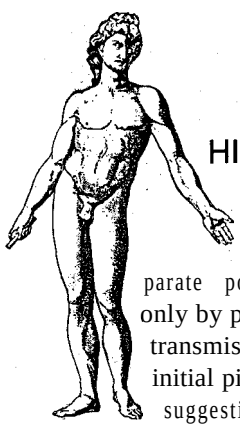
discussion by listing the biological hallmarks shared by all the lentiviruses: their host range tends to be genus-specific rather than species-specific; their transmission occurs horizontally through blood, milk, other body fluids, and inflammatory exudates containing either infected lymphocytes, infected macrophages, or free virus; they cause lifelong infections in monocytes, macrophages, and lymphocytes; they replicate irregularly or 'continuously at enhanced or restricted rates; and they may or may not cause disease after variable or often prolonged periods of subclinical infection, depending on various virus and host factors. Table 2 lists the clinical manifestations of the various lentiviral diseases.



The appearance of AIDS in disparate populations connected only by probable routes of transmission was among the initial pieces of evidence suggesting an infectious cause to the forthcoming worldwide epidemic. First described among homosexual men in June 198 1, AIDS was recognized among intravenous drug users and Haitians the following year and among recipients of blood or blood products, infants born to mothers at risk, heterosexual sexual partners of patients with AIDS, and Africans by early 1983. Thus the search for a blood-borne infectious agent resulted, in the discovery of the human immunodeficiency virus in 1983. Thus far two strains have been identified, HIV I, which appears to be the predominant virus affecting Africa and the western world, and HIV II, more closely related to SIVs and currently responsible for infecting various West African populations, albeit at a slightly attenuated mortality rate.

Humans infected with HIV generally develop an early flu-like syndrome that includes fever, malaise, loss of appetite, sore throat, night sweats, generalized swollen lymph nodes, and diarrhea. As the disease progresses over the next one to seven years, the lymph nodes remain enlarged and the circulating T4 cell population in the body progressively declines. The decline leaves the body vulnerable to a large number of opportunistic infections, such as a rare type of protozoa1 pneumonia, a nervous system infection due to a parasite of cats, and an unusual type of cancer of blood vessel origin (Kaposi's sarcoma). The infected human generally succumbs to one of these opportunistic infections.

The virus is spread predominantly in blood and blood products and has been discovered in saliva, breast milk, and cerebrospinal fluid. Soon after the initial infection and at various unpredictable times during incubation and throughout the disease, large amounts of cell-free virus are found in blood. At these times the immune system appears to be inactive as the virus increases its chances for transmission through mediums such as serum, plasma, or breast milk.

The virus has been found to infect and is recovered from T4 cells, monocytes, and macrophages in blood, lung, and brain tissues. Current studies suggest that various cells of the central nervous system can be infected at a low level. Infection of the lymphocytes generally leads to rapid cell death and the release of large numbers of cell-free virus particles. Infection of monocytes and macrophages, on the other hand, leads to an event in which variable numbers of virus particles are found budding within the cell without killing it.

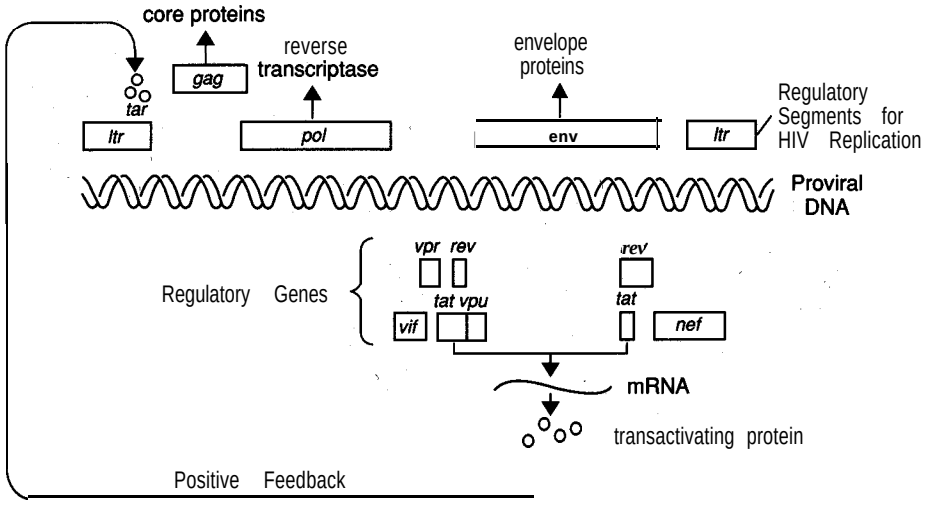
All human races appear susceptible to infection and the subsequent development of fatal immunosuppression. The previously mentioned carrier state of other animal lentiviruses is not as common in HIV. Although less pathogenic viruses have been isolated, extensive investigations into adapted native African populations have, to date, not been reported. We know that some individuals have been infected for greater than nine years with no identifiable symptoms, but we have no substantial database or explanation as to how this occurs. Tnvestigations currently underway to study the genetic predisposition to the virus in the human population should eventually yield general statements about variations in susceptibility to disease. Our discussion suggests that virus-adapted African subpopulations should already exist in some parts of Africa.

Mechanisms of Viral Persistence

Viral persistence, or the inability of the host to completely rid itself of the virus, may be the outcome of a number of viral properties. First, the virus may disguise itself or mimic properties of the host's normal cells. Second, the virus may infect a small subset of cells situated in the brain, reproductive organs, and parts of the eye and joints that are immunologically privileged, that is free from the usual scrutiny of the immune system. Third, the virus may paralyze or destroy certain immune functions directly responsible for its elimination. Fourth, it may integrate itself into the genetic make-up of the cell, thereby insuring itself subsistence as long as the normal cell is not eliminated. Fifth, the virus may have genetic controlling elements that regulate and limit its expression. Lastly, the virus may have an ability to continually change itself on a regular basis such that the immune system is never able to "catch up." Although some of the six strategies just mentioned are found in other

Table 3

Genetic Map of HIV



The HIV genome contains about 10,000 nucleotide pairs. Nine genes are shown here, arranged in sequence along the viral DNA. (Since protein-coding regions can be read in three ways, a number of genes can overlap on one DNA segment.) The genes are flanked by long-terminal-repeat (Ztr) regions, noncoding regions that initiate expression of viral genes. The gag, pal, and *env* genes code for core proteins, reverse transcriptase (and other enzymes), and envelope proteins, respectively. HIV also contains an unusually large number of regulatory genes, described below.

Regulatory Genes

- *tat* — A positive regulator that amplifies viral replication. The tat gene does this by producing a transactivating protein that stimulates a transacting response sequence (tar) in the *ltr* region of the genome. The tar sequence is included in every mRNA transcript of every HIV gene. Thus, tat boosts production of both regulatory and structural viral proteins, including its own protein, and can amplify viral replication by a factor of a thousand.
- *rev* — A differential regulator that enables selective production of either regulatory proteins or new virion components by a transacting antirepressive mechanism. The tat and *rev* genes can counteract each other to produce steady-state levels of *tar* and *rev* regulatory proteins.
- nef — A negative regulatory factor that suppresses viral expression.
- *vif* — A viral infectivity factor whose protein product enhances the ability of new virus particles to fuse with and enter uninfected cells.
- vpr — This segment has an unknown function, but codes for protein.
- *VPU* — This segment has an unknown function, but codes for protein.

persistent viral infections, such as Herpes viruses (I, II, and cytomegalovirus) adenoviruses, and influenza viruses, only the lentiviruses appear to have adopted them all. In the following sections we will bring together data on the mechanisms of lentiviral persistence from the previously described animal models and from recent studies of HIV-infected humans.

Cellular-Viral Regulation. The slowness or persistence of lentiviral infections reflects the fact that viral replication in T lymphocytes and monocytes is often minimally productive-viral replication generally takes place at a very slow rate. It is, however, the limited production of viral antigens that allows the infected cells to go unnoticed by the immune system for long periods. Alternatively, the virus's life cycle stops at the proviral DNA or the RNA transcription stage. Infected cells that are invisible to the host's immune defenses, yet capable of: transmitting the virus from cell to cell, are sometimes referred to as the "Trojan Horse" phenomenon.

As mentioned in our earlier discussion of the immune system, immunological signals that activate T cells and signals that initiate the maturation and differentiation of monocytes into macrophages are the norm in daily immune functions. It is these signals, however, that seem to initiate, enhance, and control lentiviral replication within infected cells. Although viral replication does not necessarily kill infected cells, the presence of the virus seems to impair the cell's functioning and to preclude the cell's ability to eliminate other foreign invaders. Moreover, activation of the latent viral state appears to occur at just those times when viral replication will assure transmission of the virus to new host cells.

The ability of lentiviruses to go from a state of "controlled hibernation" to a state of "controlled activation" following

SYNCYTIUM — A GIANT MULTINUCLEATED CELL

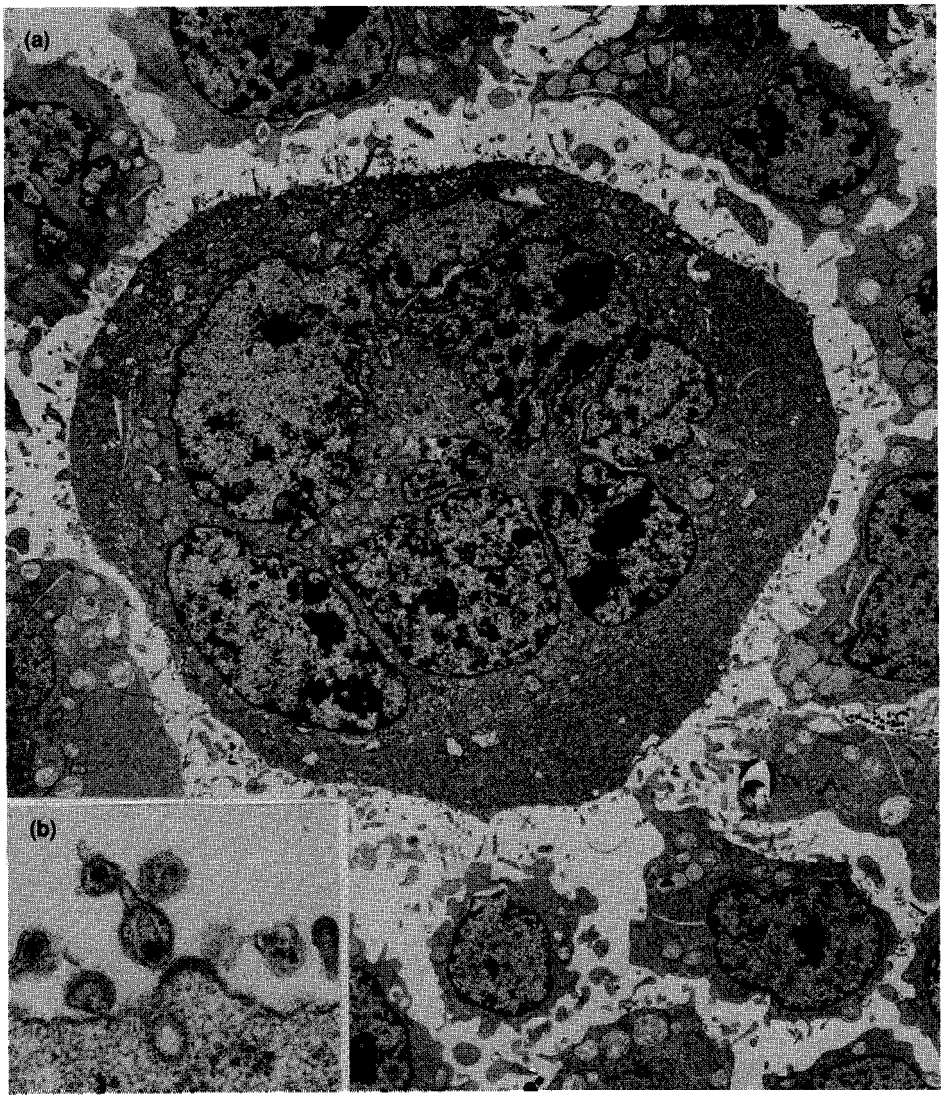


Fig. 8. (a) Transmission electron micrograph of a giant multi-nucleated cell formed in vitro by the fusion of an HIV-infected transformed human T4 lymphocyte with other lymphocytes from the same cell line (magnified 1200 times). The syncytium is rapidly producing virus particles. (b) The budding of viral particles in (a) (magnified 25,000 times). The transformed, or tumor, cell line shown here and developed by Robert Gallo produces large numbers of HIV particles without undergoing cytolysis and has therefore been instrumental in AIDS research. (Photograph by Kunio Nagashima, NCI-Frederick Cancer Research Facllity.)

stimulation of the immune system must be related to their unusually large number of regulatory genes. These "extra" genes, which were either evolved independently by the virus or were pirated from the host's immune cells, appear to work in concert with the host cell's machinery and extracellular signals to limit or enhance viral gene expression as needed for survival of the virus. Table 3 lists the known regulatory genes in HIV, for which the detailed functions are only partially known.

The state of controlled viral replication is lost in all species of AIDS viruses when they are placed in tissue culture. Viral replication takes place rapidly in peripheral blood lymphocytes when stimulated artifically to divide. An infected T4 cell transcribes proviral DNA into several thousand copies of viral RNA, which serve as genomes for new virus particles and templates for production of viral proteins. The redirection of cellular machinery for the massive production of viral components leads to a loss of the normal protein synthesis required to maintain cellular integrity. In addition, the RNA genomes and viral proteins assemble into infectious virus particles, which, in some instances, massively bud from the cell surface, thereby destroying the cell. A single infected cell may produce 500 to 1000 of these. Massive viral replication may occur in vivo as evidenced by detectable levels of viral antigens or infectious cell-free virus circulating in the serum of about half of the AIDS patients at various times during the course of the disease.

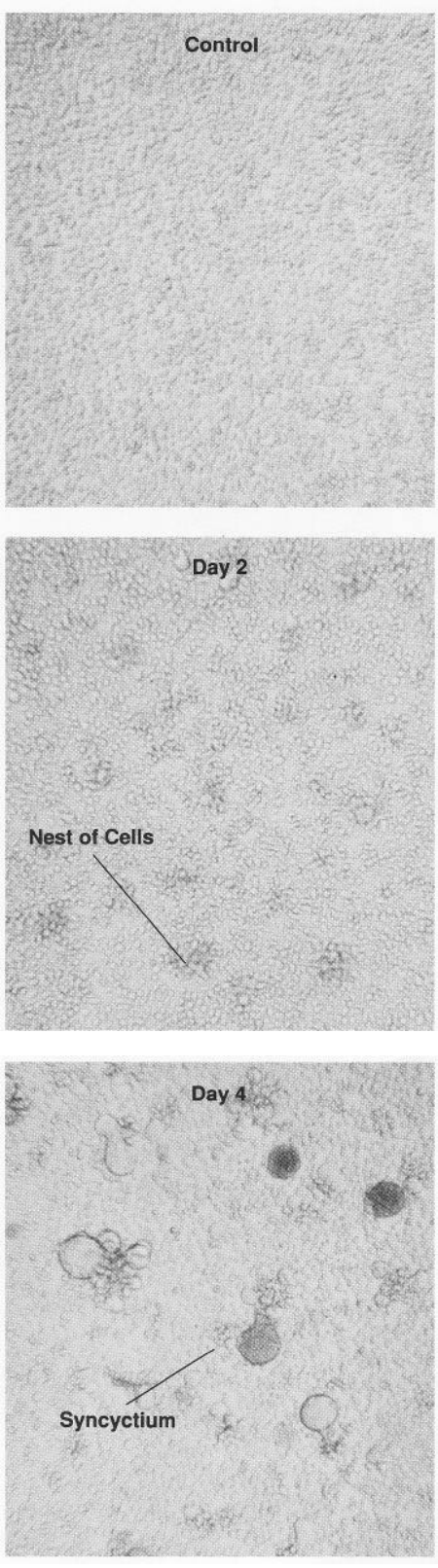
Detailed knowledge of the cellular factors controlling the virus life cycle in monocytes and macrophages comes from in vitro studies of visna-maedi virus. The visna-maedi life cycle is highly dependent on maturational factors in these cells. Less differentiated monocytes are more difficult to infect and the viral life cycle stops after proviral DNA is transcribed into RNA. As monocytes age, they are more easily infected, and viral replication proceeds all the way to the production of viral proteins. This regulatory program as-

sures that viral proteins are produced at exactly the same time that monocytes mature into wandering macrophages and can thus interact with additional cells of the host immune system that are susceptible to infection.

Additional evidence for the interaction of viral regulatory genes and cellular factors comes from work in my laboratory. We have been developing sensitive, quantitative, in vitro assays of both the infectiousness of the AIDS virus and the effectiveness of antibodies or antiviral agents against the virus. Initially, we screened many human tumor T4 cell lines for their ability to become infected readily with HIV. We then used cell cloning strategies to select those that grow in uniform monolayers and then react to viral infection by rapidly fusing with nearby cells. Thus, when infectious virus particles are introduced onto the monolayer, each cell that becomes infected fuses with other cells to form a large, distinct single cell with many nuclei, called a *syncytium* (Fig. 7). The number of infectious viral events can be determined directly by simply counting the number of these large cells (Fig. 8).

On refining this assay we noticed that initially no new virus particles were produced by infected cells during the cell fusion process-they were produced only after the cells had exhausted their ability to fuse. These observations suggested that the virus has a two-stage strategy for assuring its persistence in the immune cells of the host (Fig. 9). Once inside a cell the first stage causes the virus to direct its effort toward cell fusion. This mechanism accomplishes the business of spreading in the host without direct exposure to the antiviral actions of the host's immune system.

What are some of the details of this first stage? The viral regulatory genes within an infected lymphocyte or macrophage seem to be chemically connected to the host cell's normal surface receptors, for example, any of the

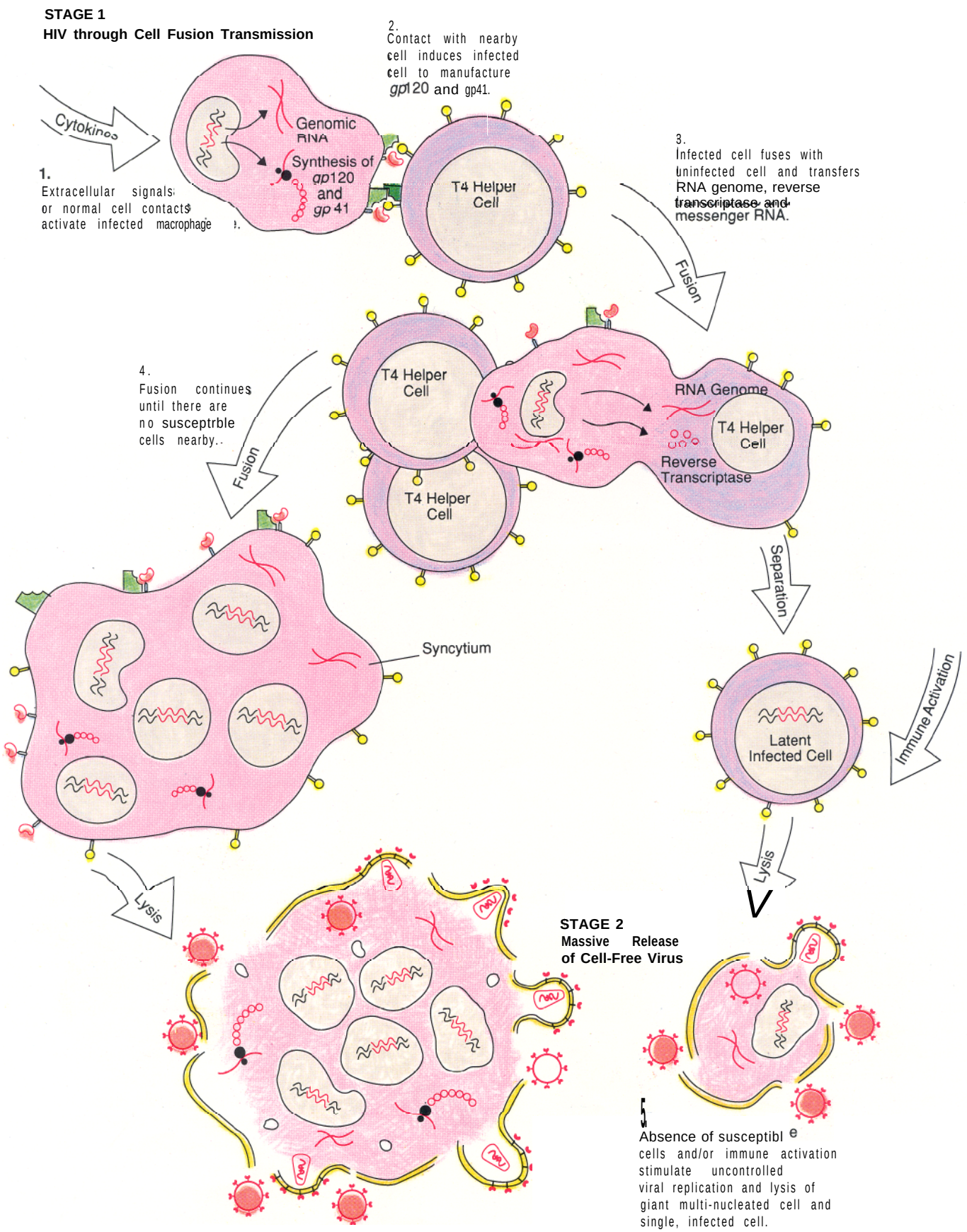


FORMATION OF SYNCYTIA IN MICROASSAY

Fig. 9. Photomicrographs of sequential stages of cell fusion and syncytial formation in the quantitative HIV l-induced infectivity microassay. The top picture depicts normal unInfected cells forming a monolayer. The middle and bottom pictures demonstrate cell-to-cell fusion. Note the cell nests or clusters (arrow) that occur by day two in culture. By day four or five, these cell nests form the typical syncytia described In the text and shown in Fig. 8.

lymphokine, or cell-recognition, receptors, that is, the MHC receptors. These cell-surface receptors receive chemical signals that direct the cells around the body and induce normal immune activity in the lymph system. Normal signals that prepare the various neighboring immune cells to interact with each other seem to activate the HIV envelope genes within the infected cell to produce the "fusigenic" envelope proteins, *gp* 120 and gp41, that cause cells to stick together and fuse.

What of the second stage? It seems that if the HIV-infected fusigenic cells fail to find neighboring cells susceptible to fusion, a new set of cell-membrane signals induces the viral genes to redirect the cell's machinery toward producing the additional structural components required to assemble new infectious virus particles. The massive production of these new particles, sometimes at the expense of the cell, can be considered a terminal last ditch effort on the part of the virus to infect new cells and thus survive in the host. As virus particles bud from the cell, they strip off pieces of the protective cell membrane. Normally, cell membrane components are constantly being re-formed through protein synthesis to keep up with the everyday import and export of cellular


STAGE 1
HIV through Cell Fusion Transmission
Cytokines
1.
Extracellular signals or normal cell contacts activate infected macrophage.
Genomic RNA
Synthesis of gp120 and gp41
2.
Contact with nearby cell induces infected cell to manufacture gp120 and gp41.
T4 Helper Cell
3.
Infected cell fuses with uninfected cell and transfers RNA genome, reverse transcriptase and messenger RNA.
Fusion
T4 Helper Cell
T4 Helper Cell
RNA Genome
T4 Helper Cell
Reverse Transcriptase
4.
Fusion continues until there are no susceptrble cells nearby..
Fusion
Separation
Syncytium
Latent Infected Cell
Immune Activation
Lysis
Lysis
STAGE 2
Massive Release of Cell-Free Virus
5.
Absence of susceptible cells and/or immune activation stimulate uncontrolled viral replication and lysis of giant multi-nucleated cell and single, infected cell.

TWO-STAGE MODEL OF VIRAL REPLICATION

Fig. 10. HIV regulatory genes, in response to extracellular signals, seem to produce two distinct stages of viral replication that assure survival of the virus in the host. Stage 1. In the presence of CD4-positivecells, the Infected cell produces the fusigenic viral proteins, gp41 and gp120, that cause fusion of the infected cell's membrane with the membrane of a neighboring CD4-positive cell. The viral genome and reverse transcriptase Is then transferred to the uninfected cell. The newly infected cell may then separate to become a latent infected cell. Alternatively, it may take part in the fusion process with other nearby CD4-positivecells to form a giant multl-nucleated cell called a syncytlum. In this way, the infection spreads slowly wlth no interference by the Immune surveillance system. Stage 2. When no uninfected CD4-positive cells are nearby, the syncytlum switches into a state of uncontrolled viral replication, which produces thousands of new infectious' virus particles. As these bud from the surface, they tear, or lyse, the membrane and thereby destroy the giant cell. A single latent uninfected cell, when stimulated by extracellular signals, may also undergo uncontrolled viral replication, resulting in lysls of the single cell. The infectious viral particles now encounter immune defenses as they travel through the body to find new infectible cells.

materials. However, the uncontrolled production of 500 to 1000 particles per cell and the holes they create as they bud from localized areas on the cell surface, cause the cell to take on excess extracellular fluids, burst, and die.

The newly created HIV particles, unlike some other viruses, appear to undergo a relatively rapid predetermined decay caused by the spontaneous shedding of the gp120 molecule, the molecule that binds to CD4. The shedding is apparently due to the interactive yet weak protein structure of gp120. Studies in my laboratory show that the shedding takes from 8 to 15 hours. Hence a race begins to find a new infectible host cell before the virus particle loses its ability to infect. (See "The Kinetics of HIV Infectivity" for a detailed discussion of this process in vitro.) In summary, if the infected cell is locked in a compartment of the body with no direct access to infectible cells and therefore no chance for fusing, the virus programs the cell to produce hundreds of virus particles, which can rapidly diffuse in extracellular fluids or in the bloodstream.

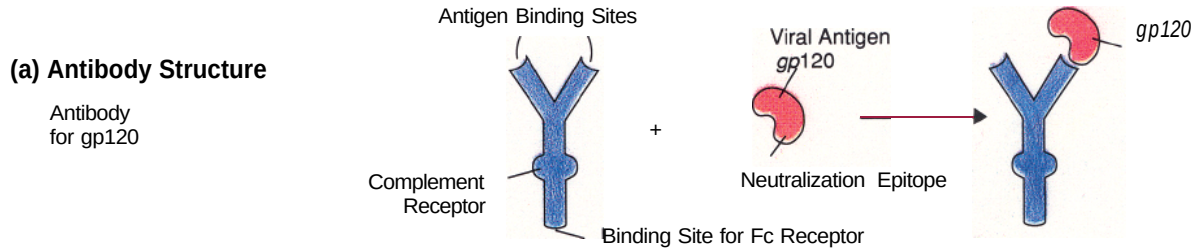
Biological Properties of the Virus. Having discussed *regulatory* processes that help assure presistence of the virus, we now turn to *structural* properties that help the virus escape from host immune defenses. The glycoproteins gp 120 and gp41 forming the envelope of HIV have two biological properties important to the survival of the virus: 1) they contain large amounts of carbohydrate (sugar), which serves to minimize and hide their protein binding sites from the host immune system and 2) they insert themselves next to or within the host cell's own self-recognition proteins, such as the MHC molecules. Both properties help the virus to escape from normal antiviral immune mechanisms previously outlined in Fig. 5.

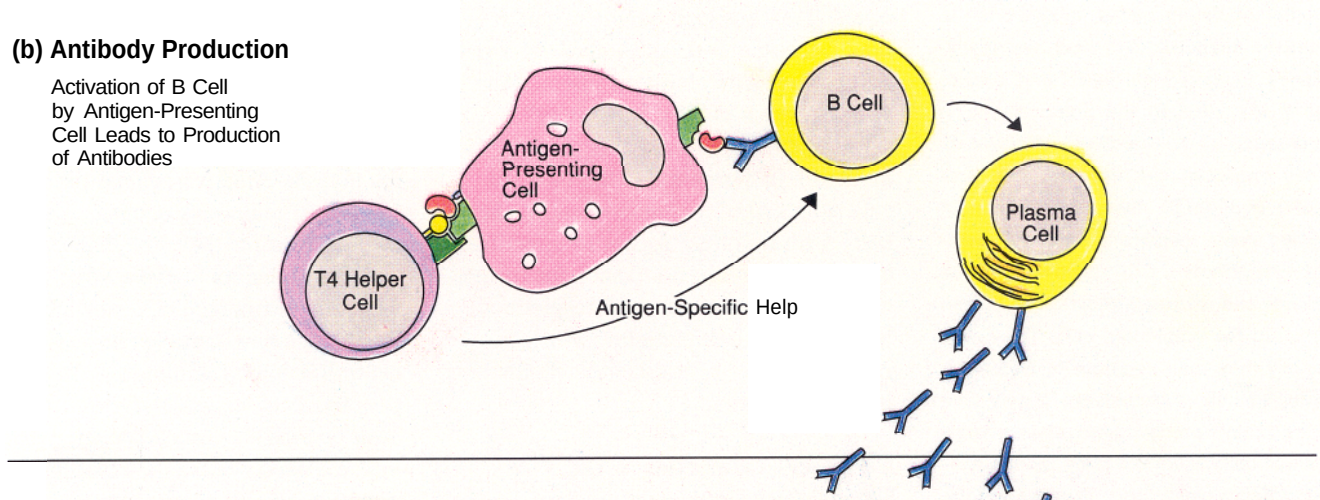
Antibodies are Y-shaped proteins that neutralize the virus by binding to specific molecular protein shapes, called *epitopes*, on the viral envelope proteins (Fig. 10). In most lentiviruses, almost all neutralization epitopes are highly glycosylated (sugar coated), and these carbohydrate moieties completely conceal neutralization epitopes from immune recognition. As a result, the B lymphocytes are not able to produce highly effective neutralizing antibodies. In the case of HIV, we are a bit more fortunate in that some effective neutralizing antibodies are produced (see "The Search for Protective Host Responses").

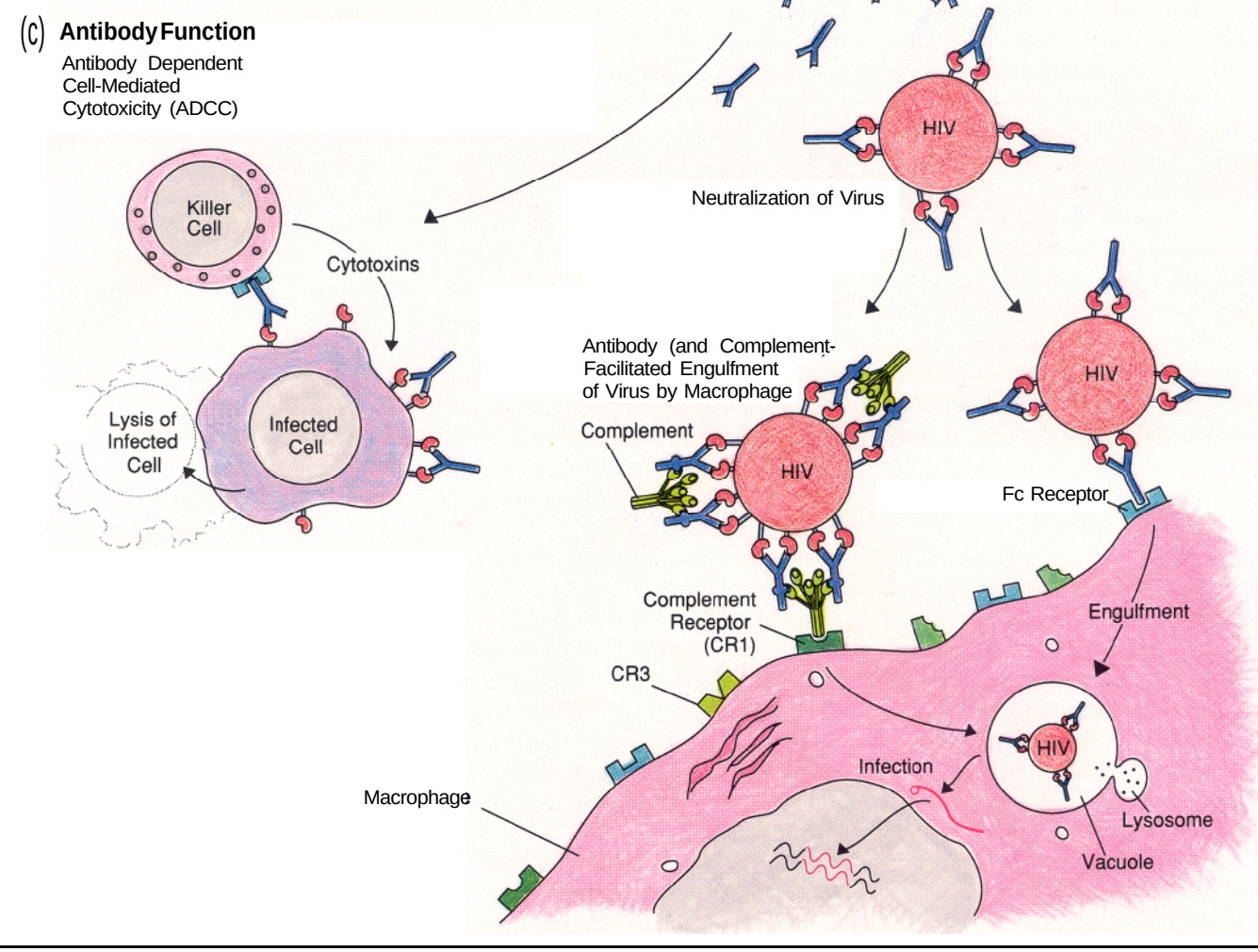
In all strains of lentiviruses, some epitopes are variably exposed and induce the production of neutralizing antibodies of very narrow specificity (that is, they recognize only the one viral strain). While the neutralizing antibodies may be effective against the original virus, mutations occur frequently in me genes for the viral envelope and lead to production of new virus particles with rearranged neutralization epitopes. The new particles now escape neutralization by antibodies. This process has been called *antigenic drift*, a term previously coined for influenza viruses, which cause the common cold. The mutational phenomenon is seen in sheep infected with visna-maedi virus, in horses infected with the EIA virus, and in humans infected with HIV.

Moreover, non- or poorly-neutralizing antibodies *can facilitate* the infection of macrophages. The loosely associated virus-antibody complex sticks to an antibody receptor present on the surface of the macrophage. The macrophage then engulfs the virus-antibody complex and thereby becomes infected (Fig. 10). Thus, certain antiviral antibodies produced during the lentiviral infection serve no useful biological purpose and therefore seem to perpetuate rather than eliminate infection in the host.

As previously mentioned, after a host cell has become infected, the viral glycoproteins insert themselves strategically next to or within the MHC antigens normally present in the cell membrane. Since MHC proteins are precisely the surface antigens that cells of the immune system use to recognize each other as self, the viral glycoproteins act very much like a "wolf in sheep's clothing." The net result is a form of molecular mimicry. In particular, recall that the presence of gp120 in the membrane of the infected cell allows it to fuse with any neighboring cell that has a


(a) Antibody Structure
Antibody for gp120
Antigen Binding Sites
Viral Antigen gp120
gp120
+
Complement Receptor
Neutralization Epitope
Binding Site for Fc Receptor


(b) Antibody Production
Activation of B Cell by Antigen-Presenting Cell Leads to Production of Antibodies
B Cell
Antigen-Presenting Cell
Plasma Cell
T4 Helper Cell
Antigen-Specific Help


(c) Antibody Function
Antibody Dependent Cell-Mediated Cytotoxicity (ADCC)
HIV
Neutralization of Virus
Killer Cell
Cytotoxins
Lysis of Infected Cell
Infected Cell
Antibody (and Complement-Facilitated Engulfment of Virus by Macrophage
Complement
HIV
HIV
Fc Receptor
Complement Receptor (CR1)
Engulfment
CR3
HIV
Infection
Macrophage
Lysosome
Vacuole

ANTIBODY STRUCTURE, PRODUCTION, AND FUNCTION

Fig. 11. (a) Antibodies are Y-shaped protein molecules whose arms contain antigen-specific binding sites. The antibody shown here is specific to gpl20. The base of all antibodies contains a binding site for the Fc receptor present on macrophages and killer cells. Antibodies also have binding sites for some complement proteins and thereby work in conjunction with complement to coat foreign invaders and attract scavenger cells, which destroy them. (b) Antibodies are produced by B lymphocytes. Here a B cell binds through its antibody receptor to an antigen-presenting macrophage and also receives chemical signals from a T4 helper cell. The combination stimulates the B cell to proliferate and mature into antibody-secreting plasma cells. (c) One function of antibodies is to neutralize viruses; as shown in the figure, they accomplish neutralization by binding to the virus's surface receptors, which prevents the virus from infecting a host cell. The figures also show how antibody-coated virus may bind to the Fc receptors on macrophages, which leads to engulfment and digestion of the antibody-virus complex. If complement binds to the antibody-virus complex, engulfment by macrophages is further facilitated. In the case of HIV, coating of the virus by nonneutralizing antibody may lead to engulfment by and subsequent infection of the macrophage. A second major function of antibodies (bottom left) is to coat infected cells and thereby attract, bind to, and stimulate killer cells, to secrete cytotoxins, which lyse the infected cells. This process is called antibody-dependent, cell-mediated cytotoxicity (ADCC).

CD4 receptor on its surface and then to dump its viral genetic payload into that cell without the virus itself ever being assembled or encountering neutralizing antibodies, killer T8 lymphocytes, or other complex extracellular antiviral moieties that might interfere with the infection process.

Table 4

Factors and Processes Leading to T4 Cell Depletion

1. Accumulation of unintegrated viral DNA.
2. Massive budding of new viruses, leading to breakup, or lysis, of cell membrane.
3. Abundance and maintenance of CD4 receptors on T4 cells, promoting infection, autoinfection, and cytopathic effects.
4. Cell fusion between T4 cells, promoted by complexing of viral envelope proteins with CD4.
5. Infected T4 cells expressing gp120 are recognized as non-self and destroyed by immune reaction.
6. Binding of free gp120 to uninfected T4 cells, leading either to binding of anti-gp120 antibodies or to direct attack by cytotoxic cells.
7. Antibodies to gp120 cross-react with MHC II expressed on activated T4 cells, and the antibody-coated T4 cells are subsequently destroyed by K (killer) cells.
8. HIV infection of bone marrow stem cells, leading to decreased production of mature T4 cells or HIV infection of a T4-cell subset that is critical to the propagation of the entire T4 cell pool.
9. Secretion by HIV-infected cells of soluble factors that are toxic to T4 cells or secretion of such factors induced by the free virus.

Immune Dysregulation and Destruction

We have stressed that the lentiviruses are adapted to the very essence of the host immune system. Ironically, our attempts to understand HIV are teaching us more and more about the human immune system. Although we know that infection by HIV and SIV results in a progressive loss of T4 cells, that loss is not completely understood because, at any one time, only one in ten thousand to one in a million circulating T4 cells are infected with HIV.

Thus, the simple fact that HIV and SIV can destroy T4 cells through massive viral replication in vitro (Fig. 11) does not seem to explain the dramatic T4 cell depletion in vivo. Therefore, the search is on for other mechanisms. It has been discovered that antibodies and killer T8 lymphocytes in human AIDS patients are capable of attacking their own normal, uninfected T4 cells. This attack on self is probably due in part to molecular mimicry, that is, MHC II, which is expressed by normal activated T4 cells, may "look like" gp120 to anti-gp120 antibodies and to T8 killer cells. (As shown in Fig. 4, the T4 cell receptor CD4 binds to both MHC II and gp120.) These and other possible mechanisms of T4 cell depletion are listed in Table 4. The fact that we list them illustrates not only our knowledge but also our ignorance about how the depletion process works.

We do know that the loss of T4 cells from the body induces a progressive loss of immune regulation. Because T4 cells orchestrate directly or indirectly all of the other T, B, monocyte, and macrophage cells of the immune system

FUNCTIONS OF T4 HELPER CELLS

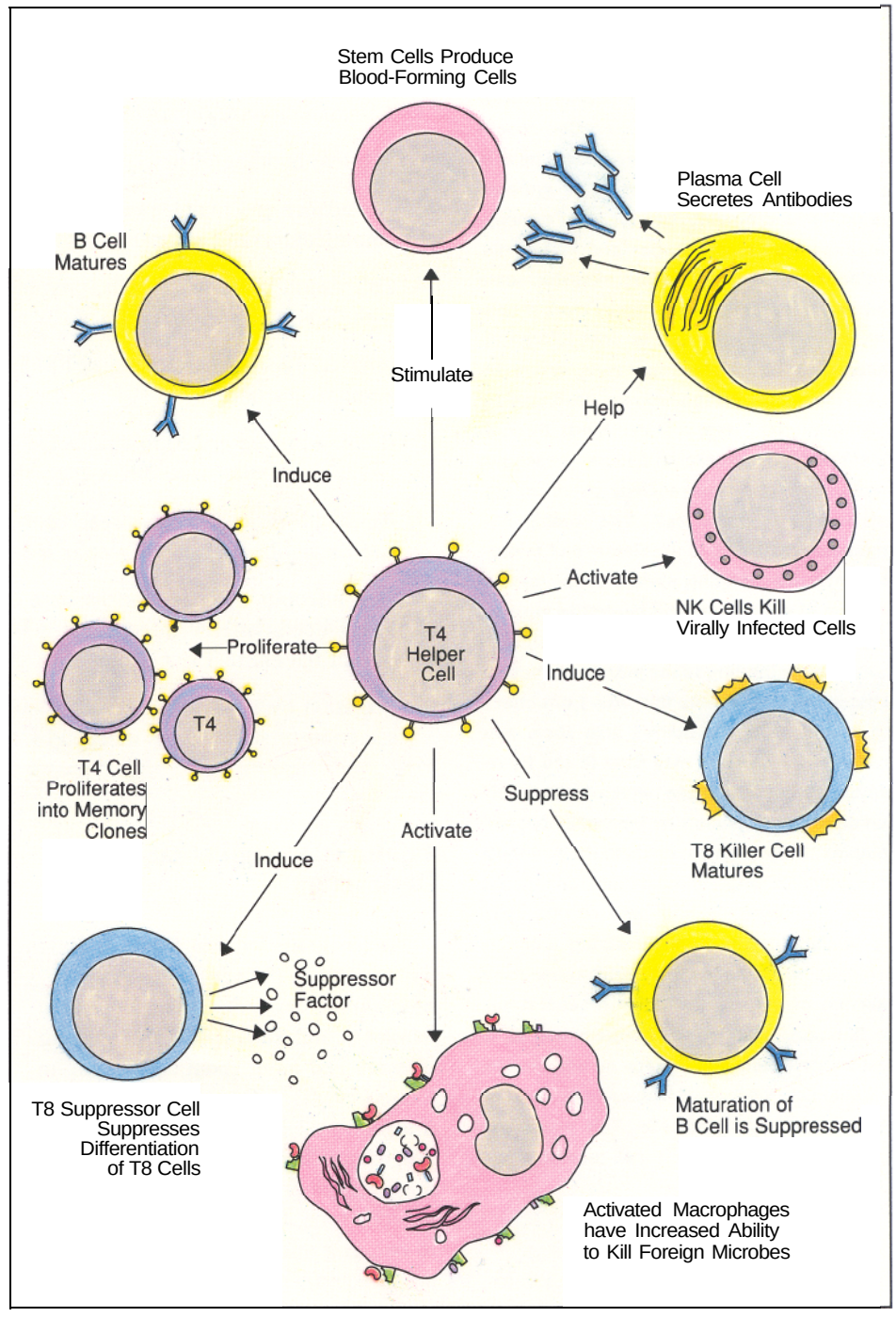
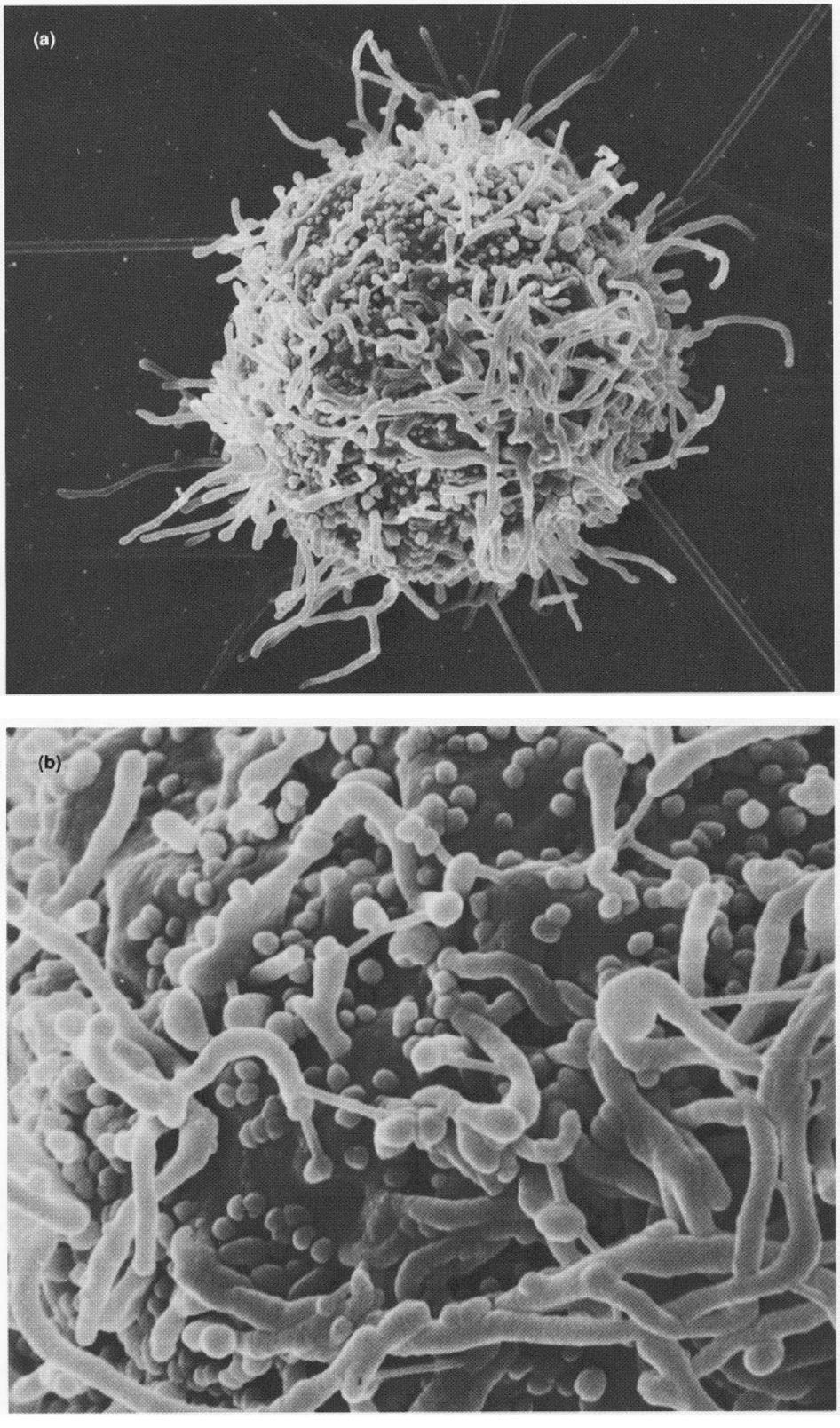


Fig. 12. T4 lymphocyte cells are called helper/inducer cells because they secrete many soluble chemicals that induce responses in other white cells. Thus T4 helper cells play a critical role in the immune response. The chemicals they secrete induce growth and differentiation of T and B lymphocytes, stimulate bone marrow stem cells, induce the killing function of T8 killer and natural killer cells, induce the suppression function of T8 suppressor cells, activate macrophages, and induce the functions of other nonlymphoid immune cells.

(Fig. 12), their loss leads to a general uncontrolled activation of the immune system, which is revealed by an excess of circulating antibodies in the blood and tissues. Moreover, helper events prompted by chemical messages from T4 lymphocytes are diminished or absent. In this setting of immune suppression, ubiquitous microbes in the environment, the body's own flora, and even some spontaneously formed tumor cells may flourish inappropriately.

HIV infection of monocytes, macrophages, and bone-marrow stem cells also leads to immune dysregulation. We have clear evidence that, in sheep and horses, respectively, the visna-maedi and EIA viruses infect monocytes and macrophages directly, although the specific celluar receptors involved have not yet been identified. Human macrophages become infected with HIV via CD4 or, perhaps, other receptors on the macrophage surface. Another infection mechanism is the binding and engulfment of antibody-coated HIV.

Whatever the mechanism of entry, the infection of monocytes and macrophages probably diminishes the performance of their various accessory functions, such as secretion of complement and clotting factors, tissue reorganization and repair, and killing of microbes and tumor cells. We have direct evidence from in vitro studies of visna-maedi of how the persistent infection of monocytes and macrophages stimulates the chronic activation of the immune responses shown in Fig. 5. In particular, lymphocytes in culture with visna-maedi-infected macrophages were found to produce a unique interferon, a soluble protein with three important effects. First, it retards monocyte maturation, thus indi-



VIRAL REPLICATION IN HUMAN T LYMPHOCYTES

Fig. 13. Scanning electron micrograph of HIV-infected human T4 lymphocyte. (a) A single cell infected with HIV showing virus particles and microvilli on the cell surface (magnified 7,000 times). (b) Enlargement of a portion of the cell surface in (a) showing multiple virus-particles budding or attached to the cell surface (magnified 20,000 times). (Photograph courtesy of K. Nagashima and D. Chisholm, Program Resources, Inc., NCI-Frederick Cancer Research Facility.)

rectly slowing the rate of viral replication. Second, it restricts the rate of virus maturation, and last, but most important, it induces an unusually high expression of MHC II antigens and viral antigens on the surface of the macrophages. It seems that the high expression of MHC antigens, when presented in association with lentiviral antigens, chronically stimulates the series of immune reactions shown in Fig. 5, which subsequently leads to abnormal accumulations of virally susceptible host immune cells and, in some cases, causes local tissue destruction.

Inherited Host Responses?

How do some hosts prevent the types of immune dysregulation just described? Are there natural immune responses induced by lentiviruses that can lead to a state of protection? In attempts to develop a vaccine against lentiviral disease, we and other researchers have investigated all known immune responses that might lead to such a state. (Some of those studies are described in "The Search for Protective Host Responses.") The progress to date has been discouraging. So far, none of the responses have been found to be effective against lentiviral disease. Moreover, none of

them have yet been thoroughly studied and identified as the cause of protection in the virus-adapted species previously mentioned.

Thus, the natural history of the lentiviruses, as well as the current lack of success of vaccine studies, suggests that the carrier state found in some species is a direct effect of host adaptation. Such adaption probably involves a combination of traditional immune responses and accumulated changes in the host's immune-response genes and the virus's genes over long periods of time.

What are some of the possible inherited-adaptive properties that may confer the carrier state on the lentivirus-adapted host? (1) There may be an absence or only a limited number of cells in the adapted host that are pathologically susceptible to the viral infection, and those cells that are infected are not altered in their normal immune function. (2) Controlling genes inherent in the cell may limit the amount of viral replication to very low levels, allowing critical host immune cells to be replaced or controlled by the host immune system faster than they are compromised. (3) The virus may be regulated or prevented from flourishing by naturally inherited or nonspecifically acquired antiviral substances present in body fluids. These substances would include cross-reactive antibodies induced from other pathogenic agents or viruses, as well as various other species- associated antiviral substances in blood and serum. Approximately thirteen such substances have been described in the scientific literature, including a heat-stable lipoprotein that inhibits the visna-maedi virus of sheep. (4) The presence of nonpathogenic, host-adapted viruses may interfere with infection by lentiviruses or at least somehow limit uncontrolled lentiviral replication. (5) Infected cells of certain hosts may specifically produce and release soluble proteins during their viral infection that prevent the infection of cells nearby or at some other location in the body. Interferon is an example of this last possibility.

Lessons from the Chimpanzee, Man's Nearest Living Relative

Due to the disappointing search for a state of immune protection in HIV-infected humans and the fact that such humans appear to possess a complete, yet nonprotective, repertoire of antiviral immune responses toward HIV, we are currently looking at animal models of host adaptation. The only model for the human virus is the HIV I-infected chimpanzee. To date, approximately one hundred chimpanzees have been infected in various laboratories with different variants of HIV obtained from human AIDS patients and tissue cultures. Preliminary studies demonstrate a state of viral infection persisting for 4 to 5 years with no clinical manifestations of disease. It can be argued that 4 to 5 years is insufficient time for disease development, however, in humans infected for this period of time, multiple cellular and immunologic abnormalities are measurable. None of these immune destructive signs are found in the infected chimpanzees at any time to date. Although an even longer incubation period may be required before these animals show clinical signs, the results of our chimpanzee studies are provocative.

Chimpanzees have received HIV I from diverse sources in various laboratories, varying from HIV I-infected cells or cell-free virus derived in tissue culture to samples of whole blood, spleen, bone marrow, or thymus from humans with AIDS. Included in the list is the intracerebral administration of suspensions of brain tissue from patients dying of AIDS-associated pathology of the brain. Also, chimpanzees that were persistently infected with HIV I have been experimentally manipulated with immunosuppressing and immunostimulating protocols without developing AIDS-associated abnormalities.

Four to six weeks after inoculating chimpanzees with as little as a single syncytial-forming unit of tissue-culture-derived HIV I, the virus can be reisolated by culturing lymphocytes from the blood of the infected animals. However, unlike the situation in HIV I-infected humans, cell-free virus could never be detected in the blood serum of chimpanzees at any time during the past 3 years. Two weeks after reisolation of the virus becomes possible, the infected animals make detectable antibodies to the viral antigens. In fact, the animals make antibodies that recognize all the known viral proteins recognized by antibodies from HIV I-infected humans. The animals also initially develop a virus-specific neutralizing antibody. With time, this neutralizing antibody is capable of neutralizing other HIV I variants, as happens in humans infected with HIV I. No abnormalities of the T4 or other lymphocytes are detected in the chimpanzee's immune system during this persistent infection.

In addition, no significant changes have been reported in the ratio of T4 to T8 lymphocytes in infected chimpanzees. During the infection the animals also make HIV I-specific cytotoxic T8 lymphocytes capable of killing HIV I-infected cells. More interesting, although humans infected with HIV I make autoreactive T8 lymphocytes capable of killing their normal cells, thus leading to immune dysregulation, chimpanzees do not. This further supports the thesis that the immune system of the