp41 placed particular emphasis on portions of this protein that could suppress immune responses (147). A related protein in other animal retrovirus systems (i.e., p15 in murine and feline retroviruses) causes depressed immune reactions (173). In addition, as discussed above, gp41 and gp120 can be toxic to $CD4^+$ cells (see Section XVII A). Finally, the formation of antibody-viral antigen complexes (811) could tie up the reticuloendothelial system, affect cytokine production (e.g., IL-1), and influence immune function. Whether any of these phenomena affect the major phenotype of immune dysfunction (loss of $CD4^+$ cells) is not clear, but again they could reduce the ability of the host to replenish sufficient fresh $CD4^+$ cells to keep up with their loss by a variety of mechanisms.

E. Cytotoxic Cells and $CD8^+$ Cell Suppressor Factors

Evidence from animal studies (primarily chimpanzees) and lymphocytes isolated from the blood of infected individuals has also indicated that cytotoxic $CD8^+$ cells might kill normal $CD4^+$ cells as well as those infected with HIV (897, 1260, 1327). Some investigators have found $CD4^+$ cells with this activity against infected $CD4^+$ cells (870). In some studies, production of immune suppression factors by $CD8^+$ lymphocytes has been described (456, 643, 644, 1098), although none has been well characterized. Recently, a factor produced by $CD8^+$ cells has been found to reduce the response of $CD4^+$ cells to certain recall antigens (186). This effect could explain the early abnormalities observed in helper T-cell function (1085).

F. Anti-Lymphocyte Antibodies

Autoantibodies to lymphocytes could also play a role in immune deficiency. In some of the early studies of HIV infection, antibodies to both helper and suppressor T lymphocytes were detected, and their presence has been confirmed (31, 257, 577, 589, 1258). In general, the anti-$CD4^+$ cell antibodies appear first, but autoantibodies to both lymphocyte subsets were noted as disease occurred. Even antibodies to B lymphocytes have been detected (575a). Some of these antibodies could result from anti-MHC responses induced by the HIV proteins (see Section XXIV B). Moreover, autoantibodies to the CD4 protein itself have been detected in HIV-infected individuals (144, 1178) and might be responsible for $CD4^+$ lymphocyte death. The reason for their origin is not known.

Some studies suggest a link of these anti-lymphocyte autoantibodies to $CD4^+$ helper-cell defects (1258) and disease (580, 1146) (see Section XXIV). However, all the observations suggesting that this humoral immune response could affect the immune system require further study. In this regard, plasmapheresis that eliminates autoantibodies and can give clinical improvement (e.g., for disorders involving platelets or nerves) (578) does not change the $CD4^+$ cell number (575a) (see also Section XXIV E).

TABLE 22. Effect of cytokines on HIV-1 replication[a]

Cytokine	Major source	Effect on HIV replication in[b]:			
		T-cell lines	PBMC	Primary macrophages	$CD4^+$ cells
TNF-α	Macrophages, T cells, B cells, keratinocytes	↑ ↑	↑ ↑	↑ ↑	↓[c] or ↑
TNF-β	T cells, B cells	↑ ↑	↑ ↑	NT[d]	↨
GM-CSF	Macrophages, T cells	–	↑ ↑	NT	↨
IL-1	Macrophages, fibroblasts, endothelial cells	↑ or –	NT	NT	–
IL-2	T cells	–	↑	NT	↑
IL-3	T cells	–	NT	↑ ↑	↨
IL-4	T cells	–	NT	↑ ↑	↑
IL-5	T cells	NT	NT	NT	↑
IL-6	Macrophages, T cells, glia, fibroblasts	–	NT	↑ ↑	↨
IL-7	Bone marrow stromal cells	NT	NT	NT	↨
IL-8	T cells, monocytes, keratinocytes, fibroblasts, endothelial cells	NT	NT	NT	–
IL-9	$CD4^+$ T cells	NT	NT	NT	↑
IL-10	T cells, B cells, mast cells	NT	NT	NT	–
IFN-α	B cells	↓ ↓	↓ ↓	↓ ↓	↓ ↓
IFN-β	Fibroblasts, B cells	↓	↓ ↓	NT	↓ ↓
IFN-γ	T cells	↓ or –	↑ or –	↑	↑
TGF-β	Platelets, macrophages, T cells	–	↓	↓ ↓	↓[c] or ↑

[a] Adapted from references 726 and 745.
[b] Data on acute HIV-1 infection of the cells listed are presented. The number of arrows indicates an increase (↑) or decrease (↓) in virus production. A line through the arrow indicates a slight effect. In limited studies, macrophage colony-stimulating factor (M-CSF) increased HIV replication in primary macrophages and granulocyte colony-stimulating factor (G-CSF) enhanced HIV production in $CD4^+$ cells.
[c] High concentration only.
[d] NT, not tested.

G. Effects of Cytokines

A great deal of information on the influence of various cytokines on the normal function of the immune system has accumulated. Macrophages produce IL-1 and other cytokines that permit $CD4^+$ cells to reach a level of maturation sufficient to produce IL-2. IL-2 is needed for self-replication of the $CD4^+$ cell population and for growth and function of $CD8^+$ cells. Other cytokines, such as IL-6 for B-cell growth and function and IL-4 for T-cell maturation, are also important in maintaining an effective immune response (for a review, see reference 745). Some encourage apoptosis (e.g., IL-4) by inhibiting the function of others that prevent this programmed cell death in some cells (e.g., TNF-α and IFN-γ in macrophages) (731). TNF-α helps maintain a balance in the production of several lymphokines but can itself be toxic to T cells and can induce apoptosis. To some investigators, TNF-α is a major cause of HIV pathology and clinical symptoms (745).

Several cytokines are produced by a variety of immune cells after the activation associated with infection and inflammation. Each can affect HIV replication in vitro (Table 22) (see Section XII B) (for reviews, see references 726, 745, 933, and 1016) and in some instances can cause cell death. For example, TNF-α increases HIV production and can be toxic for cells (see Section XIX D). Induction of IL-1 and TNF-α by macrophages infected by HIV or exposed to the viral gp120 has been observed (775). Tat expression has activated TNF-α but not IL-1 or IL-6 production by HIV-infected T cells (110) and TNF-β production in a B-lymphoblastoid cell line (1041a). Moreover, induction by HIV of IL-6 production by human B lymphocytes has also been described (88). This latter event might cause the polyclonal activation of these cells (see Sections XXII A and XXIV A). Nevertheless, some studies suggest that on stimulation, HIV-infected macrophages release diminished amounts of cytokines or show no change in production of these cellular factors (797, 1022). Thus, the relative extent of cytokine expression during HIV infection is not clear, and whether these cellular products act as cofactors to influence the $CD4^+$ cell destruction or compromise their function needs further evaluation. The reported increase in levels of TNF in sera of patients with AIDS but not in asymptomatic individuals merits further study (622a). The known importance of cytokines for intercellular activities, moreover, emphasizes their potential role in modulating or enhancing HIV pathogenesis. Their possible involvement in HIV neuropathogenesis is discussed below.

XIX. HIV-INDUCED BRAIN DISEASE

Lentiviruses are associated with encephalopathies and other brain disorders (419, 663). Similar conditions are observed in patients with HIV infection (784, 921, 950), and HIV has been readily isolated from the CNS (see Section IV C) (for a review, see references 157 and 158). In some cases, CNS disorders may be the only manifestation of HIV infection (672, 838). In animal model systems (e.g., visna virus and caprine arthritis-encephalitis virus infection), CNS disease usually results from direct infection of the brain parenchyma, particularly glial cells, astrocytes, and possibly microglia (418). These latter cells, as noted above, form the macrophage counterpart in the brain compartment. Most observations indicate that these cells enter the CNS only during embryonic development; after birth, peripheral blood macrophages do not constitute their origin (915).

A. HIV Entry into the Brain

How HIV gains entry into the CNS is not known. Studies of HIV-associated CNS disorders have indicated that the one cell type in the brain which readily shows evidence of HIV infection is the macrophage, particularly those found in perivascular areas (590, 950, 1283). Multinucleated giant cells are, in fact, an important finding in HIV infection of the CNS, particularly in children (for a review, see reference 1077). Conflicting data exist on whether these latter cells are brain microglia and whether they are infectable (922, 1253)

TABLE 23. Concepts in HIV neuropathogenesis[a]

HIV neurotropism: glial cells, microglia, neurons—membrane permeability changes
Effects on blood-brain barrier: endothelial cells, astrocytes
Effects of cytokine production (by macrophages and astrocytes), e.g., TNF-α
Effects of viral proteins (gp120, gp41, Tat, and Nef)
Immune response: autoimmunity, cytotoxicity
Cofactors, e.g., herpesviruses, papovavirus

[a] See Section XIX.

(see Section VI A). On the basis of these early findings, many researchers concluded that peripheral blood macrophages brought HIV into the brain and caused the pathologic changes observed (590, 950). Nevertheless, studies in animals have indicated that, during life, activated T cells as well as some macrophages circulate in the CNS (915, 1268). They must enter via endothelial cell spaces. Thus, both type of peripheral blood cells could be the initial source of HIV infection. Initial entry by direct viral infection of the capillary endothelial cells and astrocytes should also be considered (see Sections XIX B and C).

How HIV establishes infection in the brain is also not known. In acute HIV infection (and in asymptomatic individuals), free virus can be found in the CSF of patients without any signs of neurologic disorder (473, 479). Therefore, infectious HIV could conceivably readily enter the CSF and brain from the blood via the vascular endothelium. Brain cell infection might then occur if a "neurotropic strain" is present. In this case, macrophage-tropism is one characteristic (see below).

Observations in the SIV system support the conclusion that the virus must pass the blood-brain barrier to infect the brain. Lymphocyte-tropic SIV strains cannot replicate in the brain (1079), and certain macrophage-tropic viral isolates cannot induce CNS disease in primates unless they are injected directly into the brain. These viruses do not appear to be able to pass the blood-brain barrier (739, 1080). Therefore, their inability to infect the brain endothelial cells or to pass through their fenestrations could be the important factor. It is also noteworthy that replication of these macrophage-tropic SIV strains in the blood and other tissues of the animals studied did not induce disease (i.e., via circulating cytokines) and that infected T cells and macrophages were not found in the CNS (1080). Thus, entry of free virus seems to be the initial step in neuropathogenesis in this animal model. Subsequently, a "neurotropic" strain would emerge. Certainly, the induction of brain pathology only by macrophage-tropic and not by T-cell-tropic strains of SIV does suggest a major role of macrophages (or the microglial counterparts) in human CNS disorders, but the mechanism(s) is not well defined. This hypothesis is also supported by recent studies showing pathology in human neural xenografts only with macrophage infection (214).

Six basic concepts can be considered to explain how HIV causes pathologic changes in the brain after entry (63) (Table 23): (i) HIV neurotropism, (ii) the ability of HIV to grow in endothelial cells and cause effects on the blood-brain barrier, (iii) the induction of toxic cytokines by infected cells, (iv) the toxic effects of viral proteins, (v) autoimmune and other immunologic disorders, and (vi) viral cofactors in the pathogenic pathway (e.g., herpesviruses and papovaviruses). These concepts are considered below.

TABLE 24. Recovery of HIV from CSF and brain tissues[a]

Clinical condition	No. positive/total no. (%)
Neurologic disorders[b]	74/96 (77)
Asymptomatic	36/68 (53)

[a] Summarized from references cited in Sections IV C and XIX B. For a review, see reference 158.

[b] Meningitis, myelopathy, peripheral neuropathy, encephalopathy, and dementia.

B. Neurotropism

The concept of HIV neurotropism is supported by a large number of studies indicating the recovery of HIV from the CNS (Table 24) and its detection in glial cells (oligodendrocytes, astrocytes) and even neurons (958, 1283; for reviews, see references 158 and 950) (see Section VI A). Moreover, CD4 has been found expressed on neurons and glial cells in the brain (335), although this observation needs confirmation. Cell culture and immunohistochemical and ultrastructural examinations have also indicated that brain-derived cells (many lacking CD4) can be directly infected by HIV (161, 170, 247, 417, 439, 440, 529, 617, 778, 922, 958, 1081, 1114, 1253, 1254, 1279) (Table 25). Moreover, a cellular receptor, aside from CD4 (i.e., GalC), has been found on brain-derived cells (438) (see Section VII E).

In further support of this neurotropism is the observation that persistent noncytopathic low-level infection of glial cells can occur. It cannot be detected by in situ hybridization studies, but it can be demonstrated after exposure of the cells to lymphocytes, cytokines, or culture fluids of PBMC (1188). Without killing the cell, such a phenomenon in HIV-infected oligodendrocytes, for example, could affect myelin production by these cells and thus normal nerve transmission.

The identification of certain HIV isolates that show biologic and serologic properties distinct from blood-derived strains (Tables 17 and 18) (see Section XVI A) also supports the idea that a neurotropic strain exists (158, 165). Finally, as previously mentioned (see Section XVI A), PCR studies suggest that a viral strain in the same host can evolve differently in the brain and the blood and can be distinguished by molecular as well as biologic features (276, 421, 689, 895, 1137). Finally, the recent observations with transgenic mice containing either the LTR of a CNS-derived strain or a T-cell-tropic strain of HIV are noteworthy (203b). Only animals generated with the CNS-derived LTR showed gene expression in the brain, particularly in neurons. This observation supports a differential ability for brain-derived strains to replicate in the CNS and suggests that neurons could be

TABLE 25. Cultured brain-derived cells susceptible to HIV infection[a]

Cell	CD4 expression[b]
Astrocytes (fetal)	±
Microglia	±
Dorsal root ganglia (glia)	−
Choroid plexus	−
Glioma cell lines	±
Medulloblastoma[c]	−
Neuroblastoma	−

[a] Low virus replication observed that is amplified by addition of PBMC. See Sections VI A and XIX B for discussion and references.

[b] −, no CD4 expression; ±, CD4 detected in some cells or cell lines.

[c] Expresses glial and neuronal cell markers.

involved in a neuropathic process in infected individuals (286, 565).

The cytopathicity of HIV itself in the brain could be related to its proteins, its effects on cell membrane permeability or function, or the accumulation of unintegrated HIV-1 DNA in brain tissue (893). Effects similar to those induced in other cells by the virus might be involved (see Sections IX, X, XVII, and XVIII). In summary, transmission and development of a neurotropic strain in the brain could be a major factor in HIV neuropathogenesis.

C. Blood-Brain Barrier: Infection of Endothelial Cells and Astrocytes

The observations with cultured glioma (astrocyte) cell lines, as described above, have suggested that HIV might enter the brain compartment through infection of astrocytes associated with the blood-brain barrier. Subsequently, damage to this structure would cause further neuropathic sequelae. Detection of HIV in the brain capillary endothelium (1283) and the ability to infect these cells with the virus (813) also suggest that this tissue can be an initial portal of entry for HIV. Circulating HIV from the blood might first infect the vascular endothelial lining cells in the brain and then pass from the basolateral surface layer (882) to astrocytes. Subsequent mutational changes in the virus could determine its ability to spread and cause disease in the CNS (see below).

Since astrocytes help to maintain the integrity of the blood-brain barrier (316), this proposed infection of brain endothelium and subsequently of astrocytes could cause a disturbance within the blood-brain barrier. Toxic products as well as infected cells could then enter the brain and might induce the dementia and other neurologic disorders observed. Arguments against this concept include the fact that other viruses can infect endothelial cells and astrocytes but do not appear to give rise to certain of the neurologic conditions found in HIV infection, such as vacuolar myelopathy (921).

D. Toxic Cellular Factors

Once HIV has entered the brain, it could induce in infected cells a high production of toxic cellular products depending on the cell types infected, and these products could induce neuropathic changes (for a review, see reference 774). Several cytokines are produced by cells in the CNS (690) (Table 26). High levels of quinolinic acid have also been reported in the CSF of HIV-1-infected patients (458). It is not known which cells make this excitotoxin, an NMDA agonist (see below), but recent work with poliovirus suggests that macrophage-microglia may do so (459).

Many investigators believe that the microglia and macrophages within the brain, after HIV infection or exposure to viral envelope proteins, could be induced to produce certain cytokines (e.g., TNF-α and IL-1) that are directly toxic to the CNS (341, 745, 775, 776). TNF-α in large quantities has been shown to destroy neurons from rodent species and to be toxic for myelin and human glioma cell lines (1026, 1070). Moreover, TNF-α and lymphotoxin have been found to be cytotoxic for bovine oligodendrocytes but not astrocytes (1069). The mechanism of this cell destruction appears to be apoptosis (see Section XVII B). In addition, some studies suggest that stimulated astrocytes (perhaps via HIV infection or exposure to viral envelope proteins) could produce TNF-α that is toxic to brain cells such as oligodendrocytes (776, 994). However, only low levels of TNF-α have been found in CSF (404). Thus, the toxicity of this cytokine, if present in the CNS, would have to result primarily from apocrine secretion.

TABLE 26. Cytokine production in the brain[a]

Cell	Cytokines
Astrocytes	TNF-α, lymphotoxin; IL-1, IL-6; IFN-α, IFN-β; TGF-β
Microglia (macrophages)	IL-1; TNF-α; TGF-β; low-molecular-weight cytotoxins (?); quinolinic acid (?)
T cells	Lymphotoxin (TNF-β); neuroleukin

[a] For discussion and references, see Section XIX D.

Recently, induction of transforming growth factor beta (TGF-β) production by macrophages and astrocytes has been linked to CNS disorders (1237). Expression of TGF-β was found in the brain, and purified human moncytes infected with HIV were shown to secrete increased levels of this cytokine. Moreover, infected macrophages released substances that induced cultured astrocytes not infected with HIV-1 to secrete TGF-β. Since TGF-β is a very potent chemotactic factor and can augment the production of other cytokines including TNF-α, its role in CNS disease deserves further attention.

In support of this concept of the role of toxic cellular factors in neuropathogenesis is the observation that macrophages infected by HIV, in contrast to uninfected macrophages, release factors (in addition to TNF-α) that are destructive to rodent neuronal cells and human brain cells grown in culture (375, 956). Electron microscopy shows distinct changes in the ultrastructure of cells, particularly their tubular fibrils (955). Macrophages recovered from the PBMC of HIV-infected individuals also induce this damage in cultured human brain cells. Recent observations on neural xenografts, cited above, also support the hypothesis that infected macrophages can be responsible for neurotoxicity (214). In the two research studies cited above, low-molecular-weight substances produced by infected macrophages appear to mediate the effects. One is heat labile (956), and the other is heat stable (375). Whether these cytokines detected in vitro are produced in the brain in sufficient quantities to cause pathology is not yet known.

E. Toxic Viral Proteins

The other consequence of macrophage or microglial infection would be the production of high levels of viral proteins in the CNS. As noted above, envelope gp120 is toxic for cultured brain-derived cells from a variety of animals as well as humans (96, 705, 957) (Table 27). This viral protein can affect the permeability of the cell membrane and its electrical potential via an effect on calcium channels (262, 536, 704). It can act via the NMDA receptor to cause neurotoxicity (705). In this latter process, quinolinic acid has also been implicated (see Section XIX D). Moreover, its role in inducing membrane damage directly (299, 349) or activating, via a receptor, a toxic tyrosine kinase activity in brain cells (1055) could be involved (see Sections XVII and XVIII). Thus, normal nerve transmission could be affected not only by infection of brain cells (e.g., oligodendrocytes) directly but also by a compromise in the integrity of the cell membrane by this envelope viral protein.

In addition, certain regions of the envelope protein (par-

TABLE 27. Neurotoxic effects of HIV envelope gp120[a]

Effect	Reference
Kills cultured rodent neuronal cells	96
Kills cultured human brain cells	957
Blocked by anti-gp120 antibodies	262, 536
Inactivated by anti-CD4 antibodies (murine system; not rat retinal cells)	96, 536
Prevented by calcium channel blockers (nimodipine)	262, 686
Prevented by antagonists to NMDA receptor	705
Reversed by neuroleukin	652
Prevented by VIP	96, 873

[a] See Section XIX E for discussion.

ticularly a threonine-rich epitope called peptide T) appear to compete with neurotrophic factors, such as neuroleukin (now identified as phosphohexose isomerase) and vasoactive intestinal polypeptide (VIP) (652, 916, 917). In this regard, VIP can prevent the neuronal cell killing observed in vitro with gp120 (96). The envelope would then cause dementias and neurologic symptoms by blocking the function of these factors needed for the growth, communication, and maintenance of nerve cells (351).

Furthermore, as described previously, the envelope gp41 and Tat protein have been found to be toxic to cells in culture (790, 1029). Tat was also neurotoxic when inoculated intracerebrally into mice (1029). Like gp120, it can cause depolarization of cells and membrane degeneration. The mechanisms remain to be elucidated, but Tat shows some homology with a neurotoxin (351). Finally, a relatedness of the HIV Nef protein and perhaps part of gp41 to scorpion toxin has been suggested by sequence analysis (352, 1273). Nef protein can affect normal cellular transmembrane conduction (1273) and appears to be selectively expressed in cultured astrocytes (44, 93). It could compromise the electrical potential and function of these cells. Thus, this viral product, along with gp120, gp41, and Tat, might play a role in the neurologic conditions observed with HIV infection.

F. Immunologic Disorders and Viral Cofactors

Two other possible concepts explaining HIV pathology in the CNS are autoimmunity and other immunologic disorders and infection by other viruses. Autoimmune responses could be induced as a result of molecular mimicry (868) (see Section XXIV); certain viral proteins resemble normal cellular proteins. Autoantibodies to peripheral nerves have been described in this infection (238, 576) and appear to be responsible for peripheral neuropathy (576). Antibody levels to myelin basic protein in the CSF have also correlated with the severity of dementia (719). The reported cross-reactivity of anti-gp41 antibodies with certain proteins in astrocytes (not glial fibrillary acidic protein) could compromise the function of these brain cells (1308). Moreover, brain-reactive antibodies have been detected in the sera of infected patients (614), particularly those with neurologic disease. The presence of these antibodies in immune complexes within the CSF has recently been noted as well (cited in reference 63). In addition, antiviral or anticellular CTL that are harmful to the brain could be generated in the CNS (516). Moreover, HIV infection appears to enhance the capacity of monocytes to adhere directly to neural cells and cause cytopathic effects (1164a).

Finally, several investigators have reported the presence in the brain of other infectious agents such as CMV, herpesviruses, and papovaviruses (e.g., JC virus) that could worsen the neuropathologic condition (476, 841, 842, 1281, 1282). It is noteworthy that cells coinfected with HIV and CMV have been found (842). Nevertheless, whereas herpesviruses and papovaviruses have been shown to activate the HIV LTR in a conventional CAT assay (230, 361, 372, 468, 642, 812, 877, 968) (see Sections XII and XXVI), whether their infection in the brain has a biologic significance in terms of HIV replication and pathology is not yet known. In some in vitro cell culture studies, for example, CMV has increased HIV replication (1108); in others, the opposite effect was noted (602). Many findings suggest that the opportunistic infection, when present, can be the primary cause of the neurologic disease. Other observations, however, such as the improvement in the patient's dementia with AZT therapy (see below), suggest that HIV can be a major culprit as well.

G. Conclusions

Because some of the neurologic findings are primarily found associated with HIV infection (e.g., vacuolar myelopathy) (921), I favor the concept that neuropathogenesis depends on infection of the brain by a neurotropic HIV strain. This virus replicates sufficiently in endothelial cells and particularly astrocytes to damage the blood-brain barrier (Fig. 20). Conceivably this virus could have evolved over time from a blood-borne strain that could initially infect endothelial cells or pass through intercellular fenestrations to the astrocytes lining the blood-brain barrier. Support for this hypothesis is that the non-macrophage-tropic strains from the blood infect glioma (astrocyte) cell lines (161, 606).

A subsequent compromise in the function of the blood-brain barrier leads to further HIV infection through ingress of virus and infected cells. Subsequent emergence of a strain that (through mutations) replicates well in macrophages, perhaps microglia, and other brain cells (see Section VI A) gives rise to production of viral proteins (e.g., gp120, gp41, Tat, and Nef) that can be toxic to cells. Moreover, they could compete with neurotrophic factors to inhibit cell-to-cell communication. This macrophage-tropic virus might also most easily pass to other brain cells such as oligodendrocytes (producers of myelin needed for nerve transmission) and even neurons, with a resulting compromise in membrane integrity and intercellular communication (Fig. 20). In this regard, the loss of neurons observed in the frontal cortex in HIV-associated disease (see Section XIX B) (286, 565) could result from the viral infection itself or its sequelae.

Specific infection of macrophages or certain other cells in the brain (e.g., astrocytes) could also favor enhanced production of toxic cellular factors (Table 26) that damage other brain cells and myelin. Eventually, any approach to limit HIV replication and spread should decrease neurologic symptoms. Such a response has been reported with some patients receiving AZT (234); in recent years, the incidence of AIDS-related dementia has been markedly reduced (942). The encouraging decrease in this clinical condition has been attributed to an anti-HIV or anti-cytokine effect, or both, of AZT. The fact that the dementia is reversible with AZT argues at least for primarily a noncytotoxic effect of HIV or the presumed induced cytokines.

The role of other viruses, if not primary, could also be contributory in many cases. Autoantibodies also appear to be involved primarily in peripheral neuropathy, as shown by immunohistochemical staining and successful treatment by plasmapheresis (578) (see Section XXIV). Finally, abnormal

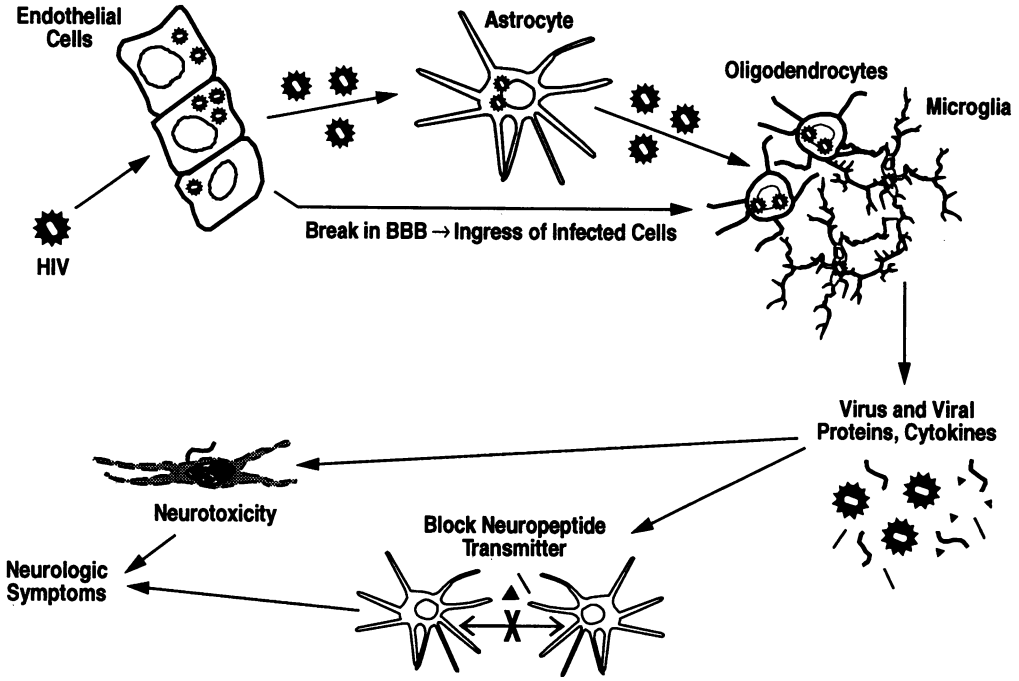


FIG. 20. HIV neuropathogenesis. It is proposed that the virus infects capillary endothelial cells of the brain and passes via the basolateral surface of these cells to astrocytes lining the blood-brain barrier. Infection of both these cell types leads to a breakdown in the blood-brain barrier and ingress of infected T cells and macrophages. The ultimate result is an infection of other brain cells (e.g., oligodendrocytes and microglia) with HIV. Production of HIV and its viral proteins ensues, as well as the release of various cytokines (e.g., TNF-α, low-molecular-weight substances). These products could lead to an interruption of cell-to-cell transmission through a blockage of neurotrophic factors. Direct infection of cells, as well as high levels of viral proteins (e.g., envelope glycoproteins, Tat, and Nef) and cytokines, could lead to direct neurotoxicity through detrimental effects on the cell membrane.

vitamin B_{12} metabolism in HIV infection has led some investigators to suggest that this deficiency contributes to neurologic disease (584).

XX. HIV-ASSOCIATED BOWEL DISORDERS

Along with the CNS disorders observed during some acute HIV infections, bowel symptoms have been reported to occur soon after infection but then subside (1183). The chronic malabsorption, malnourishment, and diarrhea that occur several years later have generally been attributed to the opportunistic infections in the bowel as a result of immune deficiency (599). In Africa, for instance, this gastrointestinal problem has been termed "slim's disease" (1072) because of the substantial loss of weight resulting from the infection.

Recent studies have now demonstrated the presence of HIV itself in the bowel mucosa of patients with gastrointestinal disorders as well as in asymptomatic individuals (453, 600, 744, 843). In several cases, it is the only pathogen found in the bowel. Thus, the virus can "home out" in this organ as well as the brain (see Sections VI A and XVI B). Its presence in enterochromaffin cells in the bowel mucosa (679, 843) is noteworthy. These hormone-producing cells are distributed throughout the intestinal tract and are responsible for normal motility and bowel function (932). The lamina propria has also shown evidence of HIV infection, most probably in infected macrophages (321, 600, 843), since, at the time of bowel symptoms, very few $CD4^+$ lymphocytes are present in the infected gastrointestinal tract (107).

HIV pathogenesis in the bowel has not yet been explained, and, similar to HIV infection of the CNS, several concepts have been considered. Moreover, as in the brain, when opportunistic infections are present, it is difficult to determine whether they caused the initial disease or contribute to an HIV infection. In symptomatic individuals in whom no other bowel pathogen can be found, direct infection of the bowel mucosa (e.g., enterochromaffin cells) causing the abnormalities should be considered (679). In further support of this conclusion, bowel-derived HIV strains with properties distinguishing them from viruses isolated from the blood of the same individual have been described (48) (see Section XVI B).

As with CNS disease, however, some investigators argue that infection of macrophages and T cells in the intestine of these patients induces the production of cytokines that have destructive toxic effects on the bowel mucosa. As noted above, macrophage-tropic HIV strains are readily isolated from bowel tissue (48). Also, histochemical studies of the gastrointestinal tract show chronic inflammation (599, 843) that is not unlike that of bowel disorders caused by a variety of infections and toxic agents. Nevertheless, the extensive diarrhea and maladsorption observed in AIDS does suggest a direct effect of the virus on intestinal cell membrane integrity, perhaps in the handling of sodium ions and water (see Section XVII A). The watery diarrhea often observed could be the effect of a toxin, perhaps a product of infected cells or a viral protein. As in the CNS, the potential role of the envelope glycoproteins, or of Tat or Nef, on cell viability

and physiologic function should be considered (see Section XIX E).

A strain of SIV, PBJ, that induces severe diarrhea in infected rhesus macaque monkeys within 10 to 21 days has been characterized (332). Proliferation of lymphoid tissue is found in the bowel, a pathology not commonly seen with HIV. Whether cytokine production by immune cells or direct toxic effects of the virus on bowel epithelium is responsible for the disorders is not yet known. Studies of this animal model, although unusual, might uncover the cause of gastrointestinal disorders associated with HIV infection in humans.

XXI. EFFECT OF HIV ON THE FUNCTION OF OTHER ORGAN SYSTEMS

HIV has been detected in the hearts of patients with cardiomyopathy (703) and the kidneys of individuals with tubular glomerulopathy (192) and has been recovered from the adrenal glands of infected individuals (1244a). In the latter case, cytokines expressed by infected hematopoietic cells in this tissue could be involved in decreased adrenal function (405). Fetal adrenal cells in culture have been found to be susceptible to HIV (47), but most evidence suggests that in vivo it is CMV and not HIV that causes the cell destruction noted in this tissue (399, 954). A role of HIV in other endocrine disorders via a variety of mechanisms merits further study (405).

It is not yet clear how HIV plays a role in the disorders of the heart and kidneys. Nevertheless, the known effects of gp120 on membrane permeability (see Sections XV C and XVII A) could explain some of the electrophysiological abnormalities that accompany heart disease. In the kidneys, direct infection of the endothelium or mesangial cells might produce the tubular destruction observed in this HIV-associated condition (192, 397, 572, 970). It is noteworthy that immune-complex glomerulonephritis occurs rarely in HIV infection but has been described with IgA-containing complexes (for a review see reference 572). Finally, the presence of HIV antigens in joint fluid and synovial membranes (278, 1291) prompts further consideration of the potential role of the virus in associated arthropathies.

XXII. HUMORAL IMMUNE RESPONSES TO HIV INFECTION

Thus far the basic biologic features of HIV and its heterogeneity have been discussed. How certain characteristics could play a part in the pathogenic pathway has also been considered. In this section, the host humoral immune responses that could influence HIV-induced disease are reviewed.

A. Neutralizing Antibodies

A conventional response of the host against viral infection is the production of antibodies that attach to the virus and inactivate or neutralize it. The HIV envelope is the major target for humoral antibody responses. By comparing a variety of strains, conserved (C) and divergent or variable (V) regions of the envelope have been identified (1127, 1286). As discussed above (see Section XIV F), the viral proteins believed to be primarily involved in antibody neutralization have been localized to the envelope gp120 and the external portion of gp41 (104, 146, 222, 425, 469, 715, 746, 962) (Table 28). Antibodies to the p17 core protein have also been reported to show neutralizing activity (899, 1040), but this finding requires further confirmation (992).

TABLE 28. Regions of HIV sensitive to antibody neutralization[a]

Viral envelope gp120
V3 loop (PND)
Conformational epitope
CD4-binding domain
Second conserved domain (C2) (?)
V2 region
Carbohydrate moieties
Viral envelope gp41
Viral p17 (?)

[a] See Section XXII A for discussion and references.

The presence of anti-HIV neutralizing antibodies in infected individuals has been reported by several investigators. Some sera show high levels of antiviral activity against common laboratory strains; however, in general, infected individuals have not consistently demonstrated strong neutralizing activity against their homologous strain (155, 482, 1265). In our laboratory, titers of only 1:10 to 1:100 are usually found, if present at all (481). The observations could reflect escape from the humoral immune response (762, 837, 981, 997, 1288). Moreover, as the disease progresses, neutralizing antibodies appear to be replaced by enhancing antibodies (482) (see Section XIV F). It is not clear why certain laboratory strains, passed for months or years in vitro, are very sensitive to neutralization by a variety of heterologous sera. With some HIV-1 strains (e.g., SF2 and MN), a common envelope epitope (i.e., in the V3 loop) can be involved (see below), but with others (e.g., IIIB/LAV), an antigenic similarity among many isolates is not evident. We have, moreover, some long-passaged laboratory strains that are resistant to neutralization and others that are even more sensitive to antibody-mediated enhancement (483). Thus, as noted above (see Section XIV F), other factors besides prolonged growth in culture can determine the antibody sensitivities of the various HIV strains.

In general, HIV-1 sera can neutralize HIV-1 but not HIV-2 strains. In contrast, sera from HIV-2-infected individuals have been reported to cross-react and neutralize some HIV-1 strains (1266). They also cross-neutralize SIV strains (995). This latter finding emphasizes further the reported similarities in envelope structure of these two lentiviruses (see Section XIV A). In addition, immunization of animal species (e.g., rodents, guinea pigs, rabbits, monkeys, and goats) with HIV envelope proteins has induced antibodies that neutralize the immunizing strain and are type specific. With several booster doses, this antibody response can be expanded to include other diverse strains, suggesting a broadening of the immune response (424, 517). This cross-reactivity could be governed by antibodies to the CD4-binding site, particularly conformational epitopes (1133) (see below); however, this possibility requires confirmation.

Most studies of neutralization sites on HIV indicate that at least six regions of the viral envelope could be involved in HIV neutralization (five portions of gp120 and a region of gp41) (Table 28). Recently, a second conserved domain in gp41 (amino acids [aa] ~647 to 671) has been suggested (104; for reviews, see references 94 and 853) (Fig. 21). Some studies with hypervariable deletion mutants also have shown that domains in V1 or V2 and in V4 or V5 of gp120 could induce neutralizing antibodies (425). These and other observations suggest that further envelope epitopes, sensitive to

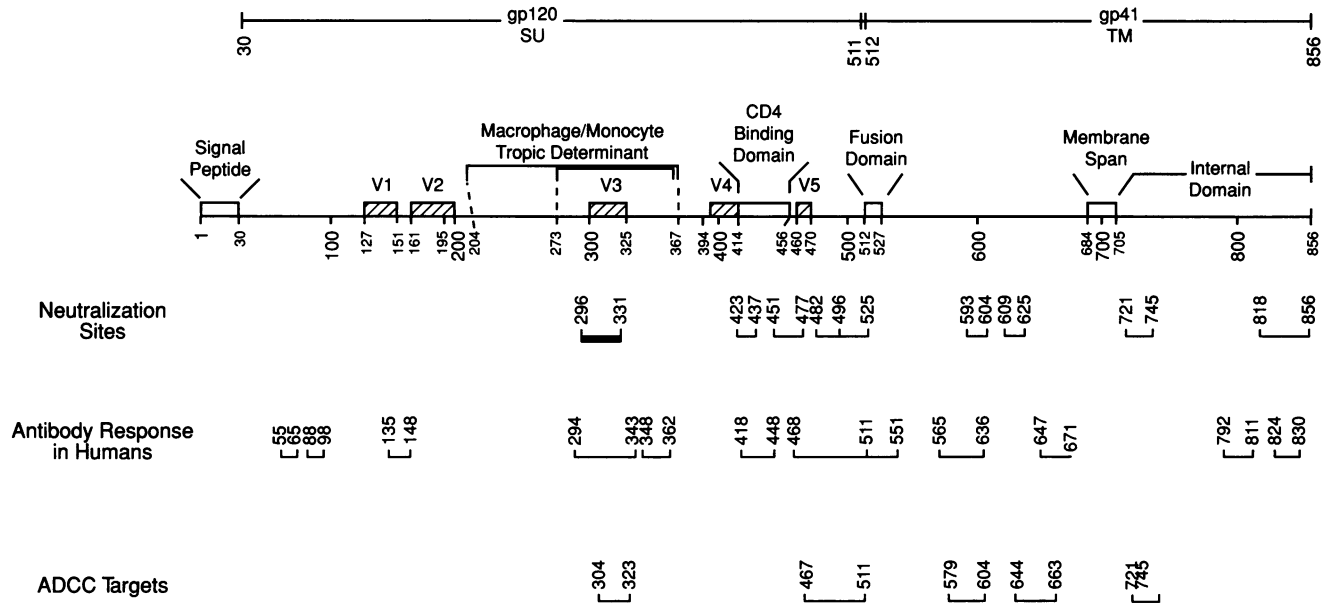


FIG. 21. The envelope region of HIV-1, with neutralization domains as well as ADCC regions in gp120 and gp41 demonstrated. Figure courtesy of J. Bradac.

neutralization, will be detected. In addition, as noted above, p17 as a potential neutralization region is under consideration. Finally, the pattern of glycosylation could also be involved or could influence the results (58, 296, 355) (see Section XIV B).

A very important neutralizing domain of gp120, the PND, is found in the central portion or crown of the third variable region (V3 loop; aa ~308 to 322), located in the N-terminal portion of the gp120 (103, 104, 517, 518, 639, 746, 1340). Although V3 is a variable region, the PND is a linear epitope conserved among many strains or differing only slightly in amino acid structure (Fig. 14). Thus, immunization with this region of gp120 will, over time, induce antibodies that neutralize a large number of HIV-1 strains that share this envelope domain (69, 517). Conceivably, this conserved region also has a conformational structure common to many viral strains that can be recognized by a wide variety of conformation-dependent neutralizing antibodies (see below) (for a review, see reference 1132). The V3 loop-directed neutralization does not involve the CD4-binding domain (702, 1106). Recently, a region suggestive of a V3 loop in HIV-2 strains has been identified (75, 80, 248) but needs further evaluation.

The V3 loop can have both neutralizing and nonneutralizing epitopes, since sera with high-titer antibody to V3 peptides do not always neutralize the homologous HIV-1 strain (1250). Moreover, work with escape mutants has indicated that regions within (837, 1298) or outside (762, 981, 1285, 1288) the V3 loop (for a review, see reference 1132) can be involved in efficient antibody neutralization. These latter mutants have the same V3 loop sequence but bear changes distal to this envelope region (1286). These other sites can apparently alter the conformation of the V3 loop, permitting virion escape from neutralization. Thus, as noted above, the V3 region can be both a linear and conformational determinant for antibody recognition. In this regard, glycosylated forms of the HIV-1 envelope can be better recognized than nonglycosylated proteins by immune sera (424, 1132, 1133). The latter observation emphasizes the potential influence on neutralization of carbohydrate moieties on the viral envelope (58, 229, 296) (see below). All these results define nonlinear conformational epitopes in gp120 (both to V3 and the CD4-binding regions) that form a second type of reaction by which HIV can be neutralized by antibodies.

A third major neutralizing region on gp120, noted above, is in the CD4-binding domain (i.e., the major region; aa ~413 to 447) (543, 640, 1133, 1150). Antibodies that cross-neutralize a large number of different strains, including those with different V3 regions, are directed against this region. The determinant is generally conformation dependent (470, 1133). Neutralizing MAbs that recognize discontinuous epitopes on gp120 involved with CD4 receptor interaction have been derived from HIV-infected patients (1177). The antibodies block the ability of the HIV strains to attach to the major cellular receptor. Recently, a synergy in neutralization has been demonstrated by using antibodies against the CD4-binding region and the V3 domain (1180).

A fourth region initially considered important in neutralization is the second conserved domain of gp120 (469), but this observation has not been confirmed (1012) and is most probably not involved. Also, a fifth neutralizing region of gp120, recently identified, is in the V2 region (334). As noted above, earlier studies had suggested this neutralizing epitope as well (425). Similar to the V3 loop, both a linear and conformation determinant could be involved since this region is recognized by antibodies to both glycosylated and nonglycosylated epitopes (468).

The neutralizing antibodies directed against gp41 have received less attention. Nevertheless, immunization of animals with the N-terminal portion of the envelope (a common fusion domain) (146, 222) has elicited antibodies to the homologous and to heterologous strains. MAbs to gp41 have also shown anti-HIV activity (1002). The immunodominant region of this envelope protein has been recognized particularly after HIV interaction with CD4; removal or displacement of gp120 is assumed to have occurred (1045) (see Section VIIB). Anti-idiotype neutralizing antibodies have also been made by using portions of gp41 (1333).

Finally, as cited above, recent reports indicate broad neutralizing activity against carbohydrate regions of the viral envelope (58, 296, 433). Whether these antibodies reflect conformational epitopes or true anticarbohydrate reactions is not clear. Since intracellular modification of HIV glycosylation has been observed (see Section XIV B), whether escape variants would be easily formed by using this mechanism should be explored.

The clinical relevance of these neutralizing antibodies remains uncertain. They would have value when elicited by a vaccine, but their effect in controlling viral spread following infection is not clear. In this regard, passive therapy with human immunoglobulins with neutralizing activity has prevented HIV infection of chimpanzees after a low-dose (10 50% chimpanzee infectious doses [CID_{50}]) but not high-dose (100 CID_{50}) challenge (951, 952). Moreover, anti-V3 specific antibodies have protected chimpanzees from infection (75 CID) when given 1 day before virus inoculation or within a few minutes after exposure to the virus (275). However, this protection was strain specific and has not been seen after longer periods of delay before treatment (950a) (see Section XXX E). Whether levels of neutralizing activity correlate directly with the clinical state is still controversial (15, 996, 1068, 1229, 1270). Patients, including those with AIDS, can have substantial titers of neutralizing antibodies as measured with laboratory strains (996). In most cases, however, their antiviral response to the homotypic strain, which would be the most important clinically, was not evaluated.

As noted above, studies by Homsy et al. (482) suggest that an AIDS patient often elicits antibodies that enhance rather than neutralize infection by the virus found in the patient. Moreover, as cited above, the virus changes under immunologic responses to escape neutralization (32, 762, 837, 981, 996). Thus, the induction of neutralizing antibodies would appear to be most beneficial early in the course of HIV infection and to have less influence in later stages.

B. ADCC and ADC

Antibodies (IgG1 isotypes) to both the gp120 and gp41 envelope proteins induce ADCC (284, 601, 707–709, 857, 867, 1201). In this process, the antibody-antigen–coated cells are recognized by effector NK cells bearing Fc receptors or by other monocytes (see Section XXIII) and killed by a cytotoxic mechanism, most probably cytokine mediated (e.g., by perforins) (for a review, see reference 1306). Certain epitopes on HIV envelope proteins induce this response (for a review, see references 94 and 853) (Fig. 21), since not all anti-Env antibodies produce this activity and they can be distinguished from neutralizing antibodies (87). Cross-reactivity with HIV-1 and HIV-2 strains has been demonstrated (857).

The ADCC process has been found to be active in destroying herpesvirus-infected cells early after virus transmission (1095). Whether ADCC is relevant clinically in HIV infection is not known; conflicting data on its association with an asymptomatic state have been presented (284, 708, 709, 1047). One detrimental effect in HIV infection could be the release by cell destruction of large quantities of infectious particles with subsequent spread in the host. Since anti-envelope antibodies mediating ADCC are present at substantial titers throughout the course of the infection (284), the extent of effector-cell activity would appear to be the important parameter influencing the ability of the ADCC process to control HIV infection (97, 1155, 1202) (see Section XXIII).

In principle, ADCC would seem most important soon after infection to kill incoming or postentry virus-infected cells. Induction of ADCC response by vaccines would then be a valuable objective, and this response might be helpful in preventing mother-to-child transmission. Thus, ADCC could be another reason to consider passive immunization with anti-HIV envelope antibodies for recently exposed individuals or infected mothers prior to delivery.

Anti-HIV antibodies in chimpanzees have been found to be involved in another process; they directly kill infected cells via a complement mechanism (1238). They attach to virus-infected cells and, without effector cells, can bring about cell death. This antibody-dependent cytotoxicity (ADC) has not been observed in humans; it has been cited as one possible reason why infected chimpanzees have not developed HIV-induced disease.

C. Enhancing Antibodies

(i) Complement- and Fc-mediated responses. We have previously discussed the presence in HIV-infected individuals of antibodies that can enhance viral infection either via the complement or Fc receptor (1005). In the U937 monocyte cell line, FcR1 was shown to be the receptor for ADE (1159). In primary macrophages, MAbs to the FcRIII receptor were the most effective in abrogating ADE (482). This receptor, identified by CD16, is found on NK cells and a variety of other human cells that could also conceivably be infected by antibody-HIV complexes.

As reviewed in Section XXII C, the role of CD4 in ADE is controversial. Studies by Robinson et al. (1007) and others (914, 980, 1191, 1331) have suggested that enhancement by the complement receptor depends on CD4 since MAbs to this molecule block viral enhancement. Takeda et al. (1159) drew the same conclusion with Fc-mediated enhancement. In contrast, Homsy et al. (483), in studies with peripheral blood macrophages, demonstrated that ADE via the Fc receptor took place in the presence of antibodies to CD4 (Leu 3a) as well as after pretreatment of the virus with large quantities of soluble CD4. In further support of a non-CD4 mechanism is the experiment with HIV-antibody complexes demonstrating HIV infection of CMV-infected fibroblasts expressing the Fc receptor (763).

If CD4 is involved in ADE, most investigators conclude that the enhancement occurs because the virus-antibody complexes are brought closer to the CD4 molecule after attachment to Fc or complement receptors. Alternatively, if CD4 is not involved, perhaps HIV is brought to the cell surface via Fc-receptor binding and then the virus fuses directly with the cell membrane.

Finally, some studies have suggested that complement alone can mediate HIV-1 infection in a CD4- and antibody-independent manner (92a). The interaction of small amounts of opsonized virus with the CR2 receptor on cells has been demonstrated; the clinical relevance of this process is not known.

(ii) Viral genetic sequences associated with enhancement versus neutralization. In contrast to the identification of several viral domains involved in neutralization, only limited regions on the virion have thus far been linked to ADE. Antisera to peptides have suggested that the process can be mediated by regions on the envelope gp120 and gp41 proteins (523). Robinson et al. (1002–1004), using MAbs, have suggested that two domains (aa ~579 to 613 and aa ~644 to 663) at the N-terminal end of gp41 are the reactive sites in the complement-mediated process.

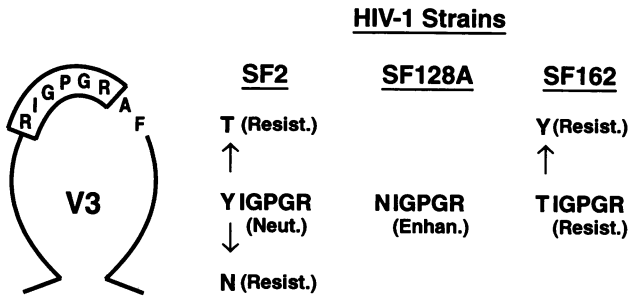


FIG. 22. The V3 loop in virus-antibody neutralization and enhancement. By using a MAb to a small epitope in the HIV-1 V3 loop (shown in the blocked area), differences in response of various virus strains can be appreciated. Some are neutralized (Neut.), others are enhanced (Enhan.), and still others are resistant (Resist.). As demonstrated, only one amino acid change appears to affect the serologic response, but the results are strain specific (data from reference 587). If the amino acid is modified by site-directed mutagenesis (arrows), the mutant virus appears to become resistant.

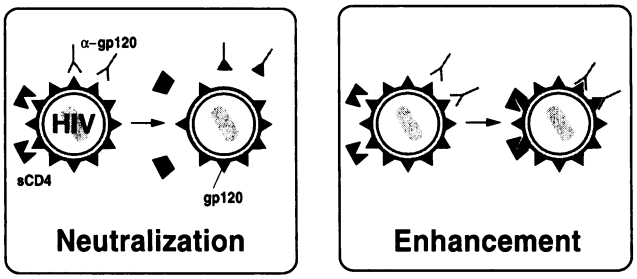


FIG. 23. Mechanisms for neutralization and enhancement. The concept is proposed that neutralization involves a strong binding of antibody (or soluble CD4) to the viral envelope with the subsequent removal of gp120, resulting in virus inactivation. Enhancement would involve binding to the virus without removal of the envelope glycoprotein. Conformational changes that increase infection by the virus, presumably via virus-cell fusion, would subsequently occur.

In the studies examining the viral envelope region responsible for Fc-mediated ADE, polyclonal antibodies against regions in gp120 and MAbs directed against the V3 region of some HIV-1 strains have been helpful. Polyclonal anti-gp120 and anti-V3 loop antibodies have shown both neutralizing and enhancing effects depending on the HIV-1 strain used and the concentration of the antibodies (524, 587). Moreover, some MAbs to gp120 were found to neutralize HIV, whereas other antibodies enhanced virus infection (587, 1158). These studies helped to narrow down a region on gp120 (i.e., particularly within the V3 loop) mediating Fc-directing ADE (587, 1158). Most recently, a human anti-gp41 MAb that enhances HIV-1 infection in the absence of complement has also been described (270).

A dramatic observation was the presence in some human and animal sera of antibodies that neutralize one HIV-1 strain and yet enhance another (483). In this regard, two human MAbs and one murine reagent that react with the V3 domain of HIV-1_{MN} were found to neutralize the SF2 and MN strains of HIV-1 but enhance the SF128A strain (587) (Fig. 22). These MAbs showed no effect on the SF162 strain; it was resistant. These latter two strains were isolated from the CNS. These MAbs were shown to bind similarly to the gp120 cloned from these viral strains. The studies therefore suggested that very few amino acid changes in the viral envelope could affect sensitivity to enhancement or neutralization after virus-antibody binding. The mechanism for the different response is not yet clear.

The SF128A strain that is enhanced has an asparagine (N) at position 311 of the V3 loop; SF2 has a tyrosine (Y) at this position, and SF162 has a threonine (T) (Fig. 22). By using site-directed mutagenesis, the tyrosine in SF2 was changed to a threonine, and the resulting virus was found to be resistant to neutralization by the MAbs. A change in that position in SF2 from tyrosine to asparagine also resulted in an antibody-resistant strain. Thus, sensitivity to enhancement could not be induced. Finally, a change of the threonine in SF162 to tyrosine also brought about a resistant strain (Fig. 22). Only when two other amino acids were changed in the V3 loop of SF162 to those of SF2 was a neutralizable strain obtained. These last two changes were outside the epitope recognized by the MAb.

These and other observations have suggested that, in general, production of a strain sensitive to neutralization or enhancement will involve several sites on the virus envelope and not just one amino acid. In further support of this conclusion, findings with interviral recombinants of SF2 and SF128A indicate that additional envelope regions besides the V3 loop determine the consequence of the antibody-virus interaction. Exchange of an envelope region encompassing the CD4-binding and fusion domains of SF128A with that of SF2 rendered the SF2 virus resistant to neutralization by a V3 MAb. However, only the exchange of a larger region to include the V3 and CD4-binding and fusion domains of SF128 resulted in enhancement of the SF2 recombinant virus (587). Once again, the data reviewed above underline the importance of envelope conformation in this biologic property.

Further studies with recombinant strains should help clarify the envelope epitopes responsible for the serologic properties observed. The findings with MAbs, however, suggest that the extent of attachment to a virion surface could determine the biologic outcome. One hypothesis under consideration is that high-affinity binding of the antibody leads to virus neutralization, perhaps through removal of the gp120 (806) (Fig. 23). In contrast, low-affinity binding might bring HIV to the cell surface, and subsequent detachment of the virus from the antibody permits infection of the cell. In some ways, this hypothesis mirrors that proposed for inactivation versus enhancement of HIV infection with sCD4 (see Sections VII A, B, and I). The concept needs further evaluation.

(iii) Conclusions. The clinical importance of ADE is not known, but its association with disease (481) (see also Section XIV F) suggests that it has a role in pathogenesis. Circulating infectious virus-antibody complexes have been described in HIV infection (811), and it is surprising that these complexes are infectious rather than destroyed in the macrophage lysosomes. The reason could be the relative affinity of antibodies for the HIV envelope protein and how the complexes are dissociated to become infectious within the cell (see above).

Results showing no biologic significance of ADE (1073) or no correlation with disease progression (801) have been presented. Nevertheless, an increase in symptoms of disease linked to ADE has been observed with dengue virus and other viruses (51, 428, 586, 948), such as retroviruses (654), e.g., the caprine (759) and equine (508) lentiviruses. Moreover, the presence or absence of enhancing antibodies has correlated with clinical disease in primates infected with

HIV or SIV (802, 803, 1006). Finally, antibodies that enhance in vitro infection of certain HIV strains (e.g., SF128) have been detected in some recipients of a vaccine consisting of a recombinant gp160 from a different HIV-1 strain (e.g., IIIB) (585b). Thus, this type of immune response should be considered in treatment approaches and vaccine development (see Section XXVIII).

Certain important conclusions can be drawn from these early findings. (i) Neutralizable HIV strains can mutate to be resistant or enhanced by the same antibody species. (ii) Immunization of individuals with a particular viral strain might induce neutralizing antibodies to the immunizing virus but enhancement of a different viral strain (524, 587), particularly one from another part of the world. (iii) Defining envelope regions that will induce only neutralizing and not enhancing antibody responses could be very difficult. Thus far, regions in gp41 and gp120 have been associated with both types of immune reactions (see above). It is particularly noteworthy that some studies suggest that only a small change at a critical region, perhaps in one amino acid, might determine the sensitivity of a virus to antibody neutralization or enhancement. Nevertheless, the overall conformation of the viral envelope appears to be the most important determinant.

D. Complement-Fixing Antiviral Antibodies

Recent studies have indicated that some neutralizing and nonneutralizing antibodies can lyse HIV via complement fixation (1117, 1118). With the neutralizing antibodies, the antiviral titer can sometimes be increased 10-fold by the addition of high levels of complement to the assay (1116). This response could counter the ADE observed with complement, since only low levels of complement initiate this latter response.

XXIII. CELL-MEDIATED IMMUNE RESPONSES TO HIV INFECTION

This section reviews cellular immune reactions that appear directed against HIV through specific recognition of the virus or virus-infected cell. In most viral infections, the cell-mediated immune response plays a vital role in arresting or eliminating the infectious agent. These observations have been made in studies of human diseases caused by viruses such as herpesviruses, paramyxoviruses, and influenza viruses (253). Some other mechanisms for virus control, particularly locally (e.g., oral, anal, and genital cavities), might involve nonspecific killing by polymorphonuclear leukocytes and the myeloperoxidase system (583). Furthermore, the potential role of polymorphonuclear leukocytes in ADCC activity has been reported (1155).

A. Cytotoxic NK Cells

A major component of cellular immunity is the NK cell, which recognizes and kills virus-infected cells in a non-MHC-directed manner. In HIV infection, this cell type has been found to have decreased function, particularly as infected individuals progress to disease (118, 317). This finding appears to reflect a reduction in NK cytotoxic factor production (84) and a defective distribution of tubulin (1105). Recently, the reduced NK-cell activity noted in vitro has been countered by addition of the B-cell cytokine IL-12 to the assay (153). The potential benefit of IL-12 for therapy is under consideration.

NK cells most probably play the important role in ADCC; polymorphonuclear leukocytes could also be involved (1155) (discussed in Section XXII B). In cell cultures measuring this process, HIV-infected cells are killed by NK cells through the recognition of antibodies bound to the viral envelope proteins on the infected-cell surface. Moreover, $CD16^+$ NK cells carrying anti-gp120 antibodies can be detected in the blood (1201). Thus, these cells can potentially mediate a form of direct ADCC as well. Most ADCC studies measuring levels of antibodies to the HIV envelope proteins have not shown a correlation with the clinical state; anti-gp120 antibody levels do not differ substantially between most symptomatic and healthy HIV-infected individuals (see Section XXII B). If, however, the amount of active effector cells in the infected individual is considered, a reduction in ADCC can be demonstrated with disease progression (97, 1155, 1202).

B. $CD4^+$ Cell Responses

$CD4^+$ cell responses can also be decreased early in HIV infection. Recent observations indicate that, similar to the murine system, human $CD4^+$ T cells can be separated into TH1 and TH2 subsets. TH1 cells secrete IL-2 and IFN-γ; TH2 cells produce IL-4, IL-6, and IL-10. From studies of HIV-infected individuals, a hypothesis has been presented that the TH1 and TH2 cytokines play an immunoregulatory role in HIV infection and can affect progression to AIDS (for reviews, see references 1085 and 1086). It is, for example, noteworthy that TH1 responses are found primarily in healthy asymptomatic individuals and in high-risk individuals who do not show evidence of HIV infection (184, 1084, 1085). Some investigators suggest that this type of response that helps induce cell-mediated immunity could be protective for an individual (1086). A subsequent TH2 response would lead to B-cell activation and hypergammaglobulinemia, most probably secondary to the IL-4 and IL-6 production by the TH2 cells. In this regard, the TH1 and TH2 subsets appear to be reduced and increased, respectively, in AIDS patients. Moreover, the secretion of high levels of IL-10 by the TH2 cells can lead to suppression of TH1 function (1084, 1086).

Since the TH1 cells produce IL-2 and other cytokines that help in enhanced $CD8^+$ cell activity, this subset could also be very important in the cellular immunologic control of HIV infection and prevention of AIDS. This new concept on TH cell interactions, including the measurement of various cellular factors, merits further attention (1086).

On another note, some studies with human T-cell clones demonstrate that certain $CD4^+$ lymphocytes, although sensitive to infection by HIV, can also show cytotoxic activity against HIV-infected targets (870, 1327). Their potential reactivity with normal $CD4^+$ cells has been discussed (see Section XVIII E). Whether this phenomenon is of clinical importance needs further evaluation.

C. Cytotoxic $CD8^+$ Cells

Another cell type, besides NK, that commonly reacts with virus-infected cells is the CTL. Classically, this response is HLA dependent and requires cell-to-cell contact. It appears to be very important in the control of certain viral infections (117, 253) and most probably in the control of HIV infection. In culture, this cellular cytotoxicity is demonstrated by a high input of $CD8^+$ cells, typically a CD8-to-target cell ratio of 50:1 to 100:1, and is measured in a 4-h ^{51}Cr release

TABLE 29. Characteristics of the $CD8^+$ cell antiviral suppressing activity[a]

Property of $CD8^+$ T cells, not NK cells or macrophages
Blocks HIV replication in naturally or acutely infected $CD4^+$ cells
Not HLA restricted
Nonlytic mechanism
Mediated (at least in part) by a soluble factor
Can block HIV replication at low effector-to-target cell ratios (<0.05:1), and is dose dependent
Active against strains of HIV-1, HIV-2, and SIV
Blocks HIV replication at RNA transcription
Correlates directly with clinical status

[a] Measured by in vitro assays (see Section XXIII D).

assay. Moreover, as expected, the cytotoxicity is observed only with viral protein-expressing cells that have the same MHC class I phenotype as the $CD8^+$ cells.

Studies of this antiviral response have shown that $CD8^+$ lymphocytes can kill cells expressing (via a variety of vector systems) several different HIV proteins, including RT, envelope, core, and some accessory proteins (e.g., Vif and Nef) (42, 185, 477, 616, 634, 854, 928, 993, 1241, 1241; for a review, see reference 853). The cytotoxic $CD8^+$ cells can be found in relatively large numbers during the asymptomatic period, but then they appear to decline, at least in antiviral activity in some individuals, with progression of disease (42, 388, 477). The antiviral response can be eliminated by incubating cells with anti-CD8 or anti-CD3 antibodies. Most surprising is the high level of anti-HIV Env CTL found in normal uninfected subjects (477). If confirmed, this observation suggests a cross-reactivity of certain viral proteins with cellular proteins (see Section XXIV).

Although this type of antiviral activity has prevented virus spread in some animal model systems (117), the role of CTL in HIV infection is not clear. Despite some correlation of CTL activity with a healthy clinical state (42, 388), progression of disease with increasing levels of HIV-infected cells occurs in the presence of these $CD8^+$ cells. Perhaps the virus-infected cells are not recognized. Conceivably, suppression of virus expression by the $CD8^+$-cell antiviral factor (see below) leads to the lack of recognition by CTL. Alternatively, the CTL may be compromised by HIV in their effectiveness. Recently a cellular factor that blocks CTL response has been identified in individuals with symptoms (42, 527). This inhibition, mediated as well by $CD8^+$ cells, could be directly involved in a pathogenic pathway that results from a depression in the control of HIV by cytotoxic $CD8^+$ cells. Finally, some recent studies suggest that HIV strains can escape the CTL response (925) (see Section XIV). This mechanism could be involved in progression to disease.

D. Anti-HIV Suppressing Activity of $CD8^+$ Cells

(i) Relationship to clinical state. In addition to having cytotoxic activity, $CD8^+$ cells can suppress HIV replication in $CD4^+$ cells (Table 29). Initially, this cellular antiviral activity was recognized by studying infected individuals who were asymptomatic and whose cultured PBMC did not yield HIV. When their $CD8^+$ cells were removed from the blood sample by the immunologic procedure of panning, high levels of virus were released from the $CD4^+$ cells remaining in the culture (1245). The replacement of $CD8^+$ cells in this culture at levels that were far below those used to demonstrate cytotoxicity (<1:1) led to complete suppression of virus replication. Subsequent removal of the $CD8^+$ cells again revealed virus-releasing cells.

Further observations indicated that the $CD8^+$ cells could suppress virus production without affecting activation markers on $CD4^+$ cells or killing the virus-infected cells (725). The latter conclusion was confirmed in a large number of studies in which the number of virus-infected cells before and after mixing with $CD8^+$ cells remained essentially the same or, in some cases, increased (1247, 1292). This noncytotoxic antiviral response can be measured with naturally infected $CD4^+$ cells obtained from infected individuals as well as with normal $CD4^+$ cells (obtained from seronegative individuals) acutely infected in culture with HIV (725, 1243).

The extent of $CD8^+$ cell activity varies among subjects (1246) and decreases in patients with disease (628, 727). In many asymptomatic individuals, a ratio of $CD8^+$ to $CD4^+$ cells as low as 1:20 in the cell culture assay suppresses endogenous virus replication; in AIDS patients, the ratio often changes to 2:1 or greater. Healthy infected individuals monitored over time also show a loss of this $CD8^+$-cell response concomitant with the onset of symptoms (628). This $CD8^+$ cell suppressing activity has also been demonstrated in the SIV system (545) and in HIV-infected chimpanzees (137). Moreover, the human $CD8^+$ cells show similar responses against many different isolates of HIV-1 (including the virulent strains), HIV-2, and SIV (727, 1247). $CD8^+$ cells from several uninfected subjects have also demonstrated this response. However, their reactivity occurs only with naturally infected cells, not acutely infected cells, and generally only at a $CD8^+$-to-$CD4^+$ cell ratio of 0.5:1 or higher. Why $CD8^+$ cell antiviral activity is lost over time is not known but may reflect reduction in the number of a particular cell subset (628) or loss of its function. The absolute number of $CD8^+$ cells in an infected individual does not correlate with this antiviral activity (628, 725a, 727). The role of apoptosis in reducing these activated $CD8^+$ cells is under study (see Section XVII B).

(ii) Role of a cytokine. A soluble factor produced by the $CD8^+$ cells is involved in part in this $CD8^+$ cell antiviral response (100, 1244). Cell-to-cell contact, however, is the most efficient method of suppressing HIV production. The presence of the factor can be shown by adding supernatant from $CD8^+$ cell cultures directly to infected $CD4^+$ cells (725, 1245). Virus replication is substantially reduced without any effect on cell viability or replication. The level of factor produced correlates with the clinical state (726, 1244). The largest amounts are found with $CD8^+$ cells from healthy HIV-infected individuals with high $CD4^+$ cell counts.

The most recent work attempting to define the factor involved in suppression has revealed that it is not any known cytokine, including the interferons and TNF (101, 678, 726) (the cytokines evaluated are listed in Table 22). The identification and characterization of this novel lymphokine await further studies.

(iii) Mechanism of action. The mechanism by which $CD8^+$ cells inhibit HIV replication has also been under study in our laboratory. The level of suppression appears to be at or before RNA transcription (725a, 678). Naturally infected $CD4^+$ cells mixed with autologous $CD8^+$ cells have a marked reduction in viral RNA and protein synthesis. However, at the time of suppression, an almost equal number of infected $CD4^+$ cells in the culture as those present in control cultures can be detected. Thus, no infected cells are lost; a reduction in virus expression occurs. Whether the cytokine shows the same activity is now under examination.

TABLE 30. Autoantibodies detected in HIV infection[a]

Antibodies to:	Associated clinical condition
Lymphocytes	Loss of $CD4^+$ $CD8^+$ B lymphocytes
Platelets	Thrombocytopenia
Neutrophils	Neutropenia
Erythrocytes	Anemia
Nerves (myelin)	Peripheral neuropathy
Nuclear protein (ANA)	Autoimmune symptoms
Sperm, seminal plasma	Aspermia
Lupus anticoagulant (phospholipid, cardiolipid)	Neurologic disease (?), thrombosis
Myelin basic protein	Dementia, demyelination
Collagen	Arthritis (?)
CD4	Helper T-cell loss
HLA	Lymphocyte depletion
Hydrocortisone	Addison's-like disease
Thymic hormone	Immune disorder
Cellular components (Golgi complex, centriole, vimentin)	Immune disorder
Thyroglobulin	Thyroid disease

[a] See Section XXIV for references.

TABLE 31. Regions of HIV that resemble normal cellular proteins[a]

Normal cellular protein	HIV region	Relation
HLA	gp120, gp41	Sequence
	nef, p17	Sequence
IL-2	gp41	Sequence
	LTR	Sequence
IL-2R	*nef*	Sequence
Thymosin	p17	Serology
Epithelial cells	p17	Serology
Astrocytes	p17, gp41	Serology
IFN	LTR	Sequence
VIP	gp120 (peptide T)	Sequence, serology
Neuroleukin (phospho-hexose isomerase)	gp120	Sequence, serology
Ig	gp120	Sequence
Neurotoxin	*nef*, *tat*, gp41	Sequence
Protein kinase	*nef*	Sequence

[a] See Section XXIV B for references and discussion. Sequence, nucleic acid level; serology, cross-reacting peptide epitopes.

One other finding related to $CD8^+$ cells that potentially affects the clinical outcome is the resistance of PBMC from asymptomatic individuals to superinfection by other strains of HIV-1. Despite the known presence of many uninfected $CD4^+$ cells in their cultured PBMC, no acute infection can take place unless the $CD8^+$ cells are first removed (546, 1244a). Apparently the uninfected $CD4^+$ cells are protected from infection, most probably by the $CD8^+$ cells, their factor, or both. Whether virus enters these PBMC has not been determined.

XXIV. AUTOIMMUNITY

Since HIV disturbs the balance of the immune system, it is not surprising that autoimmune disorders (e.g., Reiter's syndrome, systemic lupus erythematosus, Sjögren's syndrome, vasculitis, and polymyositis) accompany this viral infection (119, 810, 1050, 1209, 1216, 1336). Vasculitis in HIV-infected patients has been linked to immune complexes (119), but immune-complex glomerulonephritis is not commonly found. Autoreactive cellular immunity could be involved in HIV-associated autoimmune responses (224); the finding of anticellular CTL in the CNS needs further study (516). In this regard, anti-Env CTL activity has also been reported in uninfected individuals (477); an induction of this response could occur with HIV infection.

In terms of humoral immune responses, in early studies of AIDS, antibodies, often associated with clinical disorders, were detected against platelets, T cells, and peripheral nerves (see Sections XVIII F and XIX F) (810). More recently, they have included autoantibodies to a large number of normal cellular proteins (Table 30) (6, 31, 79, 144, 363, 396, 576, 579, 603, 719, 728, 1035, 1178, 1258). The reason for these autoimmune sequellae is not clear. Besides T-cell dysregulation, other possible processes are discussed below.

A. B-Cell Proliferation

A lack of T-cell regulation in HIV infection can lead to a proliferation of B cells with resultant polyclonal proliferation and antibody production. These kinds of reactions have been reported in other viral infections (e.g., EBV infection) in which hypergammaglobulinemia and autoimmune disorders are described (457). Polyclonal B-cell activity has been observed in HIV-infected individuals (890, 1094) and is associated with high levels of antibody production, particularly in children (23). This B-cell response can result from IL-6 production by HIV-infected or reactive macrophages (95, 745, 1016) or by B lymphocytes (88). Recently, the induction of IL-6 by the viral Tat protein has been suggested (975). B-cell growth could also result from TNF-α production (555); Tat also induces this cytokine in T lymphocytes (110). Part of the B-cell response could be secondary to TH2 cell influence (1086) (see Section XXIII B). Among the immunoglobulins released are autoantibodies. Thus, a number of processes are probably involved in this B-cell response during HIV infection.

B. Molecular Mimicry

When an organism shares either sequence or amino acid homology with a normal cellular component, molecular mimicry can exist (868). In this regard, similarities between HIV proteins and normal cellular proteins could elicit antiviral antibodies or cellular immune responses that cross-react with normal cells (74, 868) (Table 31). Evidence in favor of this possibility includes the presence of IL-1, IL-2 receptor, MHC class I and class II, and interferon-like sequences in the HIV genes, as well as potential cross-reacting epitopes on certain envelope portions of the virus (224, 351, 382, 383, 667, 668, 839, 979). Moreover, cross-reactive antibodies recognizing a platelet glycoprotein and an HIV gp120 epitope have been cited as a possible mechanism for thrombocytopenia (70a). Similarities of some regions of the viral Gag, Tat, and Nef proteins with normal proteins have also been described (350–352, 901, 1038).

Most notable are the studies by Golding and coworkers (76, 382, 383), who have shown that some antibodies to the C-terminal sequence in HIV gp41 cross-react with HLA regions, particularly the beta chain. Antibodies to HLA class II proteins are found only in HIV-infected individuals. They bind to "native" HLA class II antigens and interfere with normal activation of $CD4^+$ T cells; they also have the potential to kill class II-expressing cells by ADCC. The presence of these anti-HLA antibodies in asymptomatic

individuals correlates with subsequent losses in $CD4^+$ cell numbers (76, 383).

Other observations by Kion and Hoffmann (575) indicated that immunization of mice with murine PBMC can lead to the production of antibodies that bind to the surface of normal human lymphocytes and neutralize HIV. Such a response (most probably to shared HLA-like regions on the cell surface), as noted above, could contribute to the loss of $CD4^+$ cells observed with HIV (224, 1336). Finally, antibodies to the N-terminal region of gp41 have been found to react with normal rodent brain astrocytes, perhaps by the same mechanism (1308). These observations do suggest that molecular mimicry could represent a possible source of some pathogenic autoimmune responses.

C. Carrier-Hapten Mechanism

As shown in other viral systems, HIV could, after infecting the cell, uncover cellular proteins that are not normally recognized as foreign by the immune system (699). By linkage with an HIV protein (e.g., envelope) acting as a hapten, these cellular proteins now become immunogenic and elicit an immune response in the host. This phenomenon reflects a carrier-hapten mechanism (699). The subsequent production of autoantibodies leads to the sequelae recognized. This possibility has been examined with anti-platelet and anti-T-cell antibodies. Although HIV infection of T cells is associated with production of antibodies to a cellular protein (257, 577, 589, 1146), no direct connection with a viral protein has been demonstrated (670a). Moreover, although infection of megakaryocytes has been reported (1339), an association of anti-platelet antibodies with a viral protein or virus-cellular protein complex has not been detected (670a). Instead, other immune processes may be involved in thrombocytopenia or the virus infection itself (45a, 1030, 1339) (see Sections XXIV B and D). Finally, via a carrier-hapten mechanism, some autoantibodies might be induced by HLA molecules found incorporated onto the surface of virions during budding (33a, 490, 1059). These proteins could be the source of autoimmune responses and the nonspecific false-positive results on ELISA screening for anti-HIV antibodies (33a, 1048, 1059). Nevertheless, whether the carrier-hapten mechanism is involved in HIV autoimmunity is not yet known.

D. Anti-Idiotype Antibodies

One concept that has had some popular support as a mechanism for autoimmunity involves the network of antibodies produced after introduction of an antigen into the host. Besides making antibodies to the incoming antigen, antibodies to these anti-antigen antibodies may be induced. These so called anti-idiotype antibodies should be mirror images of the epitope against which the initial antibody was produced (261). Thus, antibodies to HIV envelope gp120 might induce autoantibodies against the CD4 epitope to which the gp120 attaches. Although the possibility for these antibodies to form and be detrimental to the host is proposed, evidence for such a phenomenon has not been shown. The anti-CD4 antibodies produced (1178) are not against the epitopes involved in the binding site to HIV-1 gp120. Nevertheless, anti-idiotype antibodies mirroring the envelope gp120 have recently been implicated in autoimmune thrombocytopenia (549, 550). This observation focuses new attention on this immunologic phenomenon in HIV pathogenesis, but it still needs further confirmation.

E. Conclusions: Potential Importance of Autoimmune Responses

Although the role of autoimmunity in HIV-induced disease is still somewhat theoretical, the presence of autoantibodies in HIV infection should be considered as a potential cofactor in the pathogenesis observed. The possible mechanisms involved are reviewed in Fig. 24. An autoimmune response has been linked to the loss of neutrophils and platelets and to the induction of peripheral neuropathy (576, 578). One explanation for the reduction in the number of $CD4^+$ cells in HIV infection has also been the production of anti-T-cell antibodies (see above) or antibodies to CD4 (257, 1178, 1258). Plasmapheresis has supported a role of this process in the first three disorders but not in T-cell loss (578). In treated individuals, neutrophils and platelets return and the neuropathy is ameliorated; no change in the $CD4^+$ cell count has been observed (575a). The potential contribution of autoreactive cells in HIV infection merits further study.

On another note, a potential danger in vaccination with HIV proteins could be the eliciting via molecular mimicry of immune responses that deplete $CD4^+$ cells, compromise the immune system further, or induce autoimmune pathology in other tissues. Measuring this response should therefore be part of the evaluation of any therapeutic approach.

XXV. COFACTORS OF HIV INFECTION

Almost from the time of the initial reports of the discovery of HIV came the appreciation that other factors besides the AIDS virus might influence the progression to disease. One obvious feature in support of this thesis of cofactors was the variation in the time from infection to development of symptoms and AIDS among different individuals. Host genetic differences were an obvious important variable, and age has been recognized as having an influence on progression (see Section XXVII). In addition, the activation of T cells needed for efficient HIV infection and spread was considered. Thus, the potential roles of other viruses (e.g., herpesviruses and papovaviruses), antigens, and cytokines that increase immune activation (and thus the ability of HIV to replicate in cells of the host) were proposed. Finally, additional immune suppression, resulting from other infectious agents, drugs, or toxins, was considered a possible contributing event.

A. Infection by Other Viruses

One potential cofactor in HIV pathogenesis is infection by another virus. In one of the first examples of viral interactions, $CD8^+$ cells established in vitro by HTLV-I infection into a continuous line were found to be susceptible to HIV infection, even without expression of CD4 on their cell surface (243). The mechanism of this phenomenon is still not known. Similarly, some strains of HHV-6 are reported to induce CD4 on the surface of $CD8^+$ cells and thus permit HIV infection (721); other HHV-6 strains do not (670a).

Further evidence supporting the role of viruses as potential cofactors in AIDS comes from molecular studies. The herpesviruses, adenoviruses, hepatitis B virus, and papovaviruses, or specific genes from these viruses, were intro-

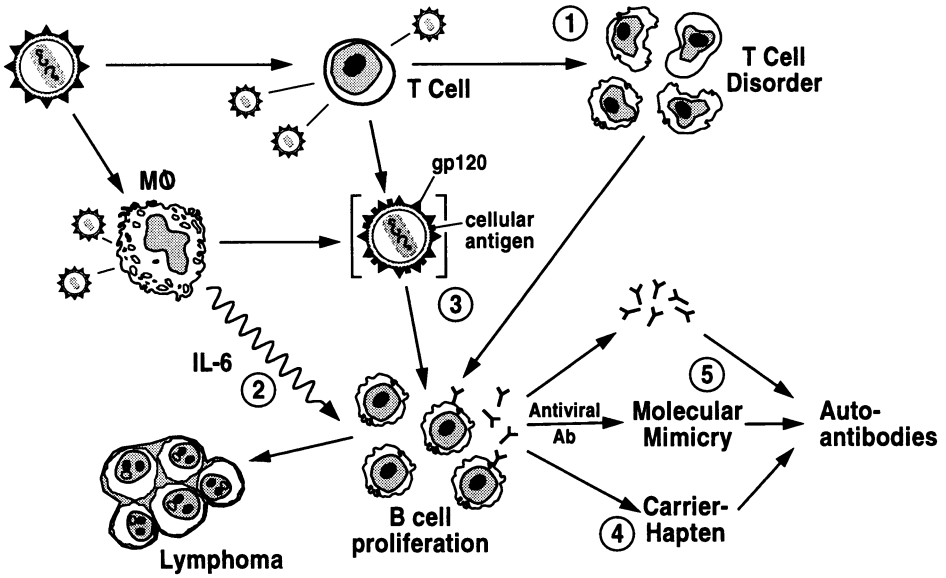


FIG. 24. Possible mechanisms for autoimmune responses in HIV infection. HIV infection of T cells could lead to T-cell disorders (step 1) with subsequent loss of T-cell control of B-cell proliferation. Similarly, infection of macrophages by HIV could lead to enhanced production of IL-6, with resultant B-cell proliferation (step 2). B-cell proliferation could eventually lead to lymphomas through chromosome changes and establishment of a transformed state. The presence of viral antigens on the surface of T cells or B cells might induce immune responses against nearby normal cellular antigens (step 3) in a carrier-hapten fashion (699) (step 4), leading to autoantibodies or autoimmune cellular reactions. Antiviral responses by B cells could also lead to autoantibodies through molecular mimicry (step 5). By this phenomenon, viral proteins may resemble normal cellular proteins sufficiently to cause an autoimmune response against these cellular components.

duced into cells transfected with a construct of the HIV LTR linked to the CAT gene. An increase in the production of the CAT protein occurred (for reviews, see references 361, 642, and 841) (see Section XII C). The early-gene products of these DNA viruses appear to be primarily responsible for this effect on the HIV LTR in a variety of promoter regions that can be different from those responsive to Tat, SP-1, and NF-κB (13, 230, 366, 372, 559, 812, 835, 877, 968, 1222; for a review, see reference 356). Recently, the bel-1 protein of the human spumavirus was shown to activate HIV gene expression via a new target sequence in the LTR U3 region (556).

Some investigators report enhanced HIV replication following infection with certain herpesviruses (CMV, HHV-1, and HHV-6) in cell culture (133, 381, 722, 1108). In contrast, others have shown that HHV-6, EBV, and CMV suppress HIV replication when coinfection of cultured cells with these agents is studied (132, 602, 677). The conflicting data could reflect the cell type or the virus strains used. However, it has been shown that prior EBV transformation of B cells or HTLV infection of $CD8^+$ T cells (243) increases the replication of HIV in these cells (455) (see Section XII C). Moreover, HTLV can induce HIV production on coinfection (437) or by mitogen stimulation in vitro (1321).

As cited above (see Section XXII C), herpesviruses can also induce the Fc receptor on the surface of cells and may therefore permit HIV infection via antigen-antibody complexes (763). Since CMV infects astrocytes and can be found together with HIV in brain cells (842), such a mechanism for HIV entry into and spread in the brain could be involved. Indeed, several instances of concomitant infection with herpesviruses and HIV can be cited as evidence for a cofactor, including their association with Kaposi's sarcoma and hairy leukoplakia and the production of genital ulcers that could enhance HIV transmission (121, 373, 401, 457, 484, 930) (Table 32). Finally, some cell culture studies suggest that HIV itself might be a cofactor in herpesvirus infections by enhancing or suppressing the replication of these viruses (476, 677, 1108).

In summary, despite these various considerations based on in vitro approaches that other viruses could be cofactors in HIV pathogenesis, clinical studies of individuals have not yet indicated a contributory role for specific viruses. They could produce the opportunistic infections or tumors observed in some patients, but an association with enhanced progression to disease has not been well documented. One study suggested that CMV infection was associated with a more rapid progression toward AIDS in hemophiliacs (1256). Moreover, some investigators have reported an increase in development of AIDS in HTLV-I-infected subjects (52, 887).

TABLE 32. Herpesviruses and HIV infection

Effect of herpesviruses	Reference
Suppress immune responses	1020
Cause genital ulcers, enhance HIV transmission	121, 484, 930
Destructive effects on brain and other tissues	1281, 1282
Induction of hairy leukoplakia (EBV)	401
Linked to HIV-associated malignancies: Kaposi's sarcoma (CMV); B-cell lymphoma (EBV)	373, 457
Enhance or inhibit HIV replication	132, 133, 677, 722, 1057
Induce Fc receptors on infected cells; potential role in antibody-mediated enhancement of infection	763
Phenotypic mixing	1334

However, recent observations suggest that HTLV-II infection that can occur in $CD8^+$ cells (503) might delay the course of disease (426a). Further clinical studies are needed in assessing other viruses as cofactors. Moreover, how dual infection by HIV-1 and HIV-2 (283, 364, 909, 976) affects the clinical outcome is not known. All these issues must be evaluated by observations on several clinical groups over longer periods.

B. Mycoplasmas

Certain studies have suggested that agents other than viruses could play a role in the pathology observed in HIV infection. Lo and coworkers identified a mycoplasma that was associated with a Kaposi's sarcoma tissue (*Mycoplasma incognitas*, a strain of *M. fermentans*) and induces immune deficiency and death in primates (710, 714). Antigens of this agent have been detected in HIV-infected individuals with renal disease (54), and DNA sequences were found in the blood of 6 of 55 HIV-seropositive individuals (451). Moreover, the organism has been found in autopsy specimens from non-AIDS patients who died of a flulike illness (711). T cells from HIV-infected individuals have been shown to respond actively to mycoplasma antigens (658), and their potential role as superantigens has also been proposed (see Section XVII C).

Whether this agent or related organisms are involved in HIV pathogenesis is under investigation. Some studies have focused on cell culture events in which noncytopathic or relatively less cytopathic HIV strains were found to be more cytopathic when infecting PBMC in the presence of a variety of different mycoplasmas (658, 713). Whereas the mycoplasmas reduced syncytium formation in culture, cell death was increased. Some effects of the mycoplasmas can be related to their close association with the cell membrane that prevents cell fusion and with their known consumption of culture nutrients needed for the survival of PBMC (558). Whether these in vitro observations have any relevance to the clinical state is unknown (451). The presence of mycoplasmas in the urine of HIV-infected individuals and the high level of anti-mycoplasma antibodies (712), most recently to *M. penetrans* (1248a), need to be confirmed (426). Moreover, the induction of immune disorders and disease in rhesus monkeys inoculated with *M. incognitas* has not been reproduced (830a).

C. Animal Studies

Our laboratory has used chimpanzees to investigate directly the hypothesis that another agent, after coinfection of a host, would compromise the immune response and enhance HIV pathology. For these studies, we inoculated HIV-1-infected chimpanzees with a chimpanzee CMV and monitored the animals for signs of disease. Although no evidence of pathology ensued, the chimpanzees began to release HIV-1 in their blood, a characteristic not observed in these animals for over a year (137). Whether immune enhancement or suppression brought about this change in viral control is not known, but increased levels of antibodies to HIV were noted at the time of virus recovery.

Other studies of the potential role of cofactors in HIV pathogenesis involved the inoculation of anti-Leu 2a (anti-CD8) antibodies into HIV-infected chimpanzees to determine whether a reduction in $CD8^+$ cell control would bring about renewed HIV replication in vivo and clinical signs. This approach was based on the observations on $CD8^+$ cell suppression of HIV production (see Section XXIII D). Animals treated for 7 to 14 days with anti-Leu 2a MAb released virus from their PBMC within 2 months, whereas no HIV had been recovered from these chimpanzees for 15 to 40 months previously. Nevertheless, neither of the two animals treated showed any symptoms of HIV infection.

Both these studies of potential cofactors indicated that other agents and the effects on $CD8^+$ cells could permit HIV replication from a relatively suppressed state. Moreover, recent observations suggest that stimulation of the immune system could increase virus release in the infected host (331). This possibility should be considered in postinfection immunization procedures (see Section XXIX B). Conceivably, although not shown in the few studies summarized, the virus could eventually become pathogenic once it is released and replicating (see Section XXVI), particularly if persistent challenges to the immune system of the host occur.

D. Conclusions

HIV is the proximal cause of AIDS, but other infectious agents or environmental factors could influence the progression to disease. How these cofactors could work in the infected individual is not clear. They might induce cytokines or intracellular factors (see Section XVIII G) that promote HIV replication or compromise immune responses. Alternatively, they might reduce the production of these cellular products (e.g., IL-1 and IL-4), and affect immune function. They could stimulate the immune system abnormally and induce autoimmune responses. Alternatively, they might reduce the cellular antiviral activity and permit the escape of HIV from host immunologic control. For this series of events to occur, however, continual compromise to the host immune system would be needed. Probably other factors, including opportunistic infections, can affect the overall health of the infected individual, but only the inherited genetic makeup of the host appears to be important in determining the direct pathogenic effects of HIV itself. Genetic factors can influence cell susceptibility and host immune response. Either by direct infection of cells or by its indirect effect on the immune system of the host, HIV appears primarily responsible for the disease progression observed.

XXVI. FEATURES OF HIV PATHOGENESIS

Given the viral and immunologic factors in HIV infection, the following hypothesis can be proposed about the steps involved in HIV pathogenesis (Fig. 25). The virus initially enters an individual primarily by infecting either activated T cells, resident macrophages, or mucosal cells in the bowel or uterine cavity. In my opinion, aside from mucosal cells, the first cells infected would be tissue macrophages (mostly in lymph nodes) that are in a differentiated state ready to replicate the virus. Very few activated $CD4^+$ lymphocytes are circulating in the blood, and peripheral blood monocytes are not very susceptible to infection (see Section XI B). In the initial days following acute infection, high levels of virus replication will take place in the lymph nodes and will be reflected by p25 antigenemia and viremia levels. $CD8^+$ cell numbers rise, as is observed in other viral infections (78). Generally, within 1 month, the viremia is reduced substantially, most probably as a result of immune reactions against the virus. Cellular immune responses could be the first effective antiviral activity, since in some cases $CD8^+$-cell HIV responses have been detected even prior to serocon-

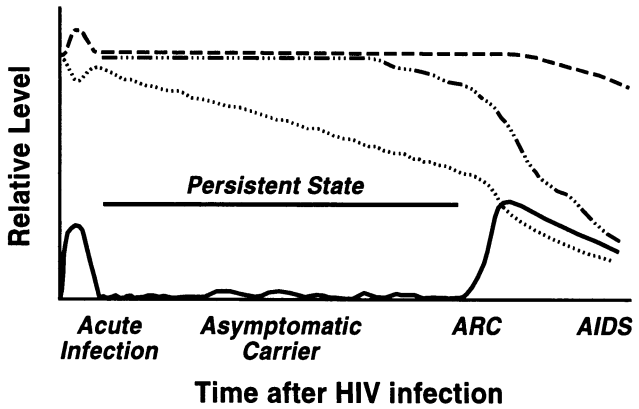


FIG. 25. Steps involved in HIV pathogenesis (see Section XXVI). During acute primary virus infection, high levels of cell-free infectious HIV can be found in the plasma. After 1 to 3 months, the virus is suppressed and only episodic releases of virus can be detected during the persistent period. At the time of symptoms, often many years later, a second release of high levels of HIV in the blood (viremia; ▬▬) is observed, and these levels remain present throughout the final phases of disease. In the host, immunologically, the $CD4^+$ cell numbers (····) drop during primary infection and then return within months to a near-normal level. Over time, a steady drop in the $CD4^+$ cell numbers occurs, and in some cases, a rapid decrease can be observed at the time of increased virus production. The association of these two events suggests that a highly cytopathic virus is released. Symptoms in the patient (ARC) occur at the time of marked reduction in $CD4^+$ cell numbers. The number of $CD8^+$ cells (– – –) during primary infection rises, as is commonly seen in viral infections. Their level then returns to just above normal and stays elevated until the final stages of disease. In contrast, the anti-HIV $CD8^+$ cell response (— · · · – · · ·) begins to decrease prior to or around the time of symptoms and then steadily decreases as progression to disease occurs. Modified from reference 665 with permission.

version (184, 725, 1084). Moreover, virus levels in plasma appear to be reduced before neutralizing antibodies can be detected in recently infected individuals (215).

Over the ensuing months to years, the $CD8^+$ cell number remains slightly elevated. Virus replication in the body persists, particularly in lymph nodes and PBMC, but levels mostly measured in the blood are low; in general, the virus is appreciatively suppressed. $CD4^+$ cell numbers usually rise to near-normal levels 3 to 4 months after the primary virus infection. They then appear generally to decrease steadily during the persistent period at a rate estimated by some at 25 to 40 cells per μl per year (630). Why this loss in antiviral response occurs over time is one of the unresolved mysteries of this infection (see Section XVIII).

At a point when the individual develops symptoms, $CD4^+$ cell counts are usually below 300 cells per μl and the levels of HIV in the blood are high compared with those during the asymptomatic state. At the same time, a reduction in antiviral $CD8^+$ cell responses can be demonstrated (725). In some cases, the number of $CD4^+$ cells drops precipitously (e.g., ~200 cells per μl) over just a few months, perhaps mirroring a return of high-level virus production (287, 665, 1051). This presages the development of disease. At this time of symptomatic infection, and certainly when the individual develops AIDS, the virus has characteristics distinct from the virus recovered soon after the infection. It takes on properties associated with virulence in the host, including an enhanced cellular host range, rapid kinetics of replication, and $CD4^+$ cell cytopathicity (Table 19). It also appears to resist neutralization and becomes sensitive to enhancing antibodies.

This virus, emerging later in the host, is related at the genomic level to the early virus (>97%), but certain molecular changes in the regulatory (e.g., *tat*) and envelope regions are associated with these altered in vitro biologic properties (see Sections XIV, XV, and XVI). However, the relevance of these in vitro properties to the pathogenic role of the virus requires further study with animal model systems (818) (see Section XVI D).

With ongoing reduction in immunologic control of HIV infection, the more virulent variants replicate to higher levels and destroy large numbers of $CD4^+$ cells. They eventually eliminate the potential for any immune response to control opportunistic infections. In the terminal stages, $CD8^+$ cells, as well as $CD4^+$ cells, decrease in number, perhaps in part because of the loss of IL-2 production by $CD4^+$ cells (Fig. 25). Included in this pathogenic pathway is the disruption in normal immune balance that can give rise to malignancies, either through immune activation (683) or through suppression. Moreover, the possibility that cytokine production and hyperresponsiveness in the immune system (i.e., autoimmunity) also contribute to the final outcome must be considered.

One important question under consideration is whether a virus showing "virulence" in one individual will do so upon transmission to another. As described in Sections VI and XII B, the PBMC of different individuals can differ in their sensitivity to virus replication and cytopathicity. Thus, the relative growth and spread of HIV in the blood and tissues of an infected subject could be one of the parameters determining the extent of pathogenesis. Moreover, the ability of the host immune response to counter virus replication is an important factor. Both of these host-associated features appear to be determined by the genetic makeup of the individual. One concern, however, is that eventually more "virulent" strains of HIV will emerge and pass through the population. Although no definitive evidence has been shown that this phenomenon is occurring, some recently infected individuals, whom we are monitoring have progressed much more rapidly to AIDS than others first seen 10 years ago. This possibility should be given further attention, particularly if strains enter individuals with similar genetic backgrounds.

How HIV strains evolve or emerge in the host is not yet known. One possibility is that a virulent strain, present early in infection, is suppressed or eliminated by an active antiviral immune system but that a less cytopathic strain remains. After a reduction in immune response, either by loss of antiviral activity or by the presence of escape mutants, a strain that has the characteristics of increased virulence reemerges or redevelops through genetic changes (Table 19). Alternatively, the initial virus is relatively nonpathogenic in the infected individual but, with increased replicative cycles resulting from reduced immune anti-HIV activity, it mutates over time to a virulent strain resistant to the immune response.

Whether the emergence of these cytopathic viruses or a suppression of the immune response occurs first is not yet known. Studies in our laboratory in which cellular immune responses appear to be similar against all strains of HIV suggest that the loss of $CD8^+$ cell activity seems to be a major factor in the progression to disease. Most recently, we have observed a drop in $CD8^+$ cell antiviral response in three subjects just prior to a loss in $CD4^+$ cell number (725a).

The importance of $CD8^+$ cells in controlling the infection over time is currently being explored through the administration to infected individuals of autologous $CD8^+$ cells previously grown in large quantities in the laboratory (306, 588).

The events leading to a reduction in anti-HIV immune responses, mirrored by loss of $CD4^+$ cells, have also not yet been defined. Most probably, multiple factors are involved, and no single one predominates as the major cause for decreased control of HIV infection. I have discussed the potential effects of direct infection of $CD4^+$ cells with HIV. Since larger numbers of these lymphocytes are now found infected, this explanation for $CD4^+$ cell loss becomes more feasible, although very few cells reflect ongoing virus replication that would lead to cell death. Nevertheless, as reviewed in Section XVIII, the virus-infected cell could still be compromised in its function and production of necessary cytokines, even without dying. For example, diminished production of IL-2 could affect the $CD8^+$ cell number and response.

Direct virus infection of $CD4^+$ cells, a compromise in cytokine production, and aberrant immune reactions (e.g., ADCC, CTL, autoreactive cells, autoantibodies, and apoptosis) can all play a role in the immunopathogenic pathway. The induction of apoptosis in $CD4^+$ cells as well as $CD8^+$ cells particularly merits consideration.

The significance of humoral immune reactions in these stages of HIV infection is uncertain. Neutralizing antibodies can be found throughout the course of the infection, albeit generally only at low level when autologous strains are tested (see Section XXII A). The role of these antibodies would appear most important during the early phase of HIV infection, when destruction of virus-infected cells (by ADCC) could be effective in preventing HIV spread in the host.

The major cofactor influencing delay in disease progression is the inherited genetic makeup of the host that determines both the susceptibility of cells to HIV replication and the extent of effectiveness of the antiviral immune response. Young age, as noted below, can also have an important influence, perhaps reflecting strong immune responses. Moreover, the relative sensitivity of the host immune system to destructive effects of viral proteins or cytokines could be important in determining whether there is rapid progression to disease or long-term survival.

XXVII. PROGNOSIS

Several studies have attempted to define the factors that might be useful in predicting progression to disease (Table 33). Among the parameters suggested are high levels of β_2-microglobulin, soluble IL-2 or TNF receptors, and soluble CD8 in blood; high levels of neopturin in the urine; low antibody titers to the p24 (p25) or p17 Gag proteins in serum; high levels of p25 (p24) antigen or infectious virus in blood; decreased dehydroepiandrosterone levels in serum; decreased delayed-type hypersensitivity reactions; and the common finding of low $CD4^+$ cell counts (194, 199, 249, 289, 319, 377, 410, 471, 513, 522, 631, 632, 692, 819, 820, 858, 876, 923, 977, 991, 1067, 1255, 1330). The recent introduction of acid dissociation has increased the sensitivity of p25 antigen assays for these evaluations (82).

Our studies show that the level of $CD8^+$ cell antiviral activity would also be a good marker of disease progression (727) but that it is not easily measured in the laboratory. Recent studies suggest that flow cytometric analyses of $CD8^+$ cell subsets might be helpful in defining phenotypic markers associated with progression to disease (628, 659a). A report has emphasized the value of β_2-microglobulin levels in serum (692). Also, observations by some researchers suggest that a rise in the level of myelin basic protein or antibodies to this CNS protein might predict the development of dementia (719). Controversies about the value of each of the assays listed above, including antigenemia (824), exist, and the parameters for predicting progression to AIDS need further evaluation. At this time, no single test appears capable of predicting the change from asymptomatic to symptomatic infection. Most physicians use more than one marker in assessing the stage and course of HIV infection. Finally, studies of hemophiliacs indicate a lower rate of progression for younger (<25 years) than for older patients (55, 287, 307, 379).

TABLE 33. Parameters suggesting progression in HIV infection[a]

Parameter	References
Low $CD4^+$ cell number	249, 289, 923
High β_2-microglobulin level in serum	693
High soluble IL-2 receptor level in serum	858
High soluble CD8 level in serum	876
High soluble TNF receptor level in serum	377
Low antibody titers to p25 or p17 Gag proteins	319, 522, 631, 632, 1067, 1255
Plasma p25 antigenemia	249, 632, 991, 1067
High viremia level	199, 471
Decreased dehydroepiandrosterone level in serum	513
Reduced CRI expression on erythrocytes	194
High neopterin level in urine	977
Reduced delayed-type hypersensitivity reactions	1330
Reduced $CD8^+$ cell antiviral response	727
Reduced number of activated $CD8^+$ cells	628

[a] See Section XXVII for discussion and other references.

XXVIII. FACTORS INVOLVED IN LONG-TERM SURVIVAL

In regard to the above discussion on cofactors, an important question considered in this review on HIV pathogenesis has been the wide variations in progression to disease observed among infected individuals. For example, a study of HIV infection in a defined cohort of subjects for 14 years in San Francisco has shown that about 80% of the individuals develop symptoms and that 55% have AIDS (691, 1025). These observations have indicated, nevertheless, that 20% of the infected people monitored remained healthy for over 10 years; 12% of these have normal $CD4^+$ cell counts (1024a). Although relatively few of the subjects are in this latter category, the reasons for their long-term survival could provide insights into possible therapeutic interventions for others.

Our laboratory has been studying such long-term-infected individuals for more than 10 years; some have had HIV infection since 1978 and remain healthy. Our findings indicate four major characteristics discussed in this review (Table 34). First, whereas the $CD8^+$ cell responses (both cytotoxic and suppressing) decrease with time as individuals progress to disease (see Section XXIII C and D), they remain strong in long-term survivors (388, 727). As little as 1 $CD8^+$ cell can suppress virus replication in 20 $CD4^+$ cells in

TABLE 34. Characteristics of long-term survivors

Strong cellular $CD8^+$ cell antiviral response
Relatively nonvirulent HIV strain present
Low virus load (plasma viremia, infected PBMC)
Infection not enhanced by antibodies to the infecting HIV strain

culture. In contrast, as noted above, symptomatic patients can require up to 100 times more $CD8^+$ cells for this control of HIV production (727). Second, relatively noncytopathic HIV strains are found in the PBMC of long-term survivors with strong $CD8^+$ cell responses (163, 725). Their viruses generally grow to low titer and only in PBMC, not established cell lines. Third, these infected individuals have a low viral load as measured by the number of infected $CD4^+$ cells and free infectious virus in the peripheral blood (see Sections IV A and XVI D). Finally, as noted above (481), neutralizing and not enhancing antibodies to the virus are found in the blood of long-term survivors. The three findings relating to the virus can be explained by the inability of the HIV strains to replicate in the presence of $CD8^+$ cell antiviral activity. Therefore, these strains cannot mutate to more cytopathic, antibody-resistant strains in the host (Table 19).

The most important question is what causes the decrease in the antiviral response of $CD8^+$ cells and permits increased virus replication and progression to disease (Fig. 25). As with other viruses, one major influence can be the genetic makeup of the individual; protection can come from strong immune responses and reduced inherent sensitivity of the host cells to virus replication. In addition, as noted above, younger age groups can have slower progression, perhaps secondary to a more vigorous immune response. Progression does not reflect a reduction in total $CD8^+$ T-cell numbers since the level of this subset often remains elevated until the late stages of disease (630, 665). The emergence of a virulent strain that cannot be controlled by $CD8^+$ cells also does not seem to be the cause. In cell culture, $CD8^+$ cells demonstrate high antiviral activity against all HIV-1 and HIV-2 strains, whether cytopathic or not (725, 727). Thus, it appears that an intrinsic loss of $CD8^+$ cell activity is involved. The reason is under study (see Section XXIII D) and might best be approached through research on the pathogenic and nonpathogenic SIV model systems.

XXIX. ANTIVIRAL THERAPY

Although this review cannot cover in detail the therapeutic approaches used to control HIV infection, some citation of work in this field is appropriate. Many steps in the viral infection cycle discussed above (Sections III and XII A) (Fig. 26) have been targeted for antiviral action (211, 233, 234, 792, 1309, 1311) (Table 35). Thus far, only a few approaches have shown any clinical promise.

A. Anti-HIV Drugs

(i) **Anti-reverse transcriptase.** Recognizing the causative agent of AIDS as a retrovirus led to an immediate emphasis on arresting the replicative cycle of the virus. It is therefore not surprising that the first successful compound found was an inhibitor of the required reverse transcription. A drug that had been previously synthesized for potential use against cancer, AZT, was noted to inhibit viral RT and HIV replication in vitro (791). Its mechanism evaluated in vitro involves both a termination of viral DNA production and a

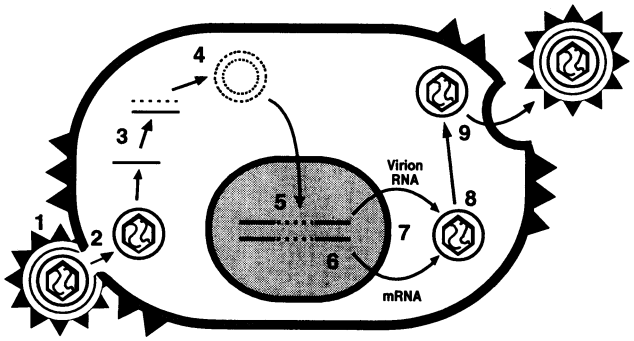


FIG. 26. HIV infection cycle. In steps 3 to 5, the viral core proteins are associated with the viral genome. ——, RNA; – – –, DNA. Double-stranded circular forms can be found both covalently and non-covalently bound. The latter are the forms that integrate into the cell chromosome. Antiviral therapies can be directed against each step and can potentially interrupt virus replication and spread (see Section XXIX). Steps shown: 1, attachment and fusion; 2, uncoating and nucleocapsid entry; 3, reverse transcription; 4, cDNA formation; 5, integration; 6, mRNA transcription; 7, translation; 8, core particle assembly; 9, final assembly and budding. Steps 8 and 9 most probably occur at the cell surface. Figure courtesy of H. Kessler.

competition for nucleotides used by the viral polymerase. The use of AZT was immediately evaluated clinically and soon reported to be effective (259, 1312). At first, large doses were administered (1,500 mg/day), and they frequently had side effects, especially toxicity to the bone marrow (302, 989). Now, the drug is given in reduced amounts (300 to 500 mg/day) and shows fewer harmful effects in infected individuals (196). It has decreased the symptoms of the disease in many patients and in some cases has delayed the progression to AIDS and perhaps prolonged life. This latter observation needs further evaluation. Some now recommend this therapy for asymptomatic individuals with a $CD4^+$ cell count of less than 500 cells per μl (1227), and its use during acute HIV infection is being assessed (1185). Some reports suggest that the drug could be harmful in primary infection (1014, 1182). The optimal time for initiating AZT treatment, at all clinical levels, is still being evaluated (395, 430, 1217).

The exact mechanism for AZT activity in vivo is also not known. It could have effects other than antiviral effects. Some individuals treated with AZT still have virus in their plasma and PBMC, although they have improved clinically. In the cases that have been evaluated, the virus load seems reduced. Cell-to-cell transmission in cultures containing AZT has been described (412). These results could reflect resistant strains (see below); alternatively, the therapeutic value of the drug could involve induction of antiviral cellular immune responses. In this regard, we have found that AZT does not affect, and might even stabilize, the anti-HIV $CD8^+$ cell response (725a).

Other nucleic acid analogs that compete with the viral RT have also been developed. ddI and ddC, now approved for therapy by the Food and Drug Administration, appear to be effective and less toxic to bone marrow than AZT (114, 211, 233, 234, 616, 624, 792, 1309, 1310). The administration of ddI and ddC has nevertheless been associated in some cases with pancreatitis and peripheral neuropathy, respectively. Some studies suggest that their use in combination with AZT would be helpful. A recent report suggests that changing treatment from AZT to ddI in symptomatic individuals with

TABLE 35. Potential approaches to therapies for HIV infection[a]

Anti-HIV
sCD4
Neutralizing antibodies (polyclonal, MAb)[b]
Virus entry
sCD4
Neutralizing antibodies[b]
Saliva glycoprotein
Sulfated polysaccharides
Peptide T
Early steps prior to integration
Anti-RT (e.g., AZT, ddI, ddC, TIBO, foscarnet)
Anti-nucleotides (e.g., mycophenolic acid)
Anti-integrase
Interferon (?)
Postintegration
Anti-Tat
Anti-protease
Antisense nucleotides
Nef
Hypericin
Virus budding
Glycosylation inhibitors (castanospermine)
Interferon
Anti-infected cells
Trichosanthin (compound Q)
Antiviral antibodies (ADCC)
rCD4 toxin
Anti-gp120 toxin
UV-A plus psoralen
$CD8^+$ cells

[a] See Section XXIX for discussion and references.
[b] Either by passive immunotherapy or by active immunization.

low $CD4^+$ cell counts could slow the progression of disease (535).

One notable problem in AZT therapy has been the emergence of resistant virus strains (345, 465, 637, 638, 988, 1013). Moreover, resistance to ddC and ddI has also been reported (988, 1128). Reversion of AZT-resistant strains to a sensitive strain after cessation of therapy appears to take many months (12). Resistance to other anti-HIV therapies should be expected. Fortunately, viruses have not shown concomitant resistance to the related anti-RT drugs, and so changes in therapy can be instituted. In addition, combination therapy can be given (526).

Nonnucleoside antiviral drugs, such as the TIBO agents which inhibit RT, have also been described. The TIBO compounds selectively inactivate the RT of HIV-1 and not HIV-2 (234), probably because of their specific predilection for the end chain of the HIV-1 polymerase (1090). Although these drugs can be given in much lower doses than AZT, they can be toxic and have been less effective in clinical trials, most probably because of the rapid development of drug resistance (771, 987).

Thus far, most data suggest that anti-RT drugs alone will help reduce and delay the symptoms of HIV infection. Nevertheless, other therapies must be found to use alone or in combination. The latter approach offers the best chance of success for permanent control of HIV infection.

(ii) Other therapeutic approaches. Other directions for antiviral therapy include attacks on the viral cellular receptor by using recombinant CD4, blocking virus attachment with sulfated polysaccharides (43, 751), the use of interferons (469, 783, 935), and approaches that destroy the virus-infected cells (73, 643) (Table 35). In this latter case, anti-gp120 antibodies or sCD4 linked to ricin or other toxins (e.g., *Pseudomonas* toxin) have been tried in culture alone and in combination with AZT (36). Moreover, tricosanthin (GLQ223 or compound Q), an abortifacient drug from the People's Republic of China, has demonstrated some promise in preferentially destroying HIV-infected macrophages and perhaps $CD4^+$ lymphocytes (758, 891). In clinical trials, modest elevation in $CD4^+$ cell counts were reported with tricosanthin (116, 534), and its efficacy is under further evaluation.

Approaches at limiting virus replication have also involved molecular procedures directed at the viral protease or integrase (1104). Protease-inactivating analogs have been tried, and certain selected compounds await clinical trials (263, 767, 768, 999). Nevertheless, resistance to these drugs could also emerge (878). Ribozymes, antisense molecules, and attempts at gene therapy with intracellular dominant inhibitors have been proposed after promising results were observed in vitro (295, 1017, 1104, 1232). Many of these theoretical approaches nevertheless need a means of drug delivery. In addition, drugs against glycosylation have been considered (409, 973). For example, castanospermine disrupts the glycosylation of the viral envelope to make the virus noninfectious. Finally, the antioxidant compound *N*-acytel-L-cysteine has been proposed as a safe therapy in HIV infection (1008). It most likely inhibits intracellular factors and cytokines that enhance HIV replication.

Recently, the antiviral effects of mycophenolic acid, under trial in organ transplantation procedures and autoimmune diseases, were evaluated (18a). This compound blocks the incorporation of nucleotides into DNA and acts on autoactive immune cells. Mycophenolic acid at nontoxic concentrations that can be reached in the blood inhibited HIV-1 and HIV-2 replication in cultured $CD4^+$ lymphocytes and macrophages. Its clinical use is under consideration. Finally, as with other incurable diseases, many nonproven approaches to antiviral therapy have been tried (1).

B. Postinfection Immunization

Postinfection therapy using immunization with a viral protein (1036) has also been evaluated. This approach should not be considered a vaccination; this term is generally reserved for preventive strategies. Instead, the procedure is an attempt at immune stimulation. In initial studies, HIV-infected individuals received immunizations with envelope-depleted virus still containing the HIV-1 Gag proteins (660). One reason for this approach was an attempt to increase the levels of p25 antibodies, which were reduced in symptomatic patients (see Section XXVII). After 4 years, no toxicity from the immunizations has been noted; the clinical conditions appear to have stabilized, but a full evaluation is in progress (660a).

In other studies, Redfield et al. (978) immunized infected individuals with recombinant gp160 (MycoGeneSys) produced in the baculovirus system. Six courses over a 6-month period were administered. After an 8-month follow-up, there was no obvious toxicity to the individuals except for some cases of erythema around the site of immunization. The $CD4^+$ cell count in the responding immunized individuals did not change, whereas it decreased in individuals who did not respond to the treatment. T-cell proliferative responses

TABLE 36. Biologic and molecular features of HIV that affect antiviral therapy

Infected cells are a major source of HIV transmission and pathogenesis
Infected T cells, B cells, and macrophages can be circulating reservoirs for HIV; tissue macrophages and stromal cells can be resident reservoirs that persistently release virus
Integrated virus can be latent and can remain unaffected by the immune response
Virus can spread by cell-to-cell transfer
Virus can infect brain cells (astrocytes and oligodendrocytes); therapy must pass the blood-brain barrier
Virus can escape neutralizing antibodies; in some cases, virus infection is sensitive to enhancement by antibodies
Antigenic variations occur widely among HIV-1 and HIV-2 strains
Sequence mutations can occur early in the regions coding for the HIV envelope and regulatory genes

were noted in vaccinees who showed stabilized $CD4^+$ cell counts. Higher levels of antibodies to certain HIV envelope peptides were found in the subjects, and neutralizing antibody titers measured in a few individuals studied were increased. In a recent study, HIV-1 envelope-specific cytotoxic T-cell responses were also increased in immunized HIV-seropositive individuals (615a). This postinfection immunization will be receiving further emphasis as a result of these preliminary studies, but long-term follow-up on the subjects is required. As noted above, immune stimulation under some circumstances might be harmful by increasing virus spread to activated $CD4^+$ cells in the host (331).

C. Passive Immunotherapy

Some investigators have considered the possibility that passive immunotherapy with plasma or purified Igs from asymptomatic HIV-seropositive individuals (512, 548, 961) would be helpful in therapy. The potential use of human anti-V3 MAbs has received attention (1338). The initial trials with anti-HIV plasma in AIDS patients showed some success as measured by improvement in clinical status and stabilization of $CD4^+$ cell counts (512, 548, 1221). The effect could result from HIV neutralization, ADCC, or nonspecific stimulation of the immune system of the recipient.

A major concern that remains is whether the Igs inoculated into a host will enhance rather than neutralize the HIV strain present in that infected individual (see Section XXII C). Prior experimentation with the isolated strain might be warranted to avoid a potential danger in this therapy. If effective, Igs can be produced (perhaps by MAb procedures) to use particularly with individuals following needlestick injuries or in mothers around the time of delivery (see Sections IV F and XXX E).

D. Conclusions

Substantial emphasis has been directed at finding therapeutic modalities for attacking the virus or virus-infected cells. Information on many different drugs showing anti-HIV activity in vitro appears regularly in the literature, but their clinical efficacy awaits further evaluation (for reviews, see references 233, 234, 643, and 1309). Most clinicians conclude that combination therapy (526) will most probably be used to avoid toxicity and drug resistance, similar to approaches for the treatment of malignancies. Therapies targeted against virus-infected cells must be given particular attention. Moreover, other approaches to enhancing the immune response of the host against the virus should be emphasized. In all antiviral therapies, the biologic and molecular features of HIV must be considered (Table 36).

XXX. VACCINE DEVELOPMENT

This review has focused on the viral and immune parameters that influence HIV pathogenesis. All the observations gathered about the virus and the natural host immune responses against it provide valuable information for use in the eventual development of therapy and an HIV vaccine (for reviews, see references 40, 83, 461, 592, 618, 664, and 1113).

Several features of HIV infection and transmission must be considered in vaccine work (Table 37). They include the appreciation of viral heterogeneity, local mucosal immunity (318, 788), the potential for autoimmune responses, and virus transmission by infected cells (666). The recent findings on the cross-reacting region in the V3 loop (i.e., the PND) and the reported broadening antiviral response in animals immunized with gp120 and the V3 loop (424, 517) have lent some encouragement to the possible development of a vaccine against HIV (see Section XXII A). Nevertheless, whether present approaches would lead to the protection of a host against high doses of the virus (>100 IP) and virus-infected cells has not been answered. Also, only recently has the problem of mucosal immunity been openly discussed (318).

A major problem has been an appropriate animal model. Chimpanzees are expensive and do not replicate HIV to high titer or contract disease. Studies with SIV are helpful but may not give the same results as studies with a human lentivirus. Observations in our laboratory on HIV-2 infection of baboons are encouraging (138, 681a), as is the most recent report on successful infection of *M. nemestrina* with HIV-1 (8). Finally, the use of HIV-SIV chimeric viruses could offer an approach to evaluating vaccines in a convenient primate model system (686, 1088).

Essentially, seven different types of vaccines are being explored (Table 38) (664). Each has provided some promise for the development of a vaccine in other viral systems, including the novel use of anti-idiotypes (40, 223, 261, 542, 1322). The three approaches that have received the most attention are reviewed below.

A. Whole Virus

The predominant vaccine studies with lentiviruses, initially showing some virus protection, involved the use of killed SIV in macaques (modeled after the Salk polio vaccine) (130, 246, 828, 1123). This approach demonstrated protection against low-dose challenge with the homologous SIV strain. In general, delays in virus challenge after the

TABLE 37. Ideal properties of an anti-HIV vaccine

Elicits neutralizing antibodies that react with all HIV strains and subtypes
Induces cellular and humoral immune responses against virus-infected cells
Induces immune responses that recognize latently infected cells
Does not induce antibodies that enhance HIV infection
Does not induce antoimmune responses
Induces local immunity at all sites of HIV entry in the host
Safe, with no toxic effects
Long-lasting effect of the procedure

TABLE 38. Approaches to HIV vaccines

Inactivated virus, natural or engineered
Nonpathogenic (attenuated) variants, natural or engineered
Subunit vaccine, natural or engineered
Envelope glycoprotein (gp120)
Envelope transmembrane glycoprotein (gp41)
Gag protein
Viral proteins in infectious chimeric virus or other vectors (e.g., vaccinia virus, poliovirus, baculovirus, adenovirus, Ty, various bacteria)
Viral cores with envelope proteins
Sequence-derived peptides of HIV
Anti-idiotypes of neutralizing antibodies

final immunization dose (up to 12 months) gave the best results and have formed the basis for further evaluation of these vaccines. Nevertheless, some studies have shown that killed-virus vaccines can protect against infection by an intravenously delivered challenge dose but not against virus inoculated onto the mucosal lining (1151). Whether these approaches with whole virus will be effective in inducing mucosal immunity obviously requires further study. Recently, similar protection of macaques immunized with killed HIV-2 strains has been reported (960). Once again, the challenge was with a low dose (10 to 40 IP) of a homotypic type. Protection against a heterologous HIV-2 strain or, most importantly, against virus-infected cells was not evaluated.

Some investigators have explored immunization with a live attenuated SIV_{mac} strain; it prevents disease by a virulent strain but does not prevent infection (739). Likewise, infection of cynomolgus monkeys with a nonpathogenic HIV-2 strain protected the animals from SIV-related disease (959). By other approaches, Daniel et al. (225) found that previous infection of monkeys with a Nef-deleted mutant of SIV prevented superinfection. This mutant virus does not cause disease in rhesus monkeys (563) and induces high-titer antibodies against the virus. Results on the cellular immune response were not reported (563). Challenge of the previously inoculated animals with up to 1,000 rhesus monkey infectious doses of a wild-type pathogenic SIV gave protection from infection (225). The mechanism for this result could be a strong cellular immune recognition of the *nef*-deleted mutants, perhaps as a result of somewhat better viral antigen expression (see Section XIII B). Attempts to improve this approach by using several independent or combined mutations (e.g., *vpr*, *vpx*, and *vif*) are in progress (368).

As a model, the attenuated agent comes closest to resembling the virion that would be infecting the host. Thus, studies with this virus should be continued and could indicate whether at least conventional vaccine approaches with virus particles would induce protective immunity against an agent such as HIV. Acceptance of this approach for a vaccine, however, will be difficult unless no other method involving a noninfectious agent is successful.

Most disturbing was the recent recognition that most trials with inactivated SIV strains as immunogens might have measured anticellular and not antiviral responses (635, 1145). Both the immunizing and challenging viruses were grown in the same human cell line. Antibodies appeared to be induced against the human cellular proteins associated with the virion and not against the viral proteins. Thus, protection occurred via these anticellular responses. One study with killed SIV and low-dose homologous SIV challenge does seem to reflect induction of a true antiviral state (246). Also, a recent successful vaccine study with inactivated, molecularly cloned SIV may indicate that antiviral and not anticellular antibodies were induced. It showed protection against both homologous and heterologous strains (525). Nevertheless, many of the aforementioned studies must be reevaluated with appropriate virus preparations grown in different cells, although approaches involving anticellular responses are also being explored. Thus, the killed-SIV model has not yet provided convincing proof of a protective vaccine capability.

With the cat lentivirus, immunization with inactivated infected cells or free FIV has protected >90% of cats against intraperitoneal infection with small amounts of homologous or heterologous strains (1308a). Finally, using a killed-virus vaccine with the equine lentivirus equine infectious anemia virus, Issel et al. (508) were able to induce protection against infection by up to 10^5 infectious doses of the homologous virus. The vaccine did not prevent infection by a heterologous virus but protected against disease. These results did not involve anticellular responses. The findings offer some needed encouragement for further vaccine approaches with HIV (see also Section XXX B).

B. Purified Envelope gp120 Alone or in Association with an Expression Vector

Limited success with a vaccine has been achieved with purified envelope glycoproteins expressed in the baculovirus system or in mammalian cells (CHO cells), in which close to normal glycosylation occurs (34, 67, 68, 374, 830). In a trial with chimpanzees, immunization with the purified HIV gp120 expressed in CHO cells but not with a variant of gp160 (modified at the cleavage site) prevented infection after a low-dose HIV challenge (67). Several trials with the SIV system have also shown some potentially positive results (830, 1074).

Vaccine studies have also been performed with vaccinia virus vectors, whereby viral proteins are produced in cells in association with vaccinia virus infection (200, 201, 1323). The approach in animals elicits good humoral and cellular (i.e., CTL) immune responses (1156, 1157). The extent of immune responses induced in humans is being evaluated in SCID-hu animals receiving PBMC from the vaccinees (see Section XXX D).

One study in which this approach was used with primates involved an initial immunization with a vaccinia virus construct and a booster with bacculovirus-produced SIV gp160 (493). Protection against low-dose homologous SIV challenge was achieved. The use of vaccinia virus vector vaccination also protected chimpanzees from low-dose HIV challenge (10 to 40 infectious doses) but only after subsequent booster immunizations with a purified baculovirus-derived gp160 and particularly a V3-keyhole limpet hemocyanin conjugate (374). In this latter case, protection could have come from the anti-V3-specific neutralizing antibodies elicited. One caveat to the use of vaccinia virus-based vaccines is the reduced response observed in individuals who have previously been vaccinated for smallpox (201).

Most recently, chimpanzees that were multiply immunized with HIV-1 antigens showed resistance to intravenous challenge with infected PBMC (333). This study provides the first evidence that immunization can induce host responses against HIV-infected cells. Further experiments to confirm these observations are needed, including those with infected-cell challenges in the anal and vaginal canals.

Purified equine infectious anemia virus envelope protein has also protected horses from infection with high-dose challenges of homologous but not heterologous viruses (508). Also noteworthy was the apparent enhancement of disease observed in some animals immunized with the baculovirus-derived envelope protein. The finding raises the potential problems involved in certain vaccine strategies.

Finally, expression of HIV envelope proteins in association with other viruses (e.g., Ty virus, hepatitis B virus, adenovirus, and poliovirus) and bacterial proteins is being evaluated in animals (14, 149, 279, 402, 656, 785, 1052). Recent observations on the induction of anti-HIV responses with poliovirus chimeras have provided promising results (235).

Use of the viral proteins and not virus as immunogens eliminates the possibility that viral nucleic acids will become transcribed or undergo cellular integration even though the virus has been killed. Moreover, a killed-virus preparation cannot guarantee stability of expression of all the viral proteins or the possibility of residual infectivity. Nevertheless, as with other agents, these vaccine procedures with purified proteins must protect against high-dose virus challenge, transmission by infected cells, and, as cited above, mucosal inoculation. In the latter case, the recent induction of mucosal immunity after vaginal immunization of primates with a recombinant SIV protein offers some hope (656). However, virus challenge of these animals must be conducted to assess the efficacy of this approach.

C. Viral Cores

Another major approach considered in vaccine development is the production of viral cores through the use of the HIV *gag* genetic region. Coinfection of cells with vaccinia virus constructs containing the core or envelope region of HIV give rise to virus-like particles that express gp120 on the surface and that lack the HIV genome (420, 494, 1093) (Fig. 27). These released retrovirus-like structures can be purified in sucrose density gradients and can potentially be used for immunization (420). The advantage is their close similarity to a virus without the potential danger of a full virion. They thus could provide an immunogen that might induce an immune response best suited to recognizing the invading organism.

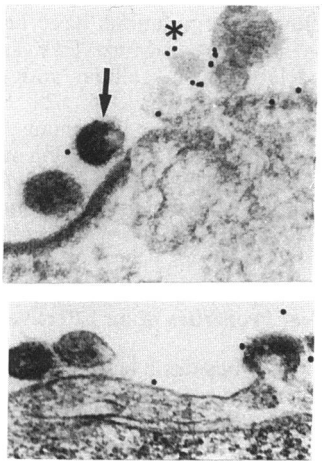


FIG. 27. Cells coinfected with recombinant vaccinia viruses containing the envelope or *gag* sequences of HIV-1. Budding particles of 100 to 200 nm in diameter (arrow) lacking the viral genome are evident in both panels. Envelope gp120 on their surface is demonstrated by antibody-colloidal gold conjugates (dark dots). Photomicrograph courtesy of S.-L. Hu. Modified from reference 420 with permission.

D. Human Trials with Viral Envelope Proteins

Several "toxicity" vaccine trials have now been conducted in humans by using the vaccinia virus-expressed or purified HIV envelope glycoproteins gp160 and gp120. No untoward clinical effects were noted. The induction of low-level neutralizing antibodies, and some noteworthy cellular immune responses has been demonstrated (4, 201, 255, 394, 592, 870, 926, 1290). Most recent studies with a muramyl tripeptide (MTP)-based vaccine (see Section XXX F) containing the glycosylated gp120 from the HIV-1_{SF2} strain have given encouraging results; relatively high levels of neutralizing antibodies and cellular immune responses were observed in human volunteers (533).

Nevertheless, whether immunized subjects are truly protected is uncertain because of the nature of monitoring the actual antiviral response. Recently, the use of the SCID-hu mouse system has offered a potential for examining the response of human subjects. A sample of the immunized human PBMC can be introduced into these immunosuppressed animals, and then the reconstituted SCID-hu mice can be challenged with infectious HIV. In preliminary studies, the best protection was observed with PBMC from vaccinia virus vector-immunized subjects who subsequently received a booster of the MicroGeneSys baculovirus gp160 protein (817).

E. Other Anti-HIV Prevention Approaches

Some investigators have explored the possibility that passive immunotherapy with antibodies or serum from HIV-positive individuals would be helpful in preventing infection. This treatment for infected individuals is discussed in Section XXIX C. Animal studies with chimpanzees at first showed no protection from HIV after the administration of anti-HIV antibodies followed by a high-dose virus challenge (100 CID_{50}) (951). Nevertheless, a subsequent study with 10 CID_{50} prevented infection (952). In one animal in the first experiment, enhancement of HIV infection was suspected (951).

In another study, an anti-V3 loop MAb protected chimpanzees from infection with 75 CID given 24 h after the antibodies (275). Moreover, when 75 CID were inoculated into chimpanzees and then the antiviral antibodies were inoculated 10 min later, protection against infection was also observed (275). A similar finding on protection by passive immunization has been made with HIV and SIV in macaques (960). However, the efficacy of this approach appears to be limited to a few minutes after virus inoculation (950a). The application of this latter approach to prevention of infection, particularly after needlestick injuries or during childbirth, requires much more study, including the use of selected antibodies (e.g., MAbs) (1338).

Finally, Watanabe and associates (1252) have reported that treatment of primates with recombinant CD4 (rCD4) led to a reduction in disease in some animals. To investigate whether antibodies to CD4 were the cause, they immunized SIV-infected monkeys with rCD4. In most animals subsequently infected, the induction of disease was greatly delayed and PBMC from these animals could not be directly infected in culture by SIV strains. Conceivably, the cells continued to be coated by the antibodies to rCD4. Similar observations were recently made with chimpanzees immu-

nized with rCD4; their sera had anti-HIV activity (1251). This observation has suggested that immunization with rCD4 might be of value to individuals pre- or postinfection. Obviously, in human subjects, the potential toxicity from autoimmune responses must be considered.

F. Adjuvants

In addition to selecting the appropriate antigen for use in a vaccine, an adjuvant can be very important for eliciting protective immune responses against the virus (for a review, see reference 18). The adjuvant should not produce unacceptable reactions at the injection sites and should have low systemic toxicity. It should induce cell-mediated immunity, including CTL, and antibodies of high affinity for vaccine antigens and of protective isotypes. Antibodies of those isotypes activate complement and function synergistically with effector cells in ADCC processes. The only adjuvants now approved for human use are aluminum sulfate and aluminum phosphate (alum). Alum augments antibody formation by most, but not all, antigens; it is ineffective with influenza virus hemagglutinin. Moreover, alum-precipitated antigens do not consistently elicit cell-mediated immunity. Hence, there is a need for adjuvants with the potency of Freund's complete adjuvant (FCA) but without inducing granulomas at injection sites and other unacceptable side effects.

Some new adjuvant formulations are listed in Table 39. In some of these, the mycobacterial cell wall component of FCA has been replaced by synthetic muramyl dipeptide (MDP) or MTP or by adjuvant-active analogs that are non-pyrogenic and have fewer other side effects, e.g., *N*-acetylmuramyl-L-threonyl-D-isoglutamine. FCA is a water-in-mineral-oil emulsion. The bulk oil phase remains at the injection site and is infiltrated by macrophages, which is why it produces granulomas. In the new adjuvants, the mineral oil in FCA has been replaced by the naturally occurring lipid squalene or squalene in the form of a 5% microfluidized oil-in-water emulsion. The lipids can thus be metabolized by the body. In addition, more highly defined surfactants, such as Tween 80 and Span 85, are used instead of the Ariacel A surfactant in FCA. Recent studies indicate that large animal species (e.g., primates), in contrast to rodents and rabbits, respond best to small-droplet stable emulsions (1213). Thus, this type of adjuvant formulation for inoculation in humans is recommended.

In the Syntex Adjuvant Formulation (115), the polyoxyethylene-polyoxypropylene triblock copolymer L121 is added. By hydrogen bonding, this surface-active agent retains antigens on the surface of the lipid microspheres and activates complement. The microspheres migrate through lymphatics to lymph nodes, and C3b on their surface targets them to antigen-presenting dendritic and follicular dendritic cells. Addition of the MDP analog to the emulsion induces the production of a cascade of cytokines, elicits CTL, and can induce mucosal immunity (e.g., with herpes simplex virus in guinea pigs [66]).

Another microfluidized formulation, MF59, consists of an emulsion containing squalene, surfactants, and, in some studies, the lipophilic muramyl peptide derivative MTP-PE (1213). In addition, it contains a phospholipid tail that facilitates association with the lipid phases. MF59 has been demonstrated to be an effective adjuvant for influenza virus, herpes simplex virus, and HIV antigens in animal models; it is currently in clinical trials with these virus vaccines (533).

In the Ribi adjuvant, the toxicity of the lipid A component of gram-negative bacterial lipopolysaccharide is decreased by removal of a labile phosphate group. The resulting monophosphoryl-lipid A is added to squalene emulsions alone or in combination with trehalose dimycolate or cell wall skeleton from *M. phlei* or both (1023). One form of the Ribi adjuvant ("Detox") has been used in clinical trials of melanoma and malaria vaccines (990). Monophosphoryl-lipid A has also been combined with liposomes, augmenting their efficacy as adjuvants (985), and these formulations have also been used in clinical trials with a malaria vaccine. For cell-mediated immunity, liposomes have the potential to carry antigens to the antigen-presenting cells such as macrophages, dendritic cells, and Langerhans cells in the skin. They can also concentrate the proteins at the site of inoculation and release them gradually, thus maintaining a constant antigenic stimulation.

Yet another group of adjuvants (the QS group) is based on saponins, glycosylated triterpenes derived from plants, usually *Quillaia saponaria*. Saponins are highly surface active and cytolytic, so they can cause tissue damage at injection sites. Such damage is reduced by using purified fractions (e.g., QS21) (560) or by decreasing the amount of residual saponin in the vaccine through the formation of immune-stimulating complexes (ISCOMS) (807). These are regular, cage-like structures containing saponin and virus envelope glycoproteins. ISCOMS containing gp120 of HIV elicit neutralizing antibodies and $CD8^+$ CTL in mice (1157). Highly purified saponin has also enhanced cell-mediated immunity responses to HIV when used as a component in an experiental gp160 vaccine with alum (1305).

The new adjuvant formulations have been shown to induce protective responses against HIV and perhaps SIV, although in the latter case, cellular antigens could be involved (see above) (130, 246, 374, 828, 830). Some have demonstrated immunogenicity in humans, e.g., in eliciting anti-HIV responses, with an encouraging safety profile (374, 533). It seems likely that these adjuvants will be components of a new generation of vaccines that contain recombinant viral antigens.

TABLE 39. New adjuvants augmenting cell-mediated and humoral immune responses[a]

Adjuvant	Vehicle
MDP analogs, e.g., *N*-acetyl-muramyl-L-threonyl-D-isoglutamine	Squalene-L121 emulsion
MTP phosphatidylethanolamine	Squalene emulsion
Monophosphoryl-lipid A (e.g., Ribi)	Squalene emulsion, liposomes
Saponin (e.g., QS-21)	Immune stimulating complexes

[a] See Section XXX F for discussion and references.

G. Ideal Properties of an Effective Vaccine

Several properties besides a lack of toxicity are necessary for a successful vaccine (Table 37) (for reviews, see references 40, 83, 461, 618, 665, and 1113). It should induce strong cellular as well as humoral immune responses (1156, 1157) that are long lasting and are present in the mucosal linings of the vagina, the bowel, and perhaps the oral cavity. This mucosal immunity might require the use of a vaccine administered orally (318) or placed in contact with the mucosal immune system via the bowel, vagina, or nasal passages (656, 789, 790). Moreover, side effects such as autoimmune phenomena and enhancing antibodies must be

avoided. In this regard, recent studies with sera of volunteers vaccinated with recombinant gp160 have indicated the induction of anti-CD4 anti-idiotype antibodies (553) and, in some cases, enhancing antibodies for certain HIV-1 strains (585b). In all these approaches, the prevention of infection is optimal but protection from disease could also be a satisfactory result.

XXXI. CONCLUSIONS

Encouraging progress has been made in understanding the pathogenesis of HIV infection from the initial isolation of representative agents in 1983 to the more recent development of potential therapeutic approaches via antiviral drugs and a vaccine. Nevertheless, the road toward the eventual control of HIV still seems long, and where we are on that road is uncertain. Although the direction appears more focused, many avenues of study must still be explored. The exact mechanism for $CD4^+$ cell depletion and immune deficiency is not known, and neither is the way in which the heterogeneity among HIV strains is produced. Latency and many features of HIV pathogenesis remain mysterious. Moreover, whether more virulent viruses are emerging in the population as a result of increased transmission merits attention.

Potential antiviral therapeutic approaches should consider inactivating the Tat protein to induce latency or elimination of HIV and using certain Nef proteins as antiviral drugs. Can the intracellular factor(s) that determine the relative replicating abilities of HIV strains be identified, and can the knowledge gained be used therapeutically? Can the virulence gene(s) of HIV be found and countered by direct approaches? Can the $CD8^+$ cell factor, purified and synthesized, be used as therapy? Can a treatment to increase the anti-HIV response of $CD8^+$ cells be developed? What action can be taken to enhance all effective immune responses against the virus in the already infected host? Many of the experimental procedures proposed to answer these questions have to be studied in animal models such as SIV and feline immunodeficiency virus. These systems provide excellent vehicles for evaluation, since the disease in these particular animals also involves lentiviruses that replicate well in $CD4^+$ lymphocytes (Table 1).

In these future studies, therapeutic and vaccine strategies must consider the potential dangers of affecting the immune system detrimentally, leading to an increase in viral replication or disease via loss of $CD8^+$ cell response, cytokine induction, cell toxicity, autoimmune responses or production of enhancing antibodies. In this regard, an indirect approach to limiting HIV pathogenesis via anti-cytokine therapies might be helpful. The ability to control HIV infection clearly requires a full understanding of the virus in all its heterogeneous forms, its genetic differences, its capacity for molecular mimicry, and its dramatic mechanisms for changing and evolving to become more virulent and to escape immune surveillance. In other viral infections, the antiviral approaches could be successfully directed at free agents that were passed through blood or body fluids. With HIV, transmission through virus-infected cells presents a major challenge to both anti-HIV therapies and a vaccine.

Certainly, infection by the AIDS retrovirus is a major medical challenge to cell biologists, virologists, immunologists, molecular scientists, physicians, and all health care workers. Although initially limited in its transmission, the disease is now pandemic. HIV is a constantly moving target, which threatens populations all over the globe. As of December 1992 in the United States, 1 in 250 individuals was estimated to be infected by HIV. On the basis of gender distribution of AIDS cases, this number suggests that 1 in 100 males and 1 in 800 females were HIV infected (Centers for Disease Control AIDS Information Office, 1992). This year alone, 40,000 to 80,000 new cases of HIV infection are expected in the United States (733). In the world today, it is estimated that a new infection takes place every 13 s and a person dies from HIV infection every 9 min. By the year 2000, 30 million to 100 million people worldwide will have been infected by HIV-1 or HIV-2; 10 million will be children (733). The number of reports written on the subject peaked at 13,669 in 1992, with a total by January 1993 of 77,085 citations since the initial reports in 1981 (National Library of Medicine AIDS Line Database).

All approaches to control will require cooperation from many different sectors of the population, including government officials and political activists advocating the support needed to continue adequate financial backing for research and care. Along the way, many new features of virology and cell biology will be uncovered. Already the recognition of the Rev, Tat and Nef proteins and their respective targets offers insights into potential eukaryotic processes that could have widespread application. Transactivation, RNA-binding proteins, and modification in RNA splicing are just a few examples of new biologic processes that have emerged from molecular studies of HIV.

Understanding how the virus can enter cells via a variety of receptors and remain latent in the cells could also shed light on mechanisms by which the host carries a variety of viruses for a lifetime. How the immune system reacts to HIV can also help in approaches at controlling autoimmune disease and other infections such as malaria. The importance of eliminating the infected cell and preventing HIV replication in the host has parallels in cancer. A vaccine against AIDS could certainly assist in developing a vaccine against cancer in which the cell is also the most important culprit. Research endeavors in either of these medical challenges could have relevance to both processes. Finally, knowledge of how variations in a virus and how the host response to that virus can affect pathogenesis will be greatly enhanced through the study of this human lentivirus.

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