Exhibit 5

AIDS and the Immune System

The AIDS virus exploits the immune system to replicate itself. New findings are showing how it wreaks havoc on the body's defenses

by Warner C. Greene

It is now 12 years since acquired immunodeficiency syndrome sprang into medical and public awareness as a fatal disease of the immune system. The term "AIDS," or its equivalent in other languages, has since become recognized around the world. Other illnesses besides AIDS cause inappropriate immune responses, as numerous examples in this issue illustrate. Yet AIDS warrants special consideration.

First, it is now tragically clear that the virus that causes AIDS, the human immunodeficiency virus (HIV), is one of the principal threats to human life and health worldwide. In an article about the epidemiology of AIDS published in *Scientific American* in October 1988, Jonathan M. Mann, James Chin, Peter Piot and Thomas Quinn estimated that more than 250,000 cases of the disease had then occurred worldwide and that between five and 10 million people were infected with HIV. Five years later the situation is far worse.

The Global AIDS Policy Coalition, which Mann coordinates, now estimates that the actual number infected by the end of 1987 was about seven million; it places the number infected by the end of 1992 at 19.5 million, almost three times the earlier figure. Although antiviral and other medications may modestly prolong the lives of those infected, the great majority of them will, barring some major advance, eventually die of an AIDS-related illness. More than three million people have developed full-blown AIDS; most have already died. Responsible estimates of the number of cases of HIV infection likely to have occurred by the year 2000 range from 40 million to more than 110 million. The second number is about 2 percent of the world's present population.

To be certain, other diseases, such as malaria, kill more people than AIDS does. But the rapid spread of HIV, together with the lack of a vaccine or satisfactory treatment, makes this disease uniquely alarming. New infections—the majority now from heterosexual contact—continue at the estimated rate of one every 15 seconds. No country or social group is immune. Currently HIV is spreading quickly in East Asia, a region that was largely spared in the early years of the pandemic. Worldwide, women now account for some 40 percent of AIDS cases; about 10 percent are children born to infected mothers. Public education campaigns aimed at reducing transmission—mainly exhortations to the sexually active to use condoms and to drug users to sterilize needles and syringes—have had limited success.

The second reason for discussing HIV is that it is the most intensively studied virus in history. We already have an outline sketch of how the genes and proteins in the HIV virion, or virus particle, operate. We still lack, however, a clear understanding of what controls its replication and how it destroys the human immune system.

I must emphasize that all responsible opinion holds that HIV is indeed the primary cause of AIDS. A small number of cases of people with immune deficiency who are not infected with HIV received inappropriately widespread publicity last year, which fostered the unsubstantiated notion that there is another cause of AIDS not detected by current blood tests. This unfortunate episode only fueled the paranoia that surrounds the disease. In fact, there is little reason to believe that the condition of these patients was caused by any virus or that it is becoming more common.

Yet there are many different strains of HIV, and epidemiological and laboratory studies suggest that some are deadlier than others. HIV-2, for example, which is prevalent in West Africa, seems to produce less severe disease than does HIV-1, the more common form elsewhere. It is even possible that some rare strains are benign. Some homosexual men in the U.S. who have been infected with HIV for at least 11 years show as yet no signs of damage to their immune systems. My colleagues Susan P. Buchbinder, Mark B. Feinberg and Bruce D. Walker and I are studying these long-term survivors to ascertain whether something unusual about their immune systems explains their response or whether they carry an avirulent strain of the virus.

The great majority of investigators believe not only that HIV is the primary cause of AIDS but also that HIV infection alone will usually cause profound immune dysfunction over time. No other specific pathogen is known to be necessary. It does seem likely that other infections in a person carrying HIV may hasten immune deficiency; this area is being actively investigated. Such opportunistic infections, which frequently complicate the clinical course of HIV-infected patients, are often the eventual cause of death. Nevertheless, if we are to understand AIDS, we must understand HIV.

High-resolution electron microscopy has shown the HIV virion to be roughly spherical and about one ten-thousandth of a millimeter across. Its outer coat, or envelope, consists of a double

T LYMPHOCYTE infected with the human immunodeficiency virus (HIV) displays a characteristic lumpy appearance. The protuberances colored green in this electron photomicrograph are virus particles in the process of budding.

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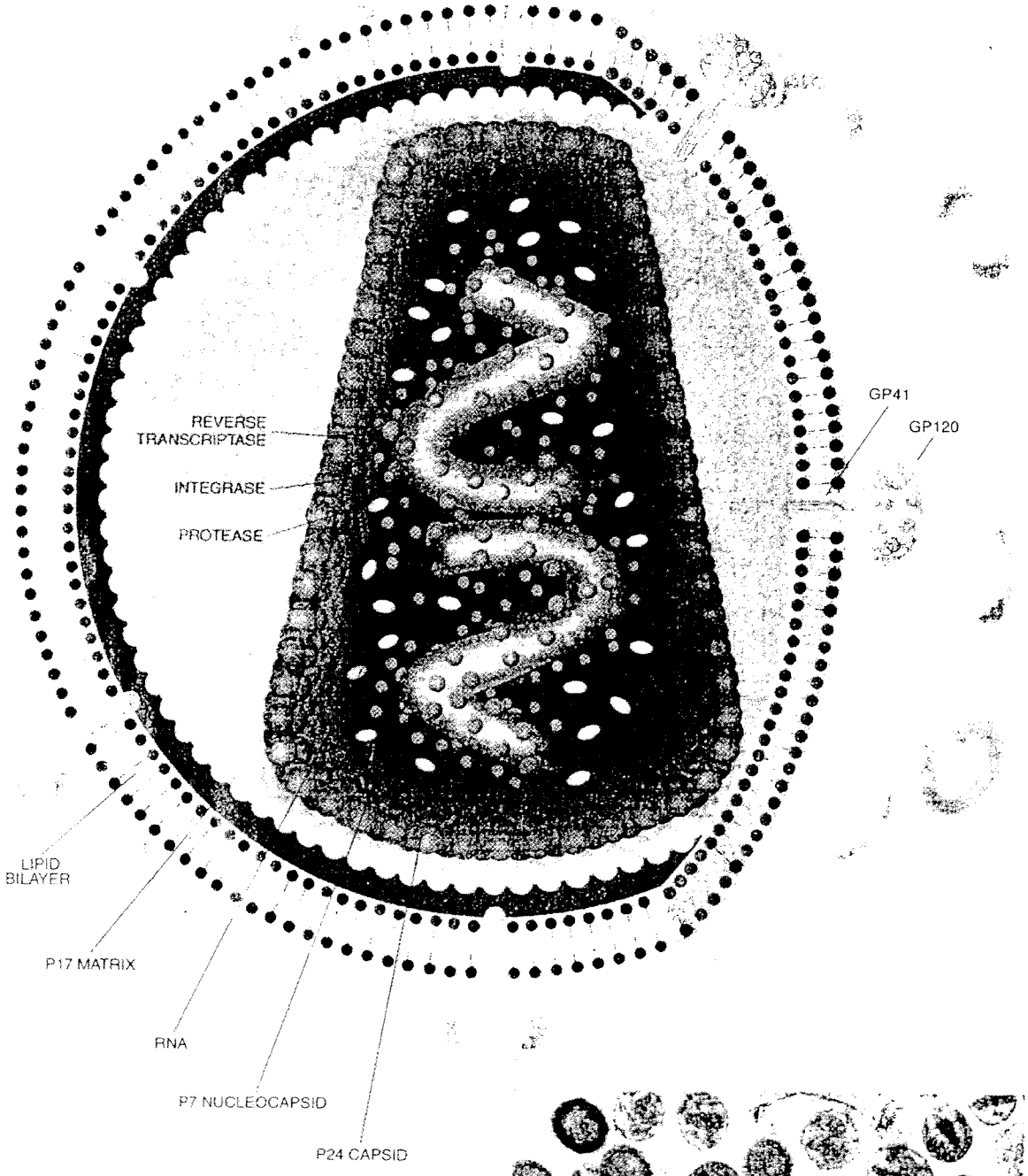
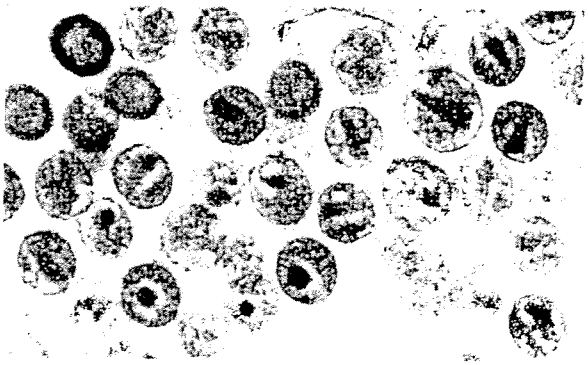




ANATOMY OF HIV: electron microscopy and other techniques have led to a consensus on the complex structure of the AIDS virus (*above*). The truncated cone-shaped core in a spherical envelope is the dominant feature. The micrograph (*right*) shows HIV particles in an intracellular space inside a cultured human macrophage. Cores can be discerned in mature virions; they are lacking in immature virus particles.

layer of lipid molecules similar to and taken from the membranes surrounding human cells. This bilayer is studded with proteins, including some of human origin. These proteins, the so-called class I and class II major histocompatibility complex molecules, are, in their normal location, important in controlling the immune response.

The coat of the virion also bears numerous viral protein "spikes" that project into the external medium. Each spike probably consists of four molecules of a protein called gp120 on the outside and the same number of gp41 embedded in the membrane. (Gp stands for glycoprotein—the proteins are linked to sugars—and the number refers to the mass of the protein, in thousands of daltons.) These envelope proteins play a crucial role when HIV binds to and enters target cells.

Underneath the envelope is a layer of matrix protein called p17, which in turn surrounds the core, or capsid. It has the shape of a hollow, truncated cone made of another protein, p24, which contains the genetic material of the virus. Because HIV is a retrovirus, its genetic material is in the form of RNA, or ribonucleic acid, rather than the more usual DNA, or deoxyribonucleic acid. Two strands of RNA, about 9,200 nucleotide bases long, fit within the viral core. They are attached to molecules of an enzyme, reverse transcriptase, which transcribes the viral RNA into DNA once the virus has entered a cell. Also present with the RNA are an integrase, a protease and a ribonuclease, enzymes whose functions I shall describe later. Two other proteins, p6 and p7, are present as well.

The gp120 envelope protein can bind tightly to CD4, a protein found in the membranes of several types of immune system cells. This property makes such cells vulnerable to HIV infection. When the gp120 of a virion binds to a cell bearing CD4, the membranes of the virus and the cell fuse, a process governed by the gp41 envelope protein. The virus core and its contents are then brought inside the cell.

Some CD4-bearing cells, known as dendritic cells, are present throughout the body's mucosal surfaces and elsewhere; it is possible that these are the first cells infected by HIV in sexual transmission. Immune system cells called macrophages and monocytes also carry the CD4 molecule and are similarly vulnerable. Macrophages, in particular, may carry HIV to other parts of the body, including the brain. But HIV's principal targets are the CD4-bearing helper *T* lymphocytes, or *T4* cells. These cells help to activate other components of the immune system, particularly killer *T* cells (which attack virus-infected cells) and *B* cells (which produce antibodies).

Once an HIV virion has entered a cell, a complex sequence of events follows that, if completed, leads to the budding of new virus particles from the infected cell. But when a person acquires an HIV infection, he or she initially mounts a vigorous immune defense. During this acute phase of the infection, *B* cells produce antibodies that neutralize the virus, and activated killer *T* cells multiply and destroy infected cells, much as they would in many other diseases. Although it is possible that the immune system may successfully fight off HIV at a very early stage, by the time antibodies to HIV are found in the blood, infection is generally permanent.

The clinical picture in acute HIV infection is that of a mild, flulike illness, typically with fever and muscle aches, that usually lasts no more than a few weeks. During this time, large amounts of the virus are present in the bloodstream, and transmission is probably relatively easy. Then the immune response is mounted and begins to eliminate infected cells and circulating viruses. A proportion of infected cells remains, however, eluding the host's defenses, and the virus continues to replicate in lower numbers for as long as a decade. For most of this period of chronic infection, the patient is usually quite well. Only after several years does the virus so significantly damage the immune system that opportunistic malignancies and infections appear.

Ideas about how the damage takes place have shifted considerably in the past two years. When Michael S. Gottlieb of the University of California at Los Angeles first described in 1981 the clinical syndrome that came to be known as AIDS, he noted that his patients had very low numbers of *T4* lymphocytes in their blood. Studies have since demonstrated that these cells decrease gradually in number during the long subclinical phase of chronic infection, from about 1,000 per cubic millimeter to less than 100. The observation naturally suggested that the decrease in *T4* cells was responsible for the decline in immune function that happens over the same period.

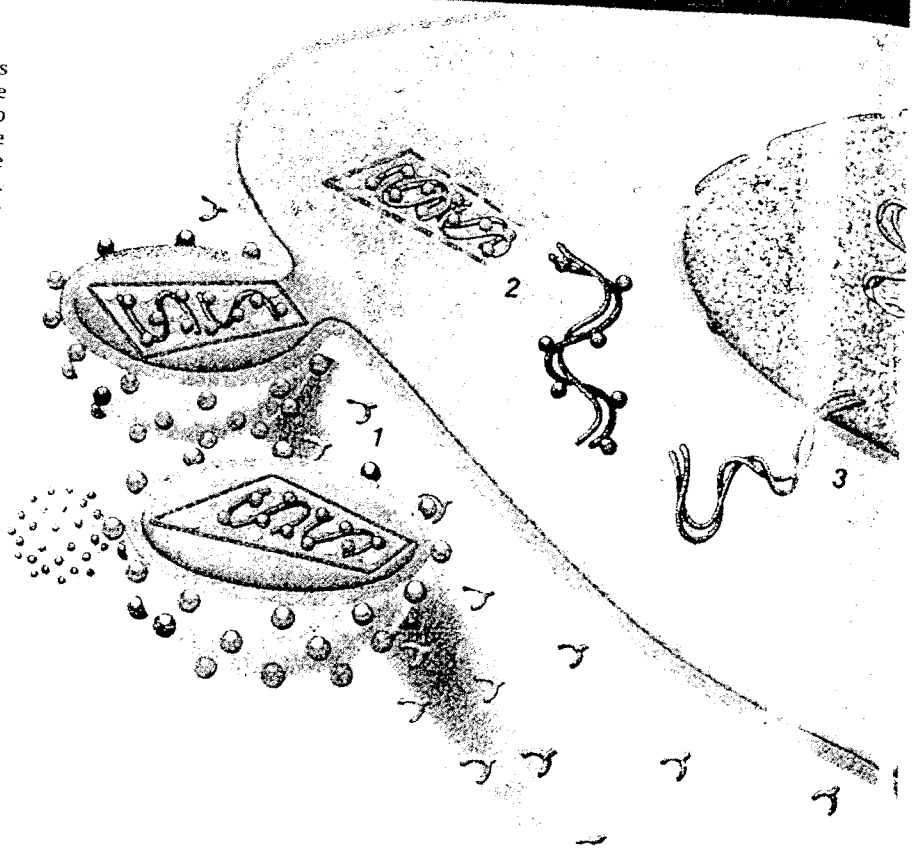
For a while, it seemed possible that HIV causes the decrease in numbers of *T4* cells solely by infecting and killing them. Most researchers now believe the process is more complex. Even in patients in the late stages of HIV infection with very low blood *T4* cell counts, the proportion of those cells that are producing HIV is tiny—about one in 40. In the early stages of chronic infection, fewer than one in 10,000 *T4* cells in blood are doing so. If the virus were killing the cells just by directly infecting them, it would almost certainly have to infect a much larger fraction at any one time.

Another clue that a more complicated process is involved comes from a recent experiment done by Donald E. Mosier and his colleagues at the Scripps Research Institute in La Jolla, Calif. They found that strains of HIV that kill *T4* cells most effectively in culture are not necessarily those that cause the biggest depletion of *T4* cells in genetically engineered mice that lack their own immune system and have been transfused with human CD4 cells.

If direct attack by the virus is not the only reason for the decline of *T4* cells in blood, what are the other possibilities? A variety of plausible theories exist, although none has yet been proved, and indeed several different mechanisms may be at work. One theory is that uninfected killer *T* cells might start destroying infected immune system cells, including helper *T* cells. Other proposals are more complex. Antibodies that recognize gp120 and gp41 in the viral envelope might also attach to and interfere with histocompatibility antigens on healthy cells, impairing immune function. This could happen, some researchers have suggested, because gp120 and gp41 have characteristics similar to the histocompatibility antigens. Alternatively, those similarities could mean that gp120 triggers an immune attack on healthy *T4* cells.

Another hypothesis rests on the fact that *T* cells are normally stimulated to divide when receptors on their surfaces recognize a foreign protein on another cell. Complexes of gp120 and gp41 that become detached from HIV, together with antibodies, may bind to the CD4 molecules on *T4* cells and so prevent them from dividing, a phenomenon called anergy [see "*T* Cell Anergy," by Ronald H. Schwartz; SCIENTIFIC AMERICAN, August].

Recent experiments point to yet another possibility. In people with HIV infection, many *T* cells—even those that are not infected—commit cellular suicide when they are stimulated by foreign proteins, rather than dividing as they should. This genetically controlled function, known as apoptosis, or programmed cell death, normally occurs in the thymus gland and serves to eliminate *T* cells that would attack the body's own tissues. But Joseph M. McCune and his colleagues at SyStemix have found evidence that HIV infection triggers widespread apoptosis in mice that, lack-



LIFE CYCLE OF HIV begins when virus particles attach to CD4 receptors on the cell membrane (*1*) and are drawn into the interior of the cell. The viral core then partially disintegrates (*2*) as reverse transcriptase (*purple*) produces DNA (*blue*) from the viral RNA (*red*). The viral DNA enters the nucleus, where it is integrated into host chromosomes (*3*). Host cell proteins bind to the DNA, initiating transcription (*4*). Short RNA molecules leave the nucleus (*5*) and make viral regulatory proteins. Later, medium-length and long RNAs leave the nucleus and generate structural and enzymatic proteins (*6*). Viral protease (*yellow*) becomes active as RNA and viral proteins (*orange*) enter the budding new virus (*7*). Core and other components form after the virus has budded (*8*).

ing an immune system, have had transplants of human fetal thymus and liver cells.

The researchers found that HIV caused a rapid loss of CD4 thymus cells in the implanted tissue, together with characteristic signs of apoptosis. A similar process might occur in infected humans. That could explain why AIDS progresses speedily in infants, whose immune systems are developing. The mechanisms that might trigger excessive apoptosis are, however, unknown.

Whatever the mechanisms, important clues have emerged about where much of the damage to the immune system is occurring. Researchers now know that *T4* cells in the blood are not the main site of viral replication during the chronic asymptomatic phase of infection. Giuseppe Pantaleo and Anthony S. Fauci and their colleagues at the National Institute of Allergy and Infectious Diseases have shown convincing evidence that much of the HIV is replicating not in the blood but in the scores of lymph nodes found throughout the body. The lymph nodes are where *T4* cells, as well as other immune cells such as *B* cells, cluster to respond to foreign invaders.

Pantaleo and his associates have documented that HIV gradually destroys the lymph nodes. The finding suggests that the decline in the number of *T4* cells in the blood could be a result of damage to the lymph nodes. In fact, swelling of these organs has long been recognized as one early sign of infection. Nevertheless, for convenience, researchers have, perhaps mistakenly, usually focused on the changing cell counts and amounts of viral RNA—a marker for the virus—in the bloodstream.

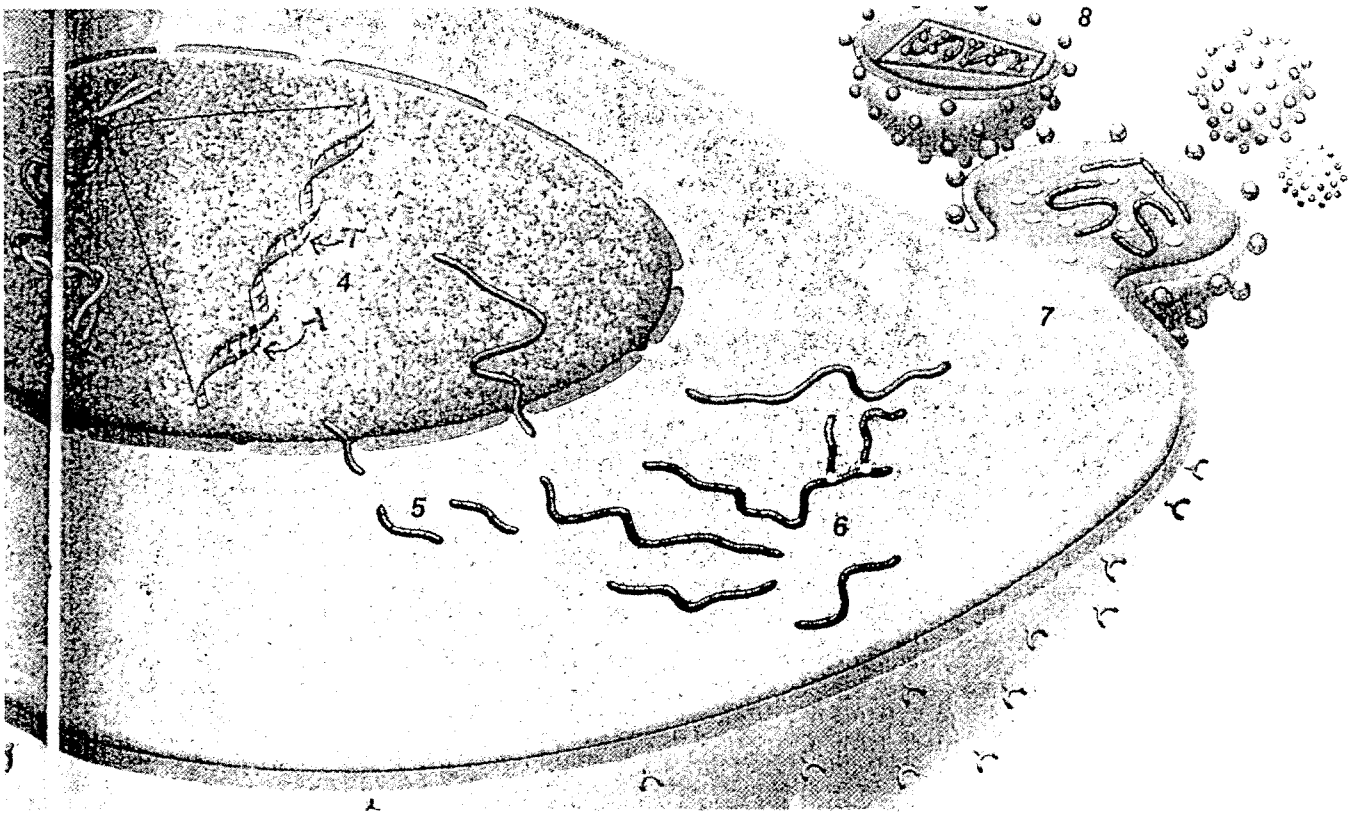
The central involvement of the lymph nodes could explain one puzzling observation. During early chronic infection, the amount of viral RNA in the blood is very low. In fact, it is often impossible to detect by conventional techniques. As symptoms develop, the amount rises rapidly and may approach the peak levels present during the initial acute phase, prior to the immune response. A few investigators have surmised that some type of signal sets off a late wave of rapid viral replication that heralds the onset of full-blown AIDS. Recent technical advances in our ability to detect small amounts of the virus make this seem unlikely.

Rather it is now clear that the viral burden is substantial and increases steadily throughout most of the chronic asymptomatic phase of infection. The abrupt rise in blood levels of viral RNA in the last stages of infection can most likely be attributed to the "burning out" of the lymph nodes. These organs contain cells with delicate, fingerlike projections, known as follicular dendritic cells, that normally present antigens to *T4* cells but also filter out various infectious agents. Collapsing nodes infected with HIV might no longer efficiently remove the virus, allowing its escape into the bloodstream. What precisely causes the death of the follicular dendritic cells remains a mystery, but the process may be as important as the loss of *T4* cells.

Such thinking gains further support from the observation that even before a patient's *T4* cells start to decline, a subset called memory *T* cells, which are responsible for remembering foreign proteins, begins responding abnormally to stimulation. Ultimately, these cells disappear. Other changes also occur. These phenomena could be a consequence of pathology in the lymph nodes.

The declining *T4* cell count in the blood might, then, be at best an indirect indicator of damage taking place elsewhere in the body. If so, it underscores the importance of stopping the virus from multiplying even in the earliest stages of infection. One strategy being tried is to release "decoy" CD4 receptor molecules into the blood. These, it is reasoned, should attract HIV particles to stick to them rather than to CD4-bearing cells. Results so far have been disappointing, particularly against natural strains of the virus. It is likely that future interventions will focus on stopping the virus from replicating after it has entered a cell.

Thousands of meticulous experiments, many involving specially disabled strains of HIV, have demonstrated that inside a cell infected with HIV there is an intricate but elegant interplay among proteins produced by viral RNA and



proteins produced normally in healthy cells. Significantly for the development of therapies, it is clear that only if the right conditions are met will HIV complete its life cycle and unleash scores of progeny that disseminate an infection.

The first thing that happens to the two strands of HIV RNA in a newly infected cell is that their encoded message is converted into DNA by the multiple reverse transcriptase molecules attached to the viral RNA. The process is the opposite of normal transcription, which makes RNA from DNA. Reverse transcriptase moves along the RNA, producing an equivalent chain of DNA by stitching together the nucleotide building blocks. When the first DNA strand is completed, the reverse transcriptase starts constructing a second DNA strand, using the first one as a template.

The reverse transcriptase that HIV uses is not very accurate: on average it introduces an error, or mutation, approximately once in every 2,000 incorporated nucleotides. This intrinsic infidelity underlies HIV's remarkable ability to become resistant to various drugs, because new variants of viral proteins are being constantly generated during the course of an infection.

The antiviral drugs that have been approved in the U.S. for treatment of HIV infection—azidothymidine (also known as AZT or zidovudine), dideoxycytidine (ddC) and dideoxyinosine (ddI)—all work by interfering with reverse transcription. Each is somewhat similar to one of the four nucleotides that reverse transcriptase connects together to build DNA. When the enzyme incorporates one of these drugs rather than a genuine nucleotide into a growing DNA strand, the reverse transcriptase cannot extend it further.

The problem is that the high rate of mutation means that within months variant reverse transcriptases appear in the body that can produce viral DNA even in the presence of the drugs. This rapid Darwinian evolution occurring within patients, as well as the toxicity of the drugs, almost certainly explains why the benefits of AZT are only temporary.

Other potential therapies aimed at blocking reverse transcriptase are on the horizon. One of these is the "convergent triple therapy" devised by Yung-Kang Chow and his colleagues at Harvard Medical School. These researchers had reported in *Nature* that the mutations reverse transcriptase undergoes in the presence of a mixture of AZT, dideoxyinosine and one other drug, nevirapine or pyridinone, are so extreme that the enzyme becomes ineffective. The workers have since found a flaw in their study, although clinical trials are proceeding. I suspect, however, that HIV will not easily succumb to drugs that are aimed at a single step in its life cycle.

Recent discoveries indicate other ways in which the early stages of viral replication might be thwarted. Irvin S. Y. Chen and his colleagues at the U.C.L.A. School of Medicine have performed experiments indicating that reverse transcription cannot be completed unless the host *T* cell is activated by a foreign protein. Other results, from Mario Stevenson and his co-workers at the University of Nebraska Medical Center, suggest that it is the next stage in the replication process that is blocked in resting cells. In this operation, the two DNA strands produced by reverse transcriptase are integrated into the host cell's chromosomes by the integrase present in the HIV virion.

In either case, the remarkable implication is that something made in a *T4* cell when it is activated is critical to the virus's becoming integrated in the host cell. When unintegrated, HIV is unstable in the cell, decaying after a few days. That could be a weakness worth exploiting. Various immunosuppressive drugs, such as cyclosporine and FK 506, reduce the activation of *T* cells. A treat-

ment protocol that intermittently decreased *T* cell activation might prevent HIV from being integrated and so prolong the asymptomatic phase of infection. Such an approach would not be without risk, since we know that a functioning immune system is vital for the initial containment of the virus. Experiments, perhaps employing monkeys infected with the HIV-like simian immunodeficiency virus (SIV), could delineate the relative benefits versus the dangers of the approach.

Once the two strands of HIV DNA have been integrated into the host cell's chromosomes, they are known as the provirus. As far as we can tell, infection of the cell is then permanent. But many processes still have to be completed before the cell can bud new virions. HIV is an extraordinarily complex virus. Whereas some retroviruses manage to get by with only three genes, HIV has nine or more, and at least five of them are essential for replication.

Before the provirus's genes can be effective, RNA copies of them that can be read by the host cell's protein-making machinery must be produced by forward transcription. This transcription stage is accomplished by the cell's own enzymes, including RNA polymerase II. But the process cannot start until the polymerase is activated by various molecular switches located in two stretches near the ends of the provirus: the long terminal repeats. This requirement is reminiscent of the need of many genes in multicellular organisms to be "turned on" by proteins that bind specifically to controlling sequences termed enhancer elements.

Some of the cellular signaling proteins that bind to the enhancers in the HIV long terminal repeats are members of an important family known as NF-κB/Rel. Present in virtually all human cells, these regulatory proteins increase the transcriptional activity of many genes. Significantly, cells step up production of some members of this family when they are stimulated by foreign proteins or by hormones that control the immune system. It appears that HIV utilizes the NF-κB/Rel proteins resulting from activation of immune cells to boost its own transcription.

The virus does not have everything its own way: my colleagues Stefan Doerre and Dean W. Ballard and I have found that one cellular protein, c-Rel, a member of the same NF-κB/Rel family, actually hinders HIV transcription. But it is made more slowly than are the factors that stimulate transcription. Clearly, the virus succeeds in getting itself transcribed often enough to spread infection. At first, the provirus relies on NF-κB and other proteins present in the activated cell to initiate its transcription into RNA. This process, though slow to begin with, can be likened to the tumbling of a stone that sets more and more stones rolling until it creates an avalanche.

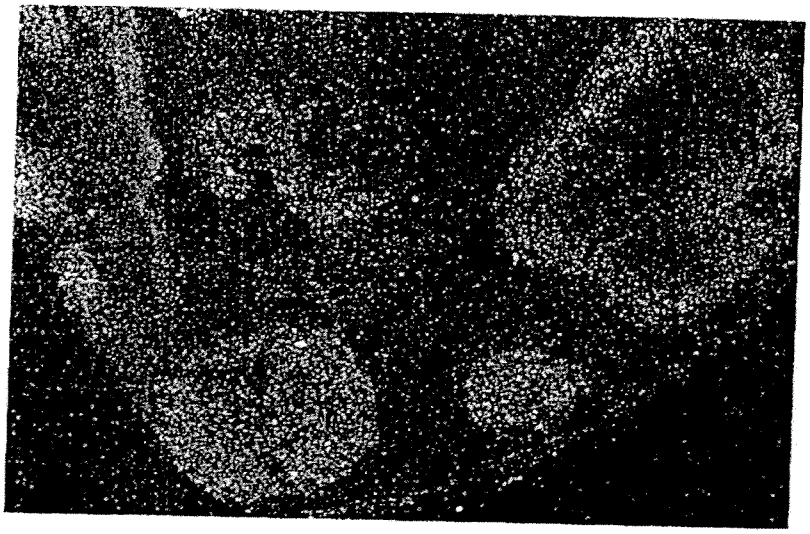
The RNA transcripts from the provirus then undergo complex processing by enzymes in the cell. Two distinct phases of transcription follow the infection of an individual cell by HIV. In the early phase, which lasts roughly 24 hours, RNA transcripts produced in the cell's nucleus are snipped into multiple copies of shorter sequences by cellular splicing enzymes. When they reach the cytoplasm, they are only about 2,000 nucleotides in length. These early-phase short transcripts encode only the virus's regulatory proteins: the structural genes that constitute the rest of the genome are among the parts that are left behind.

One of the first viral genes to be transcribed, *tat*, is encoded in the short transcripts and produces a regulatory protein that speeds up transcription of the HIV provirus. This protein acts by binding to a specific sequence within the viral RNA, called TAR. Once the tat protein binds to the TAR sequence, transcription of the provirus by cellular RNA polymerase II accelerates at least 1,000-fold. Ro 31-8959, a compound made by Hoffmann-La Roche, is in a new class of drugs that have the ability to inhibit the function of tat. It is now being evaluated in clinical trials.

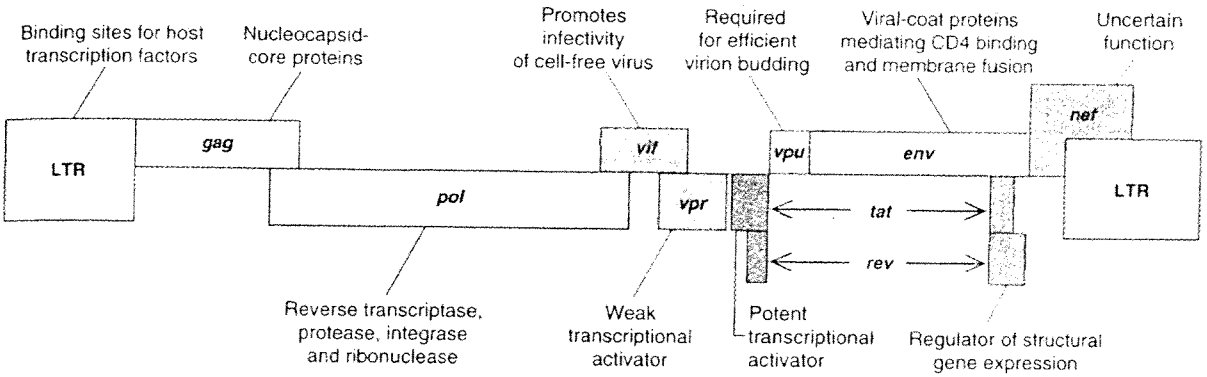
Another regulatory gene expressed in the early phase is called *nef*. Until quite recently, it was believed that *nef*'s role was to suppress transcription, but new experiments have cast doubt on that interpretation. Nef protein may somehow modify the cell to make it more suitable for manufacturing HIV virions later. In any event, it now appears that production of nef protein is required for the development of AIDS, a finding that could be important if a way can be found to block its action.

A third regulatory protein encoded in the early short transcripts is called rev. We know that rev plays an essential role in the life cycle of HIV. Specifically, this protein appears to be responsible for switching the processing of viral RNA transcripts to the pattern that dominates once a cell has been infected for more than 24 hours. Rev protein binds to viral RNA at a sequence that is absent in the early short transcripts. Longer transcripts that do contain the rev-binding sequence are confined within the nucleus during the early phase. Once the amount of rev protein in the cell has built up to a high enough level, splicing and movement of the transcripts change to the pattern characteristic of the late phase.

In this late phase, two new size classes of RNA—long (unspliced) transcripts of about 9,200 bases and medium-length (singly spliced) transcripts of some 4,500 bases—move out of the nucleus and into the cytoplasm. These longer transcripts encode HIV's structural and enzymatic proteins. The crucial function of rev as a switch that turns on production of viral structural and enzymatic proteins makes it an attractive target for drug development. Unfortunately, no substance that effec-



LYMPH NODES are believed to be an important site of HIV replication. In this section of a lymph node from a patient with early-stage infection, the tissue has been stained to show the presence of HIV (*white dots*) in localized patches.



HIV GENES are indicated by the positions of colored bars along the DNA of the provirus. Genes that overlap utilize the same region of DNA but are read differently by protein-producing machinery of the host cell. Structural and enzymatic genes are green; regulatory genes, purple; others, tan. Sections called long terminal repeats (LTRs) are yellow.

tively blocks rev's action has yet been identified that is not unacceptably toxic.

Once the long and medium-length transcripts reach the cytoplasm, the cell's protein-making machinery begins constructing the components for new virions. The viral gene called *gag* encodes the core proteins; *pol* encodes the reverse transcriptase, protease, integrase and ribonuclease; and *env* encodes the two envelope proteins. Three other proteins encoded in the longer transcripts are produced as well, encoded by the *vpr, vif* and *vpu* genes. They have as yet ill-defined effects on infectivity, and the last two may play a part in the assembly of new virions. But all three seem to be significant for HIV's pathological properties.

The newly formed precursors of the proteins that will constitute the cores of new virions aggregate in the cytoplasm, together with complete copies of the viral RNA and the precursors of its associated enzymes. They all then move to the surface of the cell and bud through the membrane, where they acquire their lipid membranes and viral envelope proteins. During this final stage of assembly, the viral protease becomes active, cutting up the precursors to complete the core proteins and the enzymes. The structure of the protease, like that of the reverse transcriptase, is known in detail, and drugs have been designed to thwart its action. Trials of HIV protease inhibitors are under way at several clinical centers; results should be available within a few months.

Hope for the future should be tempered by the recognition that it is still true in 1993, as it was five years ago, that no satisfactory treatment for AIDS is yet in sight. Nevertheless, I am encouraged by how much we have learned in the past 12 years, and I believe that by the end of the second decade of the epidemic we will have antiviral therapies substantially better than those now available. I strongly suspect that these will consist of combinations of drugs directed against different parts of the life cycle of HIV.

In contrast, I feel there is less cause for optimism about prospects for the development of a practical prophylactic vaccine for HIV in the near future. The virus's ability to mutate quickly and by other means to elude immune responses poses a serious obstacle. Although clinical trials have shown that vaccines made from various viral proteins, chiefly the envelope, can improve human immune responses to the virus in laboratory tests, this is a far cry from demonstrating useful protection against natural infection. Even if a course of vaccinations could increase immunity, economic considerations may make such an approach unfeasible in the developing countries of the world where HIV is now spreading most rapidly.

There are some bright spots. Ronald C. Desrosiers of Harvard University and his colleagues have been able to make a vaccine that protects rhesus monkeys against infection from SIV. Desrosiers used as his vaccine a live strain of SIV that had its *nef* gene artificially disabled. The resulting virus establishes a persistent low-level infection that stimulates a strong immune response but causes no illness. Perhaps it will be possible to do something similar with HIV. Yet the safety problems surrounding the use of an attenuated but live HIV vaccine are daunting.

Even bolder approaches may find application in HIV therapy. One idea has been suggested by David Baltimore of the Rockefeller University, who shared a Nobel Prize in 1975 for discovering reverse transcriptase. Baltimore proposes introducing into an infected person's *T* cells a gene that would make the cells resistant to HIV infection. This approach, a form of gene therapy that Baltimore dubs "intracellular immunization," might be possible with the technology of the next century. Some mutant HIV genes that confer immunity on *T* cells in tissue culture have already been identified.

At present, we lack gene delivery and expression systems that could make such techniques widely applicable. If an injectable delivery system for protective genes could be developed, the approach might prove practical and cost-effective even in underdeveloped countries. This avenue merits investigation.

In the meantime, there is still much to be learned about HIV. For now, efforts to educate people about the virus should be redoubled. In the final analysis, preventing transmission of HIV is the best strategy.

FURTHER READING

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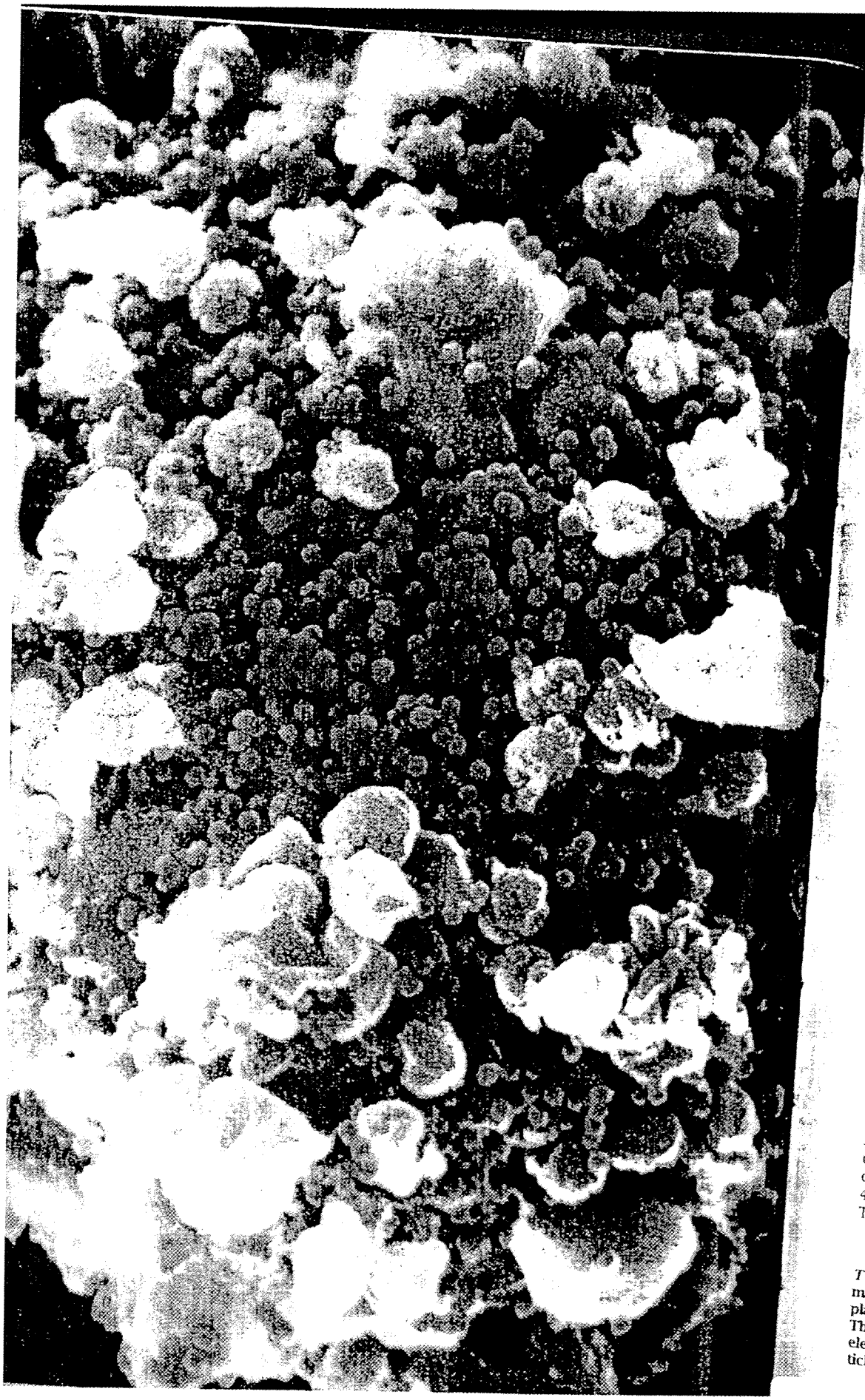

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places the number infecte
of 1992 at 19.5 million,
times the earlier figure. Al
viral and other medication
estly prolong the lives of
ed, the great majority of th
ring some major advance
die of an AIDS-related illness
three million people have
full-blown AIDS; most have a
Responsible estimates of
of cases of HIV infection lik
occurred by the year 2000
40 million to more than
The second number is ab

T LYMPHOCYTE infected wi
man immunodeficiency virus
plays a characteristic lumpy a
The protuberances colored gr
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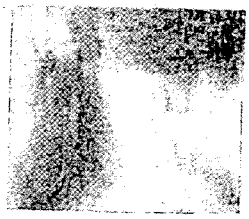
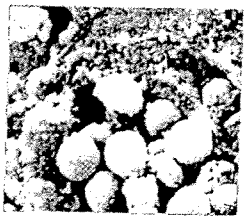
SPECIAL ISSUE





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