How HIV Defeats the Immune System

A plausible hypothesis suggests the immune devastation that underlies AIDS stems from continuous—and dangerous—evolution of the human immunodeficiency virus in the body

by Martin A. Nowak and Andrew J. McMichael

The interplay between the human immunodeficiency virus (HIV) and the immune system turns out to be significantly more dynamic than most scientists would have suspected. Recent research indicates that HIV replicates prodigiously and destroys many cells of the immune system each day. But this growth is met, usually for many years, by a vigorous defensive response that blocks the virus from multiplying out of control. Commonly, however, the balance of power eventually shifts so that HIV gains the upper hand and causes the severe immune impairment that defines full-blown AIDS.

We have put forward an evolutionary hypothesis that can explain the ultimate escape of the virus from immune control, the typically long delay between infection and the onset of AIDS, and the fact that the extent of this delay can vary considerably from patient to patient. Most infected individuals advance to AIDS over the course of 10 years or so, but some patients are diagnosed within two years of infection, and others avoid AIDS for 15 years or more.

We argue that the powerful immune response enabling many patients to remain healthy for years is finally undermined by continuous mutation of the virus. As will be seen, within any given individual, new viral variants may emerge that are able to evade the protective forces somewhat. In our view, the accumulation of many such variants can muddle the immune system to the point that it can no longer fight the virus effectively.

To understand how we came to this hypothesis, which is gaining clinical support, it helps to know a bit about how the immune system eradicates viruses in general and how it responds to HIV in particular. When any virus enters the body and colonizes cells, defensive forces launch a multipronged but highly targeted attack. Macrophages and related cells engulf some of the free particles and break them up. Then the cells fit certain protein fragments, or peptides, into grooves on proteins known as human leukocyte antigens (HLAs). The cells subsequently display the resulting complexes on their surface for perusal by the white blood cells called helper *T* lymphocytes.

The Body Fights Back

Each helper cell bears receptors able to recognize a single displayed peptide, or epitope. If it encounters the right epitope on a macrophage or similar cell, it binds to the peptide, divides and secretes small proteins. The proteins help to activate and promote replication of still other components of the immune system—notably cytotoxic, or killer, *T* lymphocytes and *B* lymphocytes.

Under the right circumstances, the killer *T* cells directly attack infected cells. Like macrophages, infected cells break up some viral particles, combine certain of the fragments with HLA molecules and exhibit the complexes on the cell surface. If a cytotoxic *T* lymphocyte, through its receptors, recognizes one of the epitopes on a diseased cell, it will bind to the epitope and destroy the cell before more viral particles can be generated. Activated *B* lymphocytes secrete antibodies that recognize specific peptides on the viral surface. The antibodies mark free viral particles, those not yet sequestered in cells, for destruction.

All these responses are believed to participate in the defense against HIV. In the initial stage of HIV infection, the virus colonizes helper *T* cells and macrophages. It also replicates unchecked for a while. As the amount of virus soars, the number of helper cells falls; macrophages die as well, but the effects on them have been less studied. The infected *T* cells perish as thousands of new viral particles erupt from the cell membrane. Soon, though, cytotoxic *T* and *B* lymphocytes mount a strong defense and kill many virus-infected cells and viral particles. These effects limit viral growth and give the body an opportunity to restore temporarily its supply of helper cells to almost normal concentrations. Nevertheless, the virus persists. In the early phase, which may last for a few weeks, about 30 percent of infected patients display some symptoms, often a fever that may be accompanied by a rash and swollen lymph glands. Even those individuals, though, usually go on to enter a prolonged symptom-free stage.

Throughout this second phase the immune system continues to function well, and the net concentration of measurable virus remains relatively low. Nevertheless, the viral level rises gradually, in parallel with a decline in the helper population. Accumulating evidence indicates that helper cells are lost because the virus and cytotoxic *T* cells destroy them, not because the body's ability to produce new helper cells becomes impaired. It is a sad irony that the killer cells required to control HIV infection also damage the helper *T* cells they need to function efficiently.

Patients are generally said to cross the line to AIDS when the helper cell count, which in healthy individuals measures 1,000 cells per microliter of blood, falls below 200. During this stage, the viral level climbs sharply, and measures of immune activity drop toward zero. It is the loss of immune competence that enables normally benign microorganisms (particularly protozoa and fungi) to cause life-threatening diseases in AIDS patients. Once AIDS develops, people rarely survive for more than two years.

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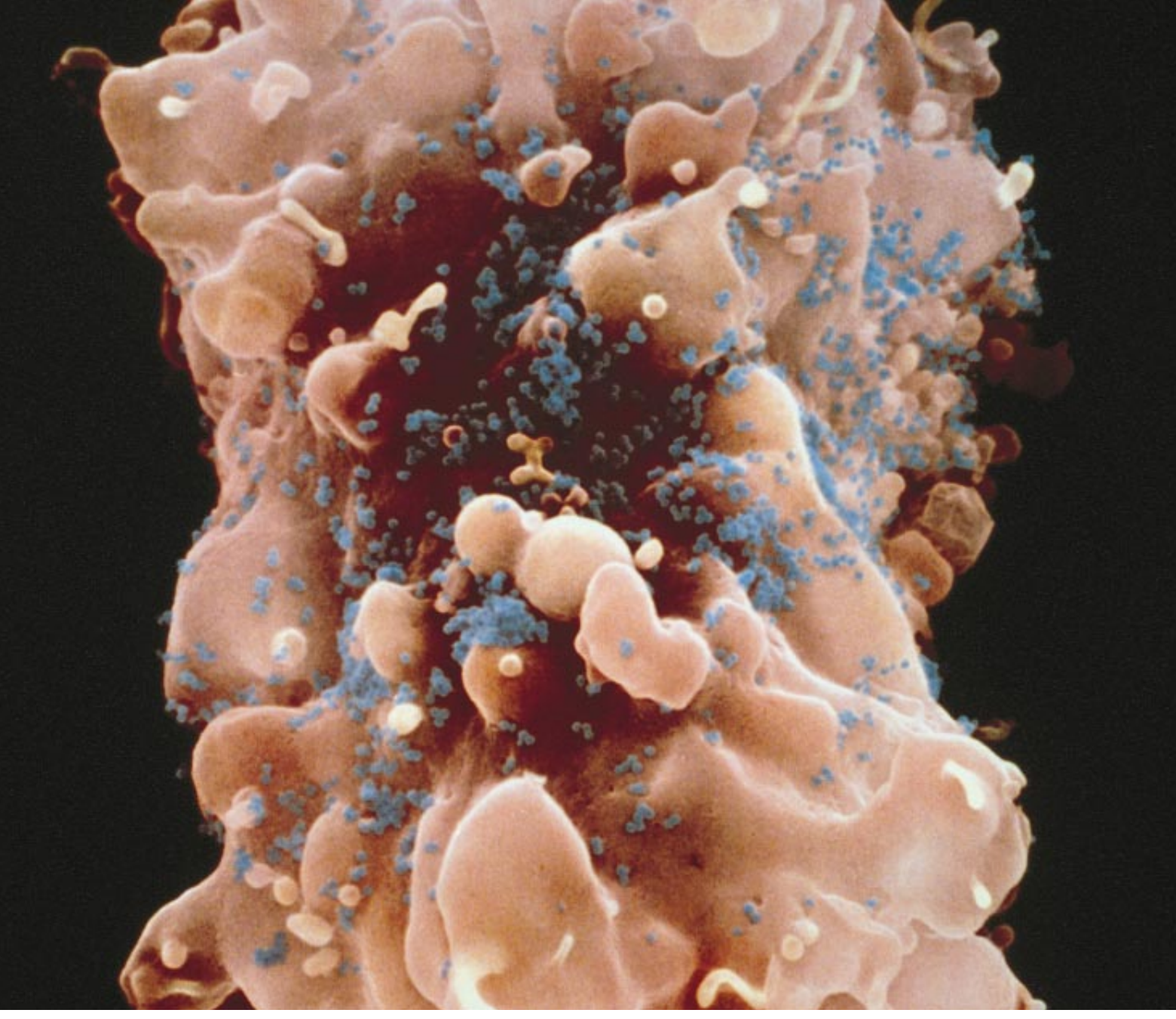


PARTICLES OF HIV (*blue spheres*), the virus that causes AIDS, bud from an infected white blood cell before moving on to infect other cells. The immune system controls such spread at first but is eventually outmaneuvered by the virus.

Persistence of a good immune response in the face of constant attack by HIV raises the issue of why the immune system is unable to eradicate HIV completely in most, if not all, cases. Several years ago various features of HIV led one of us (Nowak) and his colleagues in the zoology department of the University of Oxford to suspect the answers lay with an ability of the virus to evolve in the human body.

Evolutionary Theory Predicts Trouble

Evolutionary theory holds that chance mutation in the genetic material of an individual organism sometimes yields a trait that gives the organism a survival advantage. That is, the affected individual is better able than its peers to overcome obstacles to survival and is also better able to reproduce prolifically. As time goes by, offspring that share the same trait become most abundant in the population, outcompeting other members—at least until another individual acquires a more adaptive trait or until environmental conditions change in a way that favors different characteristics. The pressures exerted by the environment, then, determine which traits are selected for spread in a population.

When Nowak and his co-workers considered HIV's life cycle, it seemed evident that the microbe was particularly well suited to evolve away from any pressures it confronted (namely, those exerted by the host's immune system). For example, its genetic makeup changes constantly; a high mutation rate increases the probability that some genetic change will give rise to an advantageous trait. This great genetic variability stems from a property of the viral enzyme reverse transcriptase. In a cell, HIV uses reverse transcriptase to copy its RNA genome into double-strand DNA. This DNA is inserted into a chromosome of the host, where it directs the production of more viral RNA and viral proteins. These elements, in turn, assemble themselves into viral particles that can escape from the cell. The virus

mutates readily during this process because reverse transcriptase is rather error prone. It has been estimated that each time the enzyme copies RNA into DNA, the new DNA on average differs from that of the previous generation in one site. This pattern makes HIV the most variable virus known.

HIV's high replication rate further increases the odds that a mutation useful to the virus will arise. To appreciate the extent of HIV multiplication, consider findings released early this year from teams headed by George M. Shaw of the University of Alabama at Birmingham and by David D. Ho of the Aaron Diamond AIDS Research Center in New York City. The groups reported that at least a billion new viral particles are produced in an infected patient each day. They found that in the absence of immune activity, the viral population would on average double every two days. Such numbers imply that viral particles present in the body 10 years after infection are several thousand generations removed from the original virus. In 10 years, then, the virus can undergo as much genetic change as humans might experience in the course of millions of years.

A Scenario of Disease Progression

With knowledge of HIV's great evolutionary potential in mind, Nowak and his colleagues conceived a scenario they thought could explain how the virus resists complete eradication and thus causes AIDS, usually after a long time span. Their proposal assumed that constant mutation in viral genes would lead to continuous production of viral variants able to evade to some extent the immune defenses operating at any given time. Those variants would emerge when genetic mutations led to changes in the structure of viral peptides—that is, epitopes—recognized by the immune system. Frequently such changes exert no effect on immune activities, but sometimes they can cause a peptide to become invisible to the body's defenses. The affected viral particles, bearing fewer recognizable epitopes, would then become more difficult for the immune system to detect.

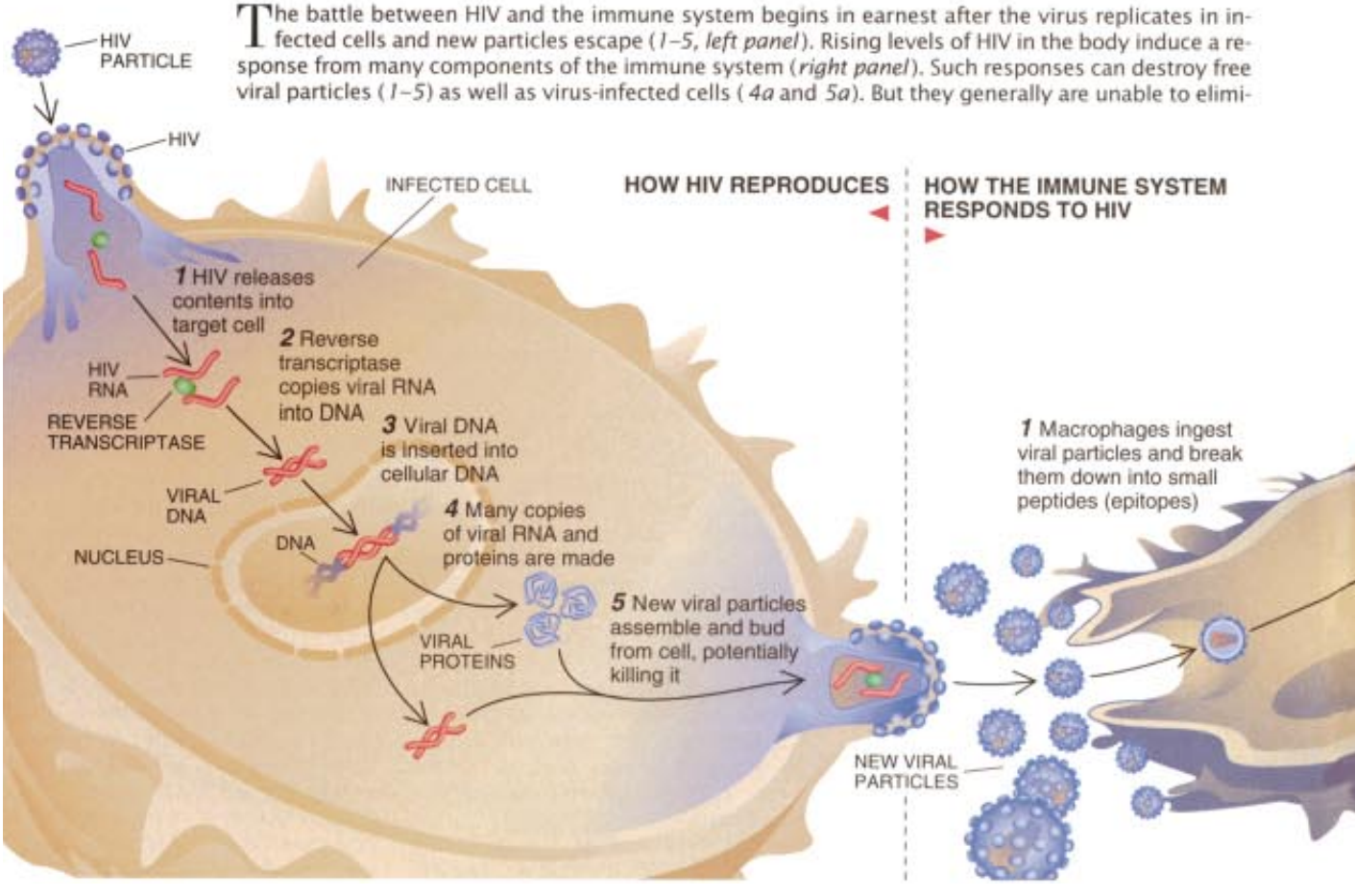
The hypothesis proposed that a mutation able to reduce recognition of an epitope would give a viral variant a survival advantage, at least until the immune system discovered and reacted to the altered peptide. This response would reduce the viral load for a time, but meanwhile other "escape mutants" would begin to break out, and the cycle would continue, preventing full elimination of the infection.

Such a scheme is extremely hard to verify with clinical tests alone, largely because the nonlinear interactions between the virus and the immune system are impossible to monitor in detail. Consequently, Nowak turned to a computer simulation in which an initially homogeneous viral population evolved in response to immunologic pressure. He reasoned that if the mathematical model produced the known patterns of HIV progression, he could conclude the evolutionary scenario had some merit.

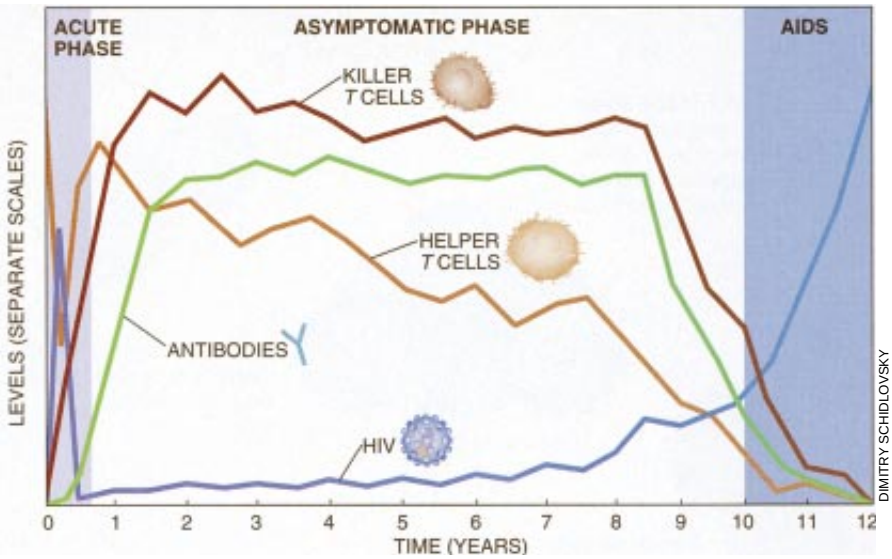
The equations that formed the heart of the model reflected features that Nowak and his colleagues thought were

HIV versus the Immune System

The battle between HIV and the immune system begins in earnest after the virus replicates in infected cells and new particles escape (*1–5, left panel*). Rising levels of HIV in the body induce a response from many components of the immune system (*right panel*). Such responses can destroy free viral particles (*1–5*) as well as virus-infected cells (*4a* and *5a*). But they generally are unable to elimi-



COURSE OF HIV INFECTION typically runs many years, during most of which the patient has no symptoms. Strikingly, the body's defenses—as indicated by levels of antibodies, killer *T* cells and helper *T* cells in the blood—remain strong throughout much of the asymptomatic period, eradicating almost as much virus as is produced. At some point, however, the immune defenses lose control of the virus, which replicates wildly and leads to collapse of the immune system.



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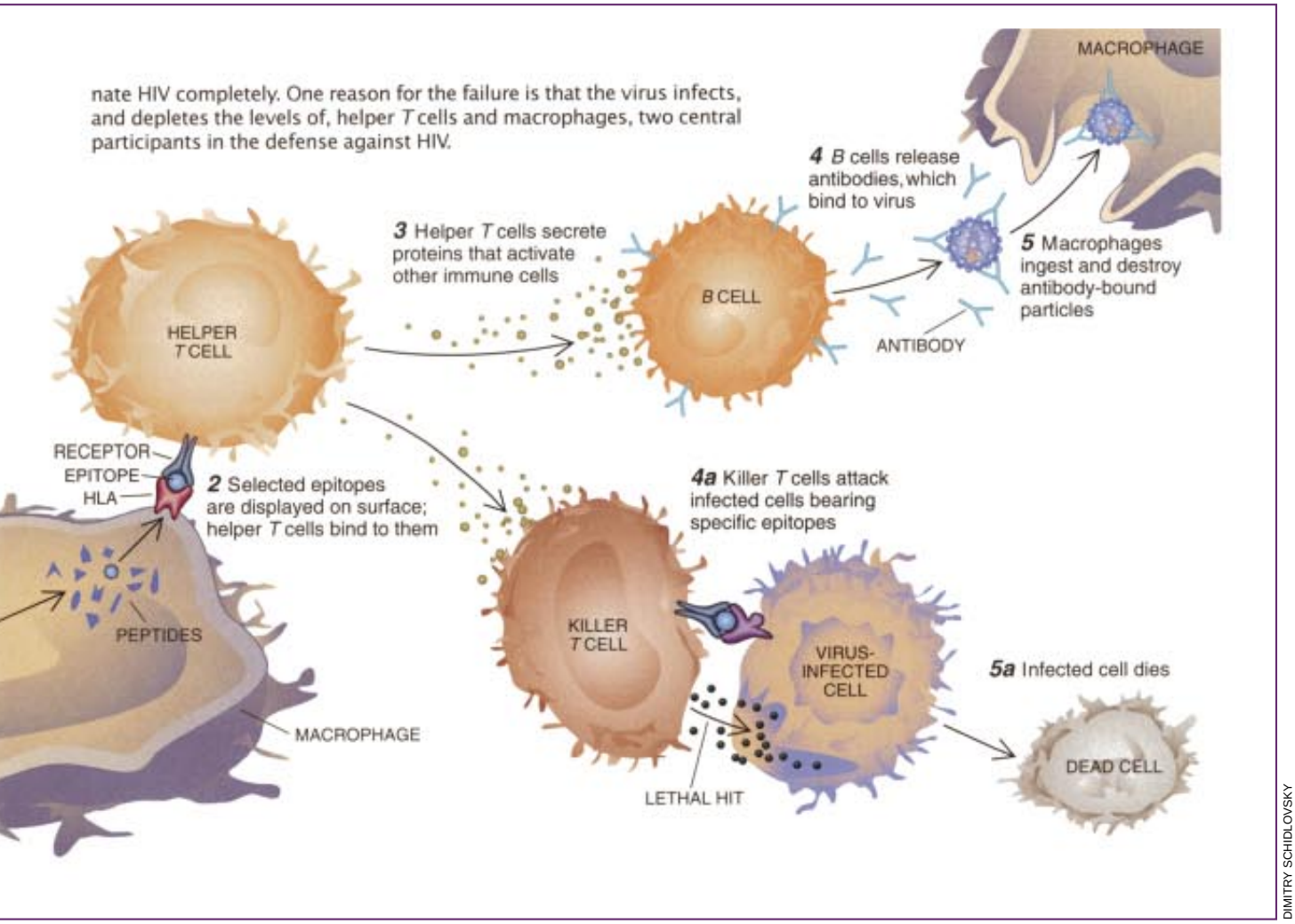
important in the progression of HIV infection: the virus impairs immune function mainly by causing the death of helper *T* cells, and higher levels of virus result in more *T* cell death. Also, the virus continuously produces escape mutants that avoid to some degree the current immunologic attack, and these mutants spread in the viral population. After a while, the immune system finds the mutants efficiently, causing their populations to shrink. The model additionally distinguished between two kinds of immune responses: those recognizing epitopes that undergo mutation readily and those recognizing conserved epitopes (ones that appear in an unchanging form on every viral particle in the body, because the virus cannot tolerate their loss or alteration).

The simulation managed to reproduce the typically long delay between infection by HIV and the eventual sharp rise in viral levels in the body. It also provided an explanation for why the cycle of escape and repression does not go on indefinitely but culminates in uncontrolled viral replication, the almost



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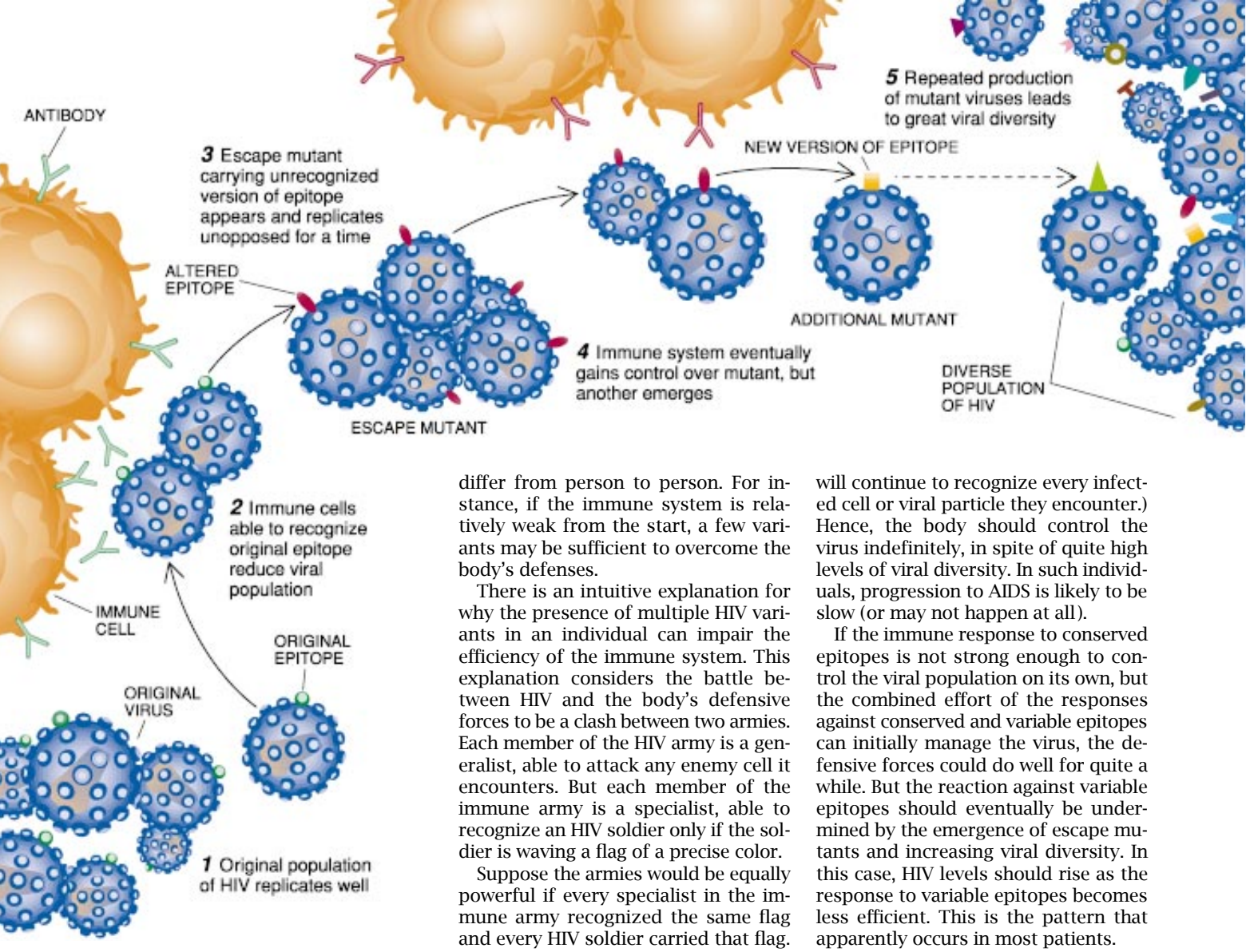


HIV EVADES IMMUNE CONTROL by evolving. In particular, it gives rise to "escape mutants"—variants able to elude immune recognition to some extent. In a simplified example, a viral population bearing just one recognizable epitope (*green in 1 and 2*) undergoes repeated mutations in that epitope (*3–5*). The immune system—represented here by antibody-producing *B* lymphocytes—can keep pace with such maneuvers for a while, but emergence of too many new viral variants apparently undermines the body's ability to cope with the virus.

complete loss of the helper *T* cell population and the onset of AIDS.

In particular, the model indicated that the immune system can often mount a strong defense against several viral variants simultaneously. Yet there comes a point, usually after many years, when there are too many HIV variants. When that threshold is crossed, the immune system becomes incapable of controlling the virus. This "diversity threshold," as we call the breaking point, can differ from person to person. For instance, if the immune system is relatively weak from the start, a few variants may be sufficient to overcome the body's defenses.

There is an intuitive explanation for why the presence of multiple HIV variants in an individual can impair the efficiency of the immune system. This explanation considers the battle between HIV and the body's defensive forces to be a clash between two armies. Each member of the HIV army is a generalist, able to attack any enemy cell it encounters. But each member of the immune army is a specialist, able to recognize an HIV soldier only if the soldier is waving a flag of a precise color.

Suppose the armies would be equally powerful if every specialist in the immune army recognized the same flag and every HIV soldier carried that flag. Now suppose that the HIV army consisted of three groups, each carrying a different flag and that, in response, the immune specialists also divided into three groups, each recognizing a separate flag. Under these conditions, the immune army would be at a significant disadvantage. Any given immune specialist would recognize and attack only one out of every three enemy soldiers it encountered—the one carrying the right flag. The HIV soldiers, meanwhile, would continue to pick off every specialist they met and would ultimately win the war.

Predicting the Course of Disease

Beyond giving us the concept of a diversity threshold, the model offered a possible explanation for why some patients progress to AIDS more quickly than do others. If the initial immune response to conserved epitopes is strong, the efficiency of the defensive attack on HIV will not be undermined very much by mutation in other epitopes. (Many active members of the immune system will continue to recognize every infected cell or viral particle they encounter.) Hence, the body should control the virus indefinitely, in spite of quite high levels of viral diversity. In such individuals, progression to AIDS is likely to be slow (or may not happen at all).

If the immune response to conserved epitopes is not strong enough to control the viral population on its own, but the combined effort of the responses against conserved and variable epitopes can initially manage the virus, the defensive forces could do well for quite a while. But the reaction against variable epitopes should eventually be undermined by the emergence of escape mutants and increasing viral diversity. In this case, HIV levels should rise as the response to variable epitopes becomes less efficient. This is the pattern that apparently occurs in most patients.

If the combined immune responses to conserved and variant epitopes are too weak to control HIV replication from the start, AIDS should develop rapidly. In that situation, the original viral particles would proliferate without encountering much resistance, and so the virus would be under little pressure to generate mutants able to escape immune reconnaissance. Such patients might progress to AIDS even in the absence of significant viral diversity.

The simulation also provided insight into probable properties of the viral population during each stage of HIV disease. In the earliest days, before the immune system is greatly activated, the viral variants that replicate fastest will become most abundant. Hence, even if a patient were infected by several variants at once, after a short time most of the virus in the body would probably derive from the fastest-growing version. And so we expect little genetic diversity during the acute phase of disease.

After the immune system becomes more active, survival becomes more complicated for HIV. It is no longer

enough to replicate freely; the virus also has to be able to ward off immune attacks. Now is when we predict that selection pressure will produce increasing diversity in epitopes recognized by immune forces. Once the defensive system has collapsed and is no longer an obstacle to viral survival, the pressure to diversify evaporates. In patients with AIDS, then, we would again anticipate selection for the fastest-growing variants and a decrease in viral diversity.

Long-term studies involving a small number of patients have confirmed some of the modeling predictions. These investigations, done by several researchers—including Andrew J. Leigh Brown of the University of Edinburgh, Jaap Goudsmit of the University of Amsterdam, James I. Mullins of the University of Washington and Steven M. Wolinsky of Northwestern University Medical School—tracked the evolution of the so-called V3 segment of a protein in the outer envelope of HIV for several years. V3 is a major target for antibodies and is highly variable. As the computer simulation predicted, viral samples obtained within a few weeks after patients became infected were alike in the V3 region. But during subsequent years, the region diversified.

Focus on Killer Cells

The original mathematical models treated the immune system as a unit and did not distinguish among the activities of the various cell types. Because killer *T* lymphocytes seem to exert tremendous immunologic pressure against HIV, the two of us and our coworkers have recently designed models that specifically examine the behavior of those cells. These newer models taught us even more about the way HIV's ability to diversify can erode the defensive competence of the immune system.

We began working on these simulations early in 1994, after one of us (McMichael) became perplexed by the results of studies in which he and several collaborators tracked responses of cytotoxic *T* cells to HIV in initially asymptomatic patients. Those studies followed the patients for about five years and were undertaken in part to assess the influence of different HLA molecules on the ability of patients to combat the virus.

HLA molecules play a critical part in the defensive response because they determine which viral peptides will be displayed on cells and how effectively they are showcased. Any two patients are likely to differ in the precise mix of HLA molecules they possess. In consequence, they will also differ in the peptide epitopes their cells exhibit and in the ability of the HLA-peptide units to attract the attention of the immune system. Most patients infected with HIV seem to recognize just a few of the many potential epitopes generated from the virus's proteins, usually between one and 10.

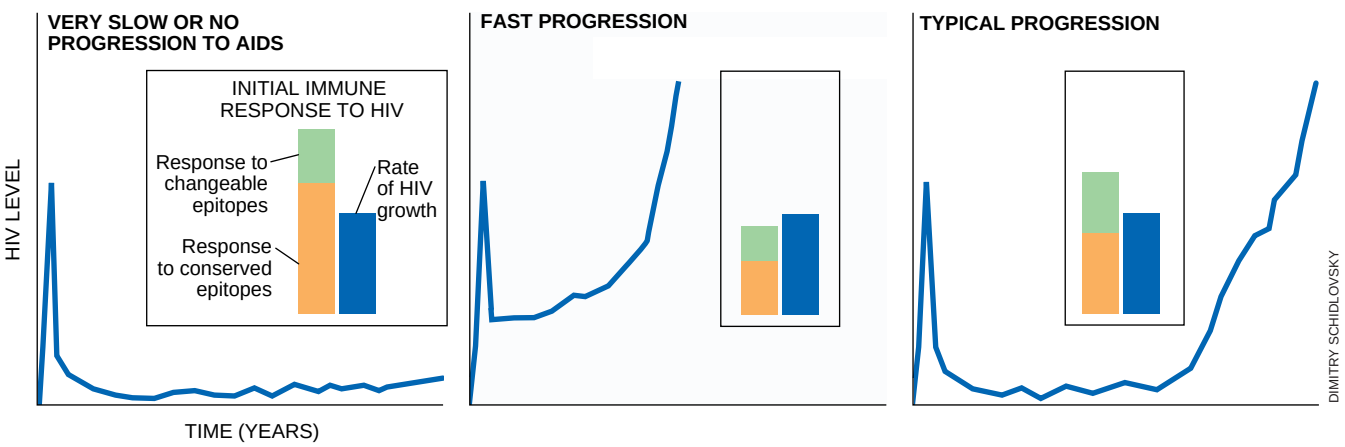
The clinical investigations examined the response of cytotoxic *T* cells to various epitopes in an internal HIV protein called gag. Three of the patients used the HLA variant B27 for such display, and two patients used HLA-B8. In the B27 patients, cytotoxic *T* cell responses were directed at a single fragment of the gag protein, which underwent insignificant variation during the course of the study. In the B8 patients, killer *T* cell activity was directed against a set of three other segments in gag. All three epitopes spawned mutants during the study, and many of the mutant peptides escaped recognition by the host's cytotoxic cells. It also turned out that the relative strength of the responses directed against the three epitopes fluctuated markedly.

These studies were the first to document the existence of mutant viruses able to evade killer *T* cells in the human body. Yet they also raised some puzzling questions, especially this one: Why did the strength of the *T* cell responses to the several epitopes fluctuate so much? In most other viral infections the responses, which are usually directed against one or a few epitopes, are much more stable.

Why Killer Cells Go Astray

It was partly to answer this question that our groups collaborated on making computer models of cytotoxic *T* cell responses to HIV. The programs assumed that breakdown of viral particles in infected cells would result in the display of many epitopes recognized by cytotoxic *T* cells. The models also presumed that most of the epitopes would be capable of mutating and hence of giving rise to viral variants bearing changes in some of their epitopes.

The models introduced random mutations in epitopes and then traced the growth of every new viral variant as well as the abundance of cytotoxic *T* cells directed against each epitope. The abundance of *T* cells recognizing a given epitope—and, hence, the killing power of



SPEED AT WHICH HIV LEVELS RISE (*linear plots*) over the years may depend greatly on the composition of the initial immune response (*insets*). Modeling suggests that if the immune attack directed against conserved epitopes (ones found on every viral particle) can limit viral growth on its own (*left*), the body might keep viral levels low indefinitely—even after the response to readily changeable epitopes inevitably decays. This pattern is uncommon. If the combined responses are weak (*center*), viral levels will rise quickly. If the combined responses are strong but the "conserved" response cannot by itself control the virus (*right*), the typical, fairly slow course of viral multiplication should result. In that situation, levels will begin to soar when the ability to respond efficiently to changeable epitopes is lost.

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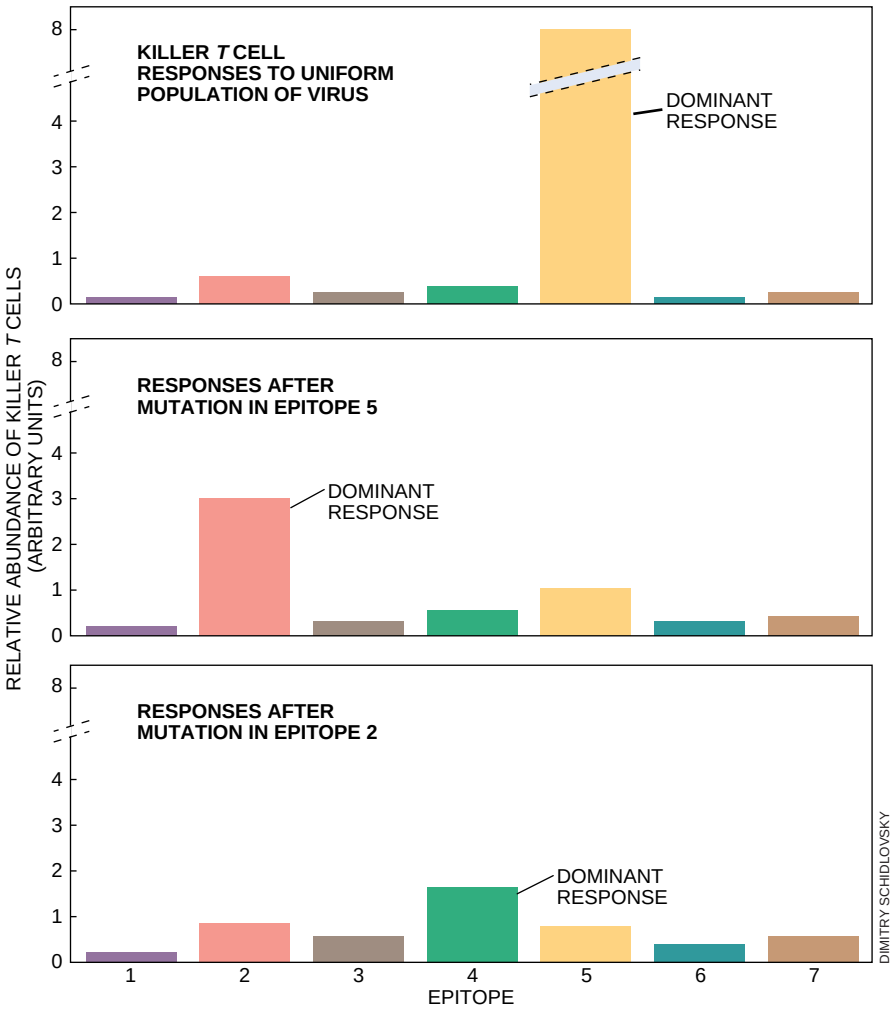
these populations—was made to depend on the number of viral particles bearing that epitope and on the excitatory power of the peptide. (Some epitopes evoke more *T* cell replication than do others.)

The results of the multiple-epitope models were complex, to say the least. In essence, though, the overall efficacy of the immune system declined over time, and the drop resulted from much the same kind of fluctuation in immune reactivity seen in the two patients who produced HLA molecules of the B8 type. The fluctuation seemed to derive from a kind of competition among killer *T* cell populations.

Our calculations suggest that in the body, one clone of killer *T* cells (a population recognizing one epitope) essentially vies with all others for dominance. As the initial killer cell response, which involves many clones, takes effect, the viral population gets smaller, thereby reducing the number of stimulatory signals received by the *T* cells. Ultimately, only the *T* cell clones recognizing the most stimulatory epitopes remain active, and the *T* cell response may even be dominated by a single clone.

Such a process could be beneficial and could potentially eliminate a virus if the microbe did not change. On the other hand, if the epitope fueling the dominant response mutates, the corresponding *T* cell clone may not recognize the mutant. Viral particles bearing this peptide may then multiply virtually unnoticed. Sometimes the immune system will catch up with the renegade group and mount a defense targeted against the new version of the epitope, but other times the defensive system may switch its attention to a different, and originally less stimulating, epitope. This switching can be repeated many times, producing a very intricate pattern in which the relative abundances of *T* cell clones fluctuate continuously. Emergence of an unrecognized form of an epitope can thus cause trouble in at least two ways. In addition to reducing directly the strength of the attack on the altered viral variant, it can induce the immune system to shift its efforts toward less stimulating epitopes.

The global picture taking shape from our recent simulations is one in which diversity of epitopes gives rise to fluctuations of immune responses and diversion to weaker and weaker epitopes. Such diversion results in high levels of HIV, leading to faster killing of helper cells and macrophages and to reduced control of the overall viral population. Put another way, viral diversity seems to drive disease progression. These multiple-epitope simulations can be applied to antibody responses as well.



COMPUTER SIMULATION tracked levels of killer *T* cells in a hypothetical patient. Initially (*top*) the *T* cells responded to a homogeneous population of HIV particles, each of which carried seven recognizable epitopes; epitope 5 elicited the strongest response (*yellow*). After a viral mutant carrying an altered, unrecognized version of this epitope emerged (*middle panel*), the dominant response became focused on a less stimulatory epitope—number 2 (*red*). And after epitope 2 mutated (*bottom*), dominance shifted again, to number 4 (*green*), an even weaker epitope. Such shifts could contribute to reduced immunologic control in HIV-infected patients.

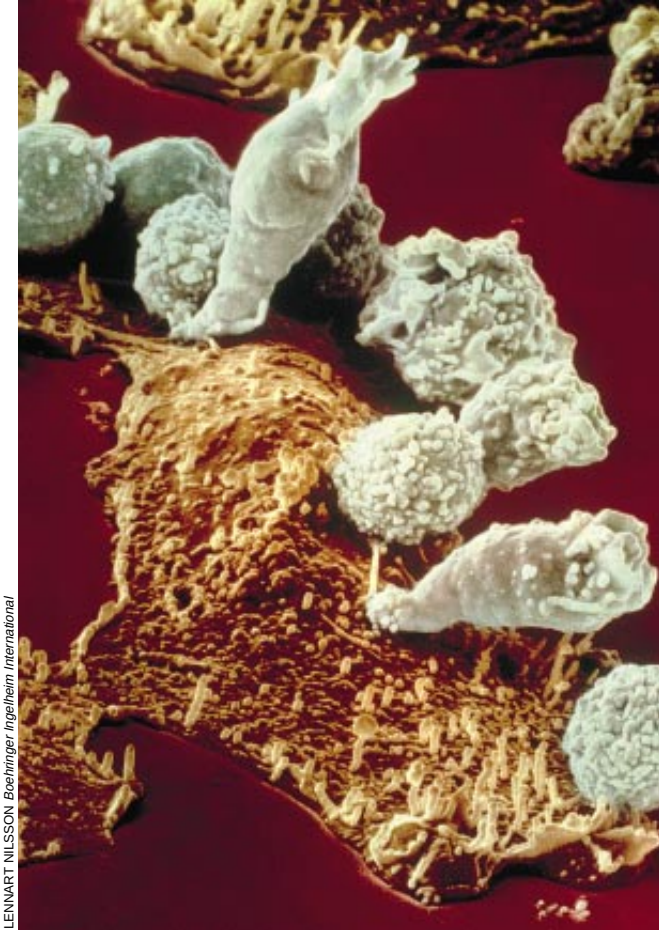
Thoughts on Therapy

Someone unfamiliar with such findings might reasonably suspect that patients who respond to many different epitopes will enjoy better control of a viral population, because a microbial particle not noticed by one clone of immune cells would probably be noticed by another clone. Yet our models predict that in the case of HIV, a response to many different epitopes can be a bad sign—an indication that important epitopes may have undergone unrecognized mutations. The simulations imply that patients whose immune defenses stably recognize one or a few epitopes probably control the virus better than those who respond to a large number of epitopes. This view is supported by an interesting finding from the HLA study described earlier. The two patients who displayed fluctuating *T* cell responses progressed toward AIDS more quickly than did patients who had consistent responses to a single epitope. This study involved too few patients to allow for definitive conclusions, however.

If the models reflect the course of HIV disease accurately, the findings have implications for the development of vaccines (for prevention or treatment) and chemical-based therapies. In the case of vaccines, it would probably be counterproductive to stimulate immune activity against a variety of HIV epitopes in an individual. After all, such stimulation would probably elicit an undesirable competition among immune forces. Rather it may be better to boost

the response against a single conserved epitope, even if that epitope is not normally recognized most readily. This response could ideally evoke a persistent, controlling response to HIV. The trick, of course, would be to identify conserved epitopes and find the best way to deliver them.

Another striking implication relates to the fact that the virus replicates quickly and continuously in all stages of infection. This realization has made many physicians conclude that chemical agents able to halt viral replication are probably most effective when delivered early, before the virus has a chance to expand too much. Combination therapies may also be more effective than single drugs, because even if the virus generated a mutant population resistant to one of the substances, the other drugs could still continue to be effective. By retarding the rate of replication, such strategies should slow the speed at which mutants are produced and so limit viral diversity. Our models further suggest that reducing viral levels and curtailing diversity in this way would help the natural immune system to contain the virus.



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MOVING IN FOR THE KILL, cytotoxic *T* lymphocytes attack a cancer cell in much the way they ambush virus-infected cells. Many lymphocytes attach to a target cell and secrete substances that drill holes into the cell membrane.

A Broad View of HIV Dynamics

The collected clinical and mathematical findings show that in addition to replicating massively in infected patients, HIV mutates repeatedly and thus spawns an enormous diversity of viral populations. These features enable the virus to evolve in response to the threats it encounters during the course of an individual infection. Mutants able to evade immune attack to some degree appear and predominate until the immune system gathers the strength to quell them—but meanwhile new escape mutants begin to multiply. Power thus moves repeatedly from the virus to the immune system and back for a time.

The reversals do not go on endlessly, though, apparently because the evolution of viral diversity gradually tilts the balance toward the virus. Diversity favors the microbe in part because the variability befuddles the patient's immune system, which becomes less efficient and therefore enables the viral population to grow and to kill increasing numbers of helper cells.

Of course, killing of helper cells impairs the functioning of killer *T* cells and *B* cells, which react strongly only when they are stimulated by proteins released from helper cells. As these two cell types become even less effective, a potentially lethal spiral ensues in which viral levels rise further, more helper *T* cells are killed and the overall responsiveness of the immune system declines.

Generation of mutants thus stimulates a continuous reduction in the efficiency of the immune system. At some point, the diversity becomes too extensive for the immune system to handle, and HIV escapes control completely. As the viral load increases, the killing of helper cells accelerates, and the threshold to AIDS is crossed. Finally, the immune system collapses. In short, it seems that an evolutionary scenario can go a long way toward explaining why HIV infection usually progresses slowly but always, or almost always, destroys the immune system in the end.

The Authors

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Further Reading

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