

Mechanisms of T-Cell Depletion and Regeneration in HIV Disease

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MORE THAN 20 YEARS SINCE THE BEGINNING of the AIDS epidemic, there is still no clear-cut explanation for HIV's most basic and insidious effect in the human body: the gradual depletion of CD4+ T-lymphocytes in the absence of antiretroviral treatment. At the same time, there is little consensus regarding the mechanism(s) by which CD4+ cell counts improve once therapy is commenced.

On some level, the fact that CD4+ cell counts do improve—both quantitatively and qualitatively—with antiretroviral therapy should be enough to satisfy the hearts and minds of HIV-treating clinicians. But there is much to be gained medicinally with the continued exploration of these fundamental questions. For example, antiretroviral therapy plays a critical role in halting the accelerated destruction of CD4+ cells, perhaps the most widely accepted mechanism of HIV-associated CD4+ cell depletion. But there is also at least one other mechanism to ponder—the impaired production of new CD4+ cells as a result of HIV infection—that may have significant bearing on the evaluation and potential use of various immune-based therapies in the clinical management of HIV-positive patients.

Understanding CD4+ Cell Depletion

IF THERE IS ONE THING VIRTUALLY ALL EXPERTS agree on, it is that untreated HIV infection results in the progressive loss of CD4+ cells from the circulation as well as depletion of CD4+ cells from total body stores. In a paper published in 1999, Dr.

Ashley Haase, Director of the Microbiology Department at the University of Minnesota, estimated that healthy young adults harbor approximately 200 billion mature CD4+ cells (Haase, 1999). In HIV-positive patients, Dr. Haase and others reckon that this total number is halved by the time the CD4+ cell count falls to 200 cells/mm³.³ And in more advanced disease, Dr. McCune pointed out that destruction of parenchymal lymphoid spaces is so extensive that enumeration of the total body CD4+ cell count has not even been attempted.

There are actually several plausible theories to explain the CD4+ cell depletion seen in HIV disease. As was discussed by Dr. McCune, CD4+ cells may be depleted because they are destroyed (the high-

turnover model) or because their production is impaired (the regenerative failure model) (see Figure 1). Another theory that is being examined, although it was not discussed by Dr. McCune, holds that the fraction of circulating cells may decrease—giving the appearance of loss—if HIV infection results in their redistribution out of the peripheral blood and into the confines of lymphoid organs. [Editor's note: *These and other theories are discussed in a comprehensive review article authored by Dr. McCune, published in the April 19, 2001, issue of Nature (McCune, 2001)*].

As discussed in several past issues of *The PRN Notebook*, the high-turnover model—developed and maintained by groups led by Dr. David Ho and others—concludes

TABLE 1. Mechanisms of CD4+ Cell Depletion: Destruction of Mature CD4+ Cells

Direct destruction of infected cells

- Envelope-mediated apoptosis
- Vpr-induced G2 arrest and apoptosis
- Disruption of cell membrane integrity/syncytia formation
- Accumulation of unintegrated viral DNA

Indirect induction of death in uninfected cells

- Cytolysis by HIV-specific cytolytic T-cells or by natural killer cells
- Autoimmune reactions of a humoral or cellular nature
- Incorporation into syncytia by neighboring infected cells
- Triggering of apoptosis upon cell activation or cross-linking of CD4-bound gp120
- Enhanced HIV transmission and/or apoptosis following interaction with nearby infected antigen-presenting cell

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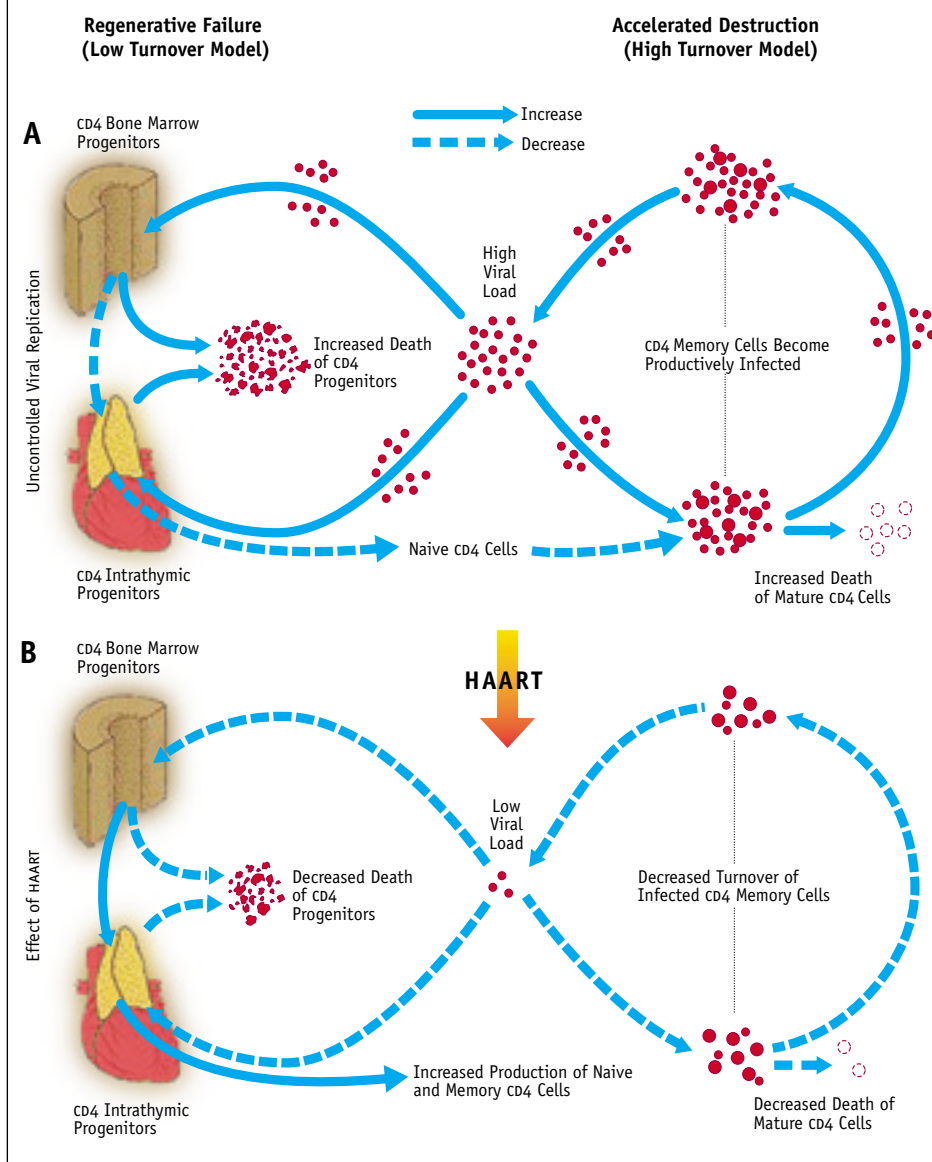
that HIV induces CD4+ cell death in the periphery. A variation on this theme—proposed by Drs. Zvi Grossman of Tel-Aviv University, Frank Miedema of the University of Amsterdam, and others—is that HIV also induces a state of chronic immune activation resulting in increased apoptosis and CD4+ cell death. Upon initiation of HAART, viral burden is dramatically reduced. Treatment, in turn, reduces immune activation, thus halting cell destruction. Some of the direct and indirect mechanisms by which CD4+ cells are destroyed as a result of HIV infection—and halted as a result of HAART—are listed in Table 1.

A critical distinction between the models for high turnover and regenerative failure is that the latter includes a primary pathogenic event in HIV disease that rests upon a failure to produce new CD4+ (and CD8+) cells (Hellerstein, 1997). The model specifies that the sources of production—namely, the bone marrow, the thymus, and other extrathymic lymphoid organs (e.g., lymph nodes, spleen, and mucosa)—are rendered dysfunctional in later stages of HIV disease, resulting in low (or no) rates of replacement in the face of continued CD4+ cell destruction. Over time, this imbalance leads to a decrease in the total body pool of mature T-cells and to immune system collapse, whether or not the destruction rate of CD4+ cells is accelerated. With the initiation of HAART, the viral assault on progenitor cells is halted, allowing for the production of new T-cells. Coupled with diminished destruction of mature T-cells, the CD4+ cell count rises.

In quantitative terms, the crux of the debate between these two models is framed by two parameters: 1) the “fractional replacement rate”—or the fraction of new T-cells made and lost each day—a term that is inversely related to the cell half-life (at steady state, the higher the fractional replacement rate of a given cell subpopulation, the shorter its half-life); and 2) the “absolute production rate”—or the estimated total number of new cells made each day—of a given cell subpopulation. The former parameter tells how long each cell in the body will live, on average; the latter tells how many new cells the body makes each day.

The difference between these two parameters may be easier to understand by drawing upon a more simple analogy: interest on a car loan. A fractional interest rate (e.g., 10% per year on a car loan) im-

FIGURE 1. Accelerated Destruction and Regenerative Failure Models of HIV



When HIV is introduced into the body (Figure 1A), it is probably concentrated with draining lymph nodes and presented as an antigen, resulting in enhanced movement of T-cells into nodes and vigorous T-cell proliferation. The high turnover model holds that immune activation caused by HIV will be associated, by direct and indirect means, with accelerated destruction of T-cells and that the initiation of highly active antiretroviral therapy (Figure 1B) slows T-cell turnover and with it a decrease in the death rate of CD4+ cells (right halves of Figure 1). The regenerative failure model (left halves of Figure 1) specifies that the source of T-cell production—namely the bone marrow, the thymus, and other extrathymic lymphoid organs—are rendered dysfunctional in later stages of HIV disease, resulting in low (or no) rates of replacement in the face of continued CD4+ cell destruction. Over time, this imbalance leads to a decrease in the total pool of mature T-cells and to immune system collapse, whether or not the destruction rate of CD4+ cells is accelerated. With the initiation of HAART, the viral assault on progenitor cells is halted, allowing for the production of new T-cells. Coupled with diminished destruction of mature T-cells, the CD4+ cell count rises.

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plies the length of time it will take to pay double the requested loan amount (i.e., ten years). The absolute interest rate (e.g., \$2,000 on a \$20,000 car) involves the actual amount of money a household must generate to stay in balance with the loan payments. Both of these parameters might be considered when someone decides whether to take out a loan.

These parameters apply to HIV infection and CD4+ cell counts. The high turnover model, in its simplest form, holds that high levels of virus drive a high fractional replacement rate, by increasing the likelihood that a given CD4+ cell will die. Low levels of virus result in a lower likelihood of cell death, and a lower fractional replacement rate. The regenerative failure model maintains that CD4+ cell counts drop because the absolute rate of cell production does not increase to compensate for increased CD4+ cell death. High levels of virus reduce the number of cells produced (the absolute production rate) more than low levels of virus do.

Only recently has it become possible to directly measure absolute production rates. While radioactive labeling has long been used in animal models, it has generally been frowned upon for use in human beings. In 1998, a novel and much safer technique—pioneered by Dr. Marc Hellerstein and his colleagues at the University of California in both Berkeley and San Francisco—permits, for the first time, the direct determination of fractional replacement rates of T-cells in humans. In this technique, the DNA of dividing cells is labeled with deuterated glucose (D-glu) or deuterated water (D₂O), compounds that are safe to administer to humans and are incorporated directly in the deoxyribonucleosides of DNA.

Drs. Hellerstein, McCune and their colleagues at the Gladstone Institute have used this technique to measure the fractional replacement rates of T-cells in HIV-uninfected control subjects and in untreated and treated HIV-infected subjects (Hellerstein, 1999). After a labeling period, circulating peripheral blood mononuclear cells are drawn and separated by a cell sorter into subpopulations, such as CD4+ and CD8+ cells. Genomic DNA from these cells is then isolated and broken into its component nucleosides. Using mass spectrometry, it then becomes possible to measure the fraction of newly made DNA—which contains a chemical signature from

the deuterated substrate (glucose or water)—permitting a direct estimate of the fraction of cells that divided during the period of label administration. A high fraction indicates that there has been a significant amount of cellular proliferation; if the fraction is low, proliferation has been limited. Given information about the number of circulating T-cells, it is possible to calculate the absolute production rate of newly made T-cells in the circulation.

In the 1999 study reviewed by Dr. McCune, three groups of subjects were evaluated: Group 1 consisted of nine HIV-negative study volunteers with a mean CD4+ cell count of 1300 cells/mm³; Group 2 included seven untreated or ineffectively treated HIV-positive individuals with a mean CD4+ T-cell count of 342 cells/mm³; and Group 3 was made up of five individuals initiating HAART with a mean CD4+ T-cell count of 184 cells/mm³. In the uninfected subjects of Group 1, the CD4+ and CD8+ cell population had average half-lives of 87 days and 77 days, respectively, with absolute production rates of 10 new, circulating CD4+ cells/mm³ per day and 6 new, circulating CD8+ cells/mm³ per day. For those infected but untreated subjects in Group 2, the half-life of each subpopulation was shorter than that observed in Group 1, but this increase in cell death was not offset by a compensatory increase in CD4+ cell production. In other words, the fractional replacement rate of CD4+ and CD8+ cells was higher among individuals in Group 2 than that seen in HIV-negative controls in Group 1, but the absolute production rate was not in-

creased. After viral replication was suppressed by HAART in Group 3 subjects for 12 weeks, the fractional replacement rate of T-cells was not significantly different than those recorded in Group 2. Importantly, the kinetic basis for increased CD4+ T-cell levels was greater absolute production, not a longer half-life, of circulating cells.

Mechanisms of Regenerative Failure

IT IS IMPORTANT TO REMEMBER THAT PROGRESSIVE HIV disease is not simply characterized by the development of lymphopenia. Patients with AIDS often face a myriad of other complications, including anemia, neutropenia, and thrombocytopenia. These observations—which are certainly not new to researchers or clinicians—suggest that HIV infection profoundly affects multilineage and lineage-specific hematopoiesis, which ultimately results in regenerative failure along several key cell lines (Table 2).

There is no shortage of evidence suggesting that bone-marrow and intrathymic T-progenitor cells can be affected and depleted by HIV, at least *in vitro*. To explore these observations *in vivo*, Drs. Morgan Jenkins, McCune, and their colleagues at the Gladstone Institute investigated the effects of HIV infection on early hematopoietic progenitor function in immune-deficient mice with surgically implanted human thymus and liver tissues (the SCID-hu Thy/Liv model) (Jenkins, 1998). The group reported that both lineage-restricted and

TABLE 2. Mechanisms of CD4+ Cell Depletion: Impaired T-Cell Production

Direct effects of virus

- Infection-mediated death of progenitor cells
- Destruction of the supporting stromal network required for multilineage or lineage-restricted hematopoiesis

Indirect effects of virus

- Cytokine dysfunction
- Opportunistic infections of bone marrow (e.g., CMV or MAC)
- HIV-induced apoptosis
- Infiltrating malignancies
- Myelotoxic effects of drugs
- Deficiencies of vitamins and of other essential factors

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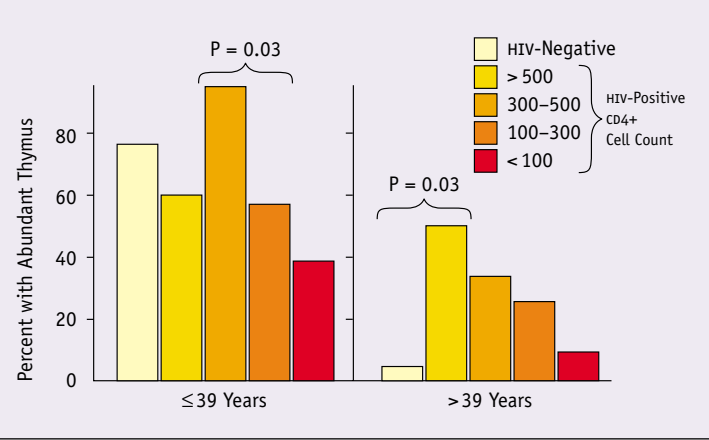
multilineage hematopoietic progenitors were depleted from the human Thy/Liv grafts infected with either a molecular clone or a primary isolate of HIV. Depletion of hematopoietic progenitors occurred several days before the onset of thymocyte depletion, indicating that the subsequent rapid decline in thymocyte numbers was due at least in part to loss of thymocyte progenitors. HIV-DNA was not detected at high frequency in hematopoietic cells earlier than the intrathymic T-progenitor cell stage, despite the depletion of such cells in infected grafts. Proviral genomes were also

not detected in colonies derived from progenitor cells from infected grafts. “These data,” Dr. Jenkins’ writes in a report published in *Blood*, “demonstrate that HIV infection interrupts both lineage-restricted and multilineage hematopoiesis *in vivo* and suggest that depletion of early hematopoietic progenitor cells occurs in the absence of direct viral infection.”

The fact that HIV does not infect hematopoietic progenitor cells may prove to be a fruitful finding. As is discussed in our lymphoma review, beginning on page 22, Dr. David Scadden and his colleagues have been looking at the possibility of tweaking hematopoietic progenitor cells to produce HIV-resistant T-lymphocytes progenies, perhaps as an adjunctive component of bone-marrow transplantation in HIV-related lymphoma cases.

As for thymopoietic progenitor cells, Dr. McCune explained that, despite the protective nature of its vascular endothelium, the thymus and its cells are a highly vulnerable target for HIV infection: greater than 90% of all thymocytes carry the CD4 receptor and many of these cells also express the co-receptor CXCR4 and/or CCR5 (Berkowitz, 1998). Evidence of HIV infection of the thymus can be found in numerous reports indicating morphologic changes in pediatric and adult thymus specimens, immunohistochemical visualization in thymocytes, and isolation of HIV from the organ (McCune, 1997).

FIGURE 2. Thymus is Abundant in Some HIV-Positive Adults



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The Thymus and HIV

WHILE DATA REGARDING THE MECHANISM(S) of HIV-mediated thymus destruction in humans are limited, there are a number of theoretical possibilities based on what is known about the effects of HIV on human T-cell subpopulations (Hellerstein, 1997). For starters, early depletion of naive (CD45RA+ CD62L+) CD4+ and CD8+ cells is a fundamental feature of HIV infection. Since these cells are relatively resistant to productive infection of HIV—because they do not divide rapidly, if at all—it is possible that they are depleted by viral-induced destruction of bone marrow- and thymus-derived progenitor cells, which was demonstrated in the Jenkins paper cited above. Second, intrauterine HIV infection of the thymus can lead to thymic aplasia in children, resulting in thymic failure, loss of naive CD4+ and CD8+ cells in peripheral circulation and rapid progression to AIDS and death. Likewise, older age at the time of HIV infection is one of the most important factors of disease progression rates in adults, a correlation that may be related to the fact that thymic reserves are diminished with age. Third, the T-cell receptor (TCR) repertoire of both CD4+ and CD8+ cells is often restricted in advanced HIV disease, indicating that the CD4+ cell pool has expanded from a limited number of TCR clonotypes. This observation, in turn, suggests that the thymus is no longer able to generate a diverse T-cell receptor repertoire.

While the above observations predict that HIV-infected adults should have little if any thymic function, a study conducted by Dr. McCune and his group instead came

to the opposite conclusion: The thymus appears to be very much present and functional in a surprisingly large percentage of HIV-infected patients, including those 40 years of age and older (McCune, 1998).

As described in a 1998 report published in the *Journal of Clinical Investigation*, Dr. McCune’s Gladstone Institute group recruited 99 HIV-positive patients and 32 HIV-negative controls to undergo CT scans, which were read by radiologists blinded to the HIV status and age of the study volunteer scanned. Each thymus was rated on a “thymic index” scale of one to four, with a score of one indicating complete involution and fat replacement and a score of four indicating the presence of a large amount of thymic tissue. In analyzing the results, study participants were divided into two groups: those with a score of three or four were said to have “abundant” thymic tissue while those with a score of one or two were said to have “non-abundant” thymic tissue.

Dr. McCune’s team hypothesized that, if the thymic index truly reflects a functional organ making CD4+ and CD8+ cells, an abundant organ seen by CT should correlate with a higher number of CD45RA+ CD62L+ (naive) T-cells in the peripheral blood. This correlation held: a thymic index of three or four—reported in 47/99 (47%) of the HIV-infected adults, aged 20 to 59—was significantly associated with both higher CD4+ cell counts and a higher percentage and absolute number of circulating naive CD4+ cells. The prevalence of abundant thymus was especially high, as expected, in younger HIV-positive adults, regardless of their CD4+ cell count. But, while the thymus appeared to become less abundant in HIV-negative study volunteers as they got older—no seronegative person past the age of 39 had an abundant thymus—the same situation did not hold for the HIV-positive group: many of these individuals showed evidence of abundant thymus even if they were over the age of 39 (see Figure 2). Strikingly, younger (39 years or less) HIV-positive subjects with a CD4+ count in the range of 300-500 cells/mm³ showed CT evidence of abundant thymus. “Contrary to our preconceived notions going into this study, we had a large number of HIV-positive patients with

complete involution and fat replacement and a score of four indicating the presence of a large amount of thymic tissue. In analyzing the results, study participants were divided into two groups: those with a score of three or four were said to have “abundant” thymic tissue while those with a score of one or two were said to have “non-abundant” thymic tissue.

healthy thymic tissue,” Dr. McCune stated in wrapping up his discussion of this study. “In such patients, we would expect HAART to permit thymic production of naive T-cells.”

Potential Roles for Interleukin-7 or Human Growth Hormone?

WHILE IT IS STILL TOO EARLY TO EXPLAIN why some HIV-positive adults have abundant thymuses, it can possibly be attributed to the increased secretion of a positive regulator, such as interleukin-7 (IL-7), growth hormone, stem-cell factor, Flt3L, or IL-2. In other words, just as a loss of red blood cells or platelets is countered with the production of erythropoietin or thrombopoietin to stimulate the proliferation of early erythroid or megakaryocytic progenitors, HIV-induced depletion of CD4+ cells might elicit a factor that stimulates increased (or renewed) production of CD4+ cells in the thymus and elsewhere.

Among these positive regulators of thymopoiesis, Dr. McCune pointed out that IL-7 has been shown to play a pivotal role. In IL-7 knockout mice, very few T-cells are found in the thymus and peripheral lymphoid organs. He noted that receptors for IL-7 are found on lineage-restricted progenitors in lymph node, thymus, and bone marrow. “We also know that elevated IL-7 levels are detected in non-HIV lymphopenic conditions, such as severe combined immune deficiency syndrome and acute lymphocytic leukemia—and these levels usually normalize when the lymphopenia resolves,” explained Dr. McCune.

First up, then, was to test the hypothesis that HIV-mediated CD4+ cell loss induces the production of factors that are capable of stimulating lymphocyte development and expansion. Drs. Laura Napolitano, McCune, and their group at the Gladstone Institute performed cross-sectional ($n = 168$) and longitudinal ($n = 11$) analyses showing that increased circulating levels of interleukin (IL)-7 were strongly associated with CD4+ lymphopenia in HIV disease (Napolitano, 2001). Using immunohistochemistry with quantitative image analysis, Dr. Napolitano—working with Dr. Jan Andersson of the Karolinska Institute in Stockholm—also demonstrated that IL-7 is produced by dendritic-like cells within peripheral lymphoid tissues and that IL-7 production by these cells was significantly increased within lymphocyte-depleted

tissues. This was characterized by an increased percentage of IL-7-positive cells and increased amounts of IL-7 produced per cell in biopsied lymph nodes.

Dr. McCune also reviewed IL-7 unpublished data presented at the 2001 Keystone Symposium, which were originally presented by Dr. Napolitano and Dr. Ruth Greenblatt of the Women’s Interagency HIV Study (WIHS). With pre- and post-HAART samples available from 237 HIV-positive women, Dr. Napolitano’s group confirmed its earlier results by demonstrating a strong and independent correlation between circulating IL-7 levels and lymphopenia. Of particular interest, pre-HAART IL-7 levels predicted the degree of CD4+ cell recovery upon initiating HAART, and post-HAART IL-7 levels decreased as the CD4+ cells recovered. “Here we were able to suggest that increased IL-7 levels may function to increase lymphocyte production and/or expansion,” Dr. McCune commented. “These data support a homeostatic role for IL-7. However, the association between IL-7 levels and immune recovery may not be evident in individuals with irreversible HIV-mediated destruction of thymus, bone marrow, or lymph nodes.”

While it will be important to continue pondering the role of IL-7 on thymopoiesis in HIV-positive patients, its potential as a therapeutic compound has barely begun to be established. “First off,” Dr. McCune said, “IL-7 is not yet available for clinical studies. It may also pose problems if administered as a therapy for HIV patients. IL-7 can increase HIV replication and, by stimulating the usually dormant thymus, may open it up to infection. However, IL-7 might be safely given to promote thymopoiesis if viral replication is controlled using HAART. In addition, IL-7 could be useful in non-HIV-infected patients with severe immune deficiency, such as in the setting of chemotherapy or bone marrow transplantation.”

With respect to growth hormone, Dr. McCune explained that animal studies have indicated that it plays an important role in mammalian thymopoiesis. Growth hormone may act directly upon immune tissues or its effects may be mediated indirectly through insulin-like growth factor-1 (IGF-1). Rodents deficient in growth hormone exhibit thymic hypoplasia that improves with growth hormone replacement. In older rodents, the administration of growth hormone or IGF-1 reverses age-re-

lated declines in thymopoiesis and accelerates immune reconstitution in immunodeficient animals. Although growth hormone-deficient humans do not appear to be immunologically compromised, Drs. Napolitano, McCune, and the rest of their team hypothesized from these observations in animal models that treatment with recombinant human growth hormone (rhGH) would stimulate thymopoiesis in HIV-1-infected individuals.

The study, which was published in a May issue of *AIDS* and discussed further at the XIV International AIDS Conference in Barcelona, involved five HIV-infected adults treated with rhGH (Serostim) 3 mg/day for six to 12 months in a prospective fashion (Napolitano, 2002; 2002a). The dose was reduced to 1.5 mg per day after the first 6 months of therapy, except in one subject, in whom GH dose reduction occurred at month 2 as a result of persistent arthralgias. Immunological analyses were performed before rhGH treatment and repeated at three-month intervals after rhGH initiation. Thymic mass was analysed using computed tomography with quantitative density and volume analysis. Analysis of circulating lymphocytes, including naive and memory T cell subsets, was also performed using multiparameter flow cytometry.

There was a marked increase in thymic tissue in all subjects after six months of rhGH therapy. At baseline, the five patients had thymic atrophy as evidenced by the near-complete replacement of the thymus by fat on CT scan (mean thymic index of one). Repeat analysis after six months of treatment revealed a prominent increase in dense thymus tissue in all of the rhGH recipients (mean thymic index of four, $P = 0.0002$ compared with baseline). Quantitative density and volume measurements at six months demonstrated a mean increase in thymic density of 86 HU ($P = 0.0008$), and a mean increase in thymic volume of 88% ($P = 0.06$). To determine whether the reversal of thymic atrophy was caused by a generalized lipolytic effect of rhGH, quantitative density analysis was performed on the axillary adipose tissue of each patient. No increase in axillary adipose density was detected (mean change of +3 HU at six months and -9 HU at one year).


Treatment with rhGH was also associated with an increase in the percentage and absolute number of naive CD4+ cells. When compared with baseline values, the mean absolute gain in the naive CD4+ cell per-

centage was 6% at six months, 10% at nine months, and 12% at 12 months; both the nine-month and 12-month increases were statistically significant. Naive CD8+ cells did not increase with rhGH treatment, and no significant changes in naive CD4+ cell percentages or naive CD8+ cell percentages were seen in historical control subjects who were maintained on effective antiretroviral therapy for a similar period of time.

To date, two study participants have been off rhGH therapy for one or more years. Repeat thymus CT scans, performed after therapy discontinuation, revealed a decrease to baseline thymic density in both individuals. However, gains in naive CD4+ cells remained stable.

It goes without saying that these findings do not support the general use of rhGH with the intent of reversing immune deficiency. Certain limitations of this study, including the small number of treated subjects and the lack of a randomized control arm, require that these data be interpreted with caution. Fortunately, a larger, randomized study is currently under way to evaluate further the role of rhGH as an immune-based therapy.

Summary

IN AN EFFORT TO SUMMARIZE THE RATHER complex components of his talk, Dr. McCune stressed that little doubt remains regarding the destructive nature of HIV on mature effector CD4+ cells in the human body. However, it is equally important to remember that compensatory feedback pathways likely help to sustain the CD4+ cell count in the face of destruction. When these pathways fail, regenerative failure is not far behind. One possible mechanism is the HIV-mediated depletion of long-lived progenitor cells, including those in the bone marrow, the thymus, and in peripheral lymphoid organs. Another possible mechanism is the loss of feedback loops, such as those mediated by IL-7 and other positive regulators, known to play a role in hematopoiesis and thymopoiesis. "More focus on regenerative failure may teach us about the hard-wiring of human T-cell homeostasis," Dr. McCune said. "At the same time, it may provide additional clues for adjunctive therapies, such as IL-7 and recombinant human growth hormone, for T-cell reconstitution." 

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