

Exhibit 6

Viral-Load Tests Provide Valuable Answers

by John W. Mellors

In the early 1990s tests that could accurately detect the amount of HIV in a patient's blood finally became available. These viral-load assays have since revolutionized understanding of HIV's behavior and have helped define new principles of therapy. The assays directly measure viral RNA per milliliter of blood plasma; each HIV particle contains two strands of RNA, so the level of actual virus is half the RNA count.

The tests enabled researchers to show that HIV never undergoes a period of slow growth. From the start, the collective viral population in a patient generates many billions of new HIV particles a day, resulting in destruction of millions of CD4 T lymphocytes—the immune cells most depleted in infected patients. The body tries to compensate for the loss by making new CD4 T cells, but the immune system remains under constant siege and eventually fails to keep up.

In 1996, as part of the federally supported Multicenter AIDS Cohort Study (MACS), my colleagues and I measured virus in stored plasma samples collected from about 1,600 untreated HIV-infected men and traced the fate of those patients. We found striking differences in prognosis, depending on the level of virus (graph). For example, 70 percent of the men whose viral load was greater than 30,000 copies per milliliter died within six years of the test, the average survival time being 4.4 years. In contrast, fewer than 1 percent of patients whose viral load was below 500 copies per milliliter died in six years, and the average survival time was more than 10 years. These results established that viral load critically influences the rate of disease progression. They also suggested that lowering viral levels as much as possible for as long as possible with therapy is essential to prolonging life.

Subsequent studies using viral-load tests have both confirmed this concept and changed how new therapies are evaluated. Until recently, investigators assessed potential treatments by comparing the incidence of AIDS or death in test subjects and a control group, often having to wait years for definitive results. After the viral-load assays became available, several large studies demonstrated that measures of viral load, often after just weeks of treatment, were valid indicators of whether a therapy could slow progression of HIV infection. For example, treatments that lowered the load by 75 to 90 percent within eight to 24 weeks reduced by 50 to 65 percent the likelihood of progressing

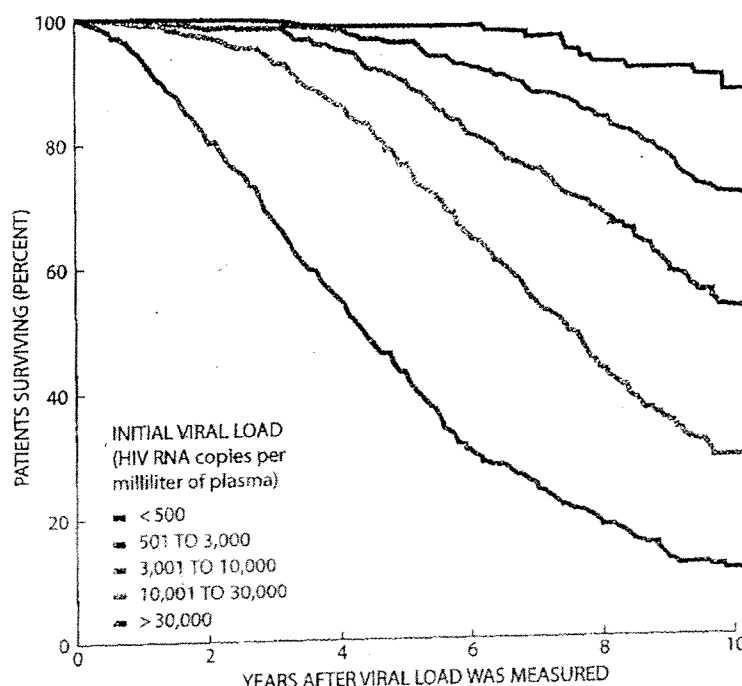
TEN-YEAR SURVIVAL in 1,604 HIV-infected men depended on the patients' viral load at the start of the 10-year period. The men were followed in the era before effective therapy for HIV was introduced; their viral load was assessed retrospectively, from stored blood samples. This finding was among the first to establish the major influence of viral load on disease progression.

to AIDS within a year. Viral-load measures have therefore replaced assessment of clinical outcome in therapeutic trials, and routine monitoring of viral levels has been incorporated into medical practice.

Recent studies have suggested a refinement of the admonition to keep viral levels low. Current treatment guidelines aim to maintain viral load below 500 copies per milliliter (the limit of detection for the tests usually used today). Failure to reach that level is associated with breakthrough of drug-resistant virus and loss of control over HIV replication. Yet trials applying more sensitive tests indicate that depressing viral load below 50 copies per milliliter offers better insurance against resistance. Moreover, such a reduction is probably necessary to halt viral replication everywhere—in lymph nodes (where the replication rate is higher than in the blood) and also in other body compartments. I believe, therefore, that viral loads below 50 should become the new goal if the more sensitive tests (now used only in research) are made readily available. Not all physicians agree, however, in part because this target may be more difficult to reach, particularly for patients in whom initial therapy has failed.

A major new challenge for therapy is finding ways to eliminate HIV from infected resting CD4 T cells, which do not produce viral particles but harbor the genetic blueprints for doing so in the future. Current antiretroviral drugs cannot eliminate these HIV reservoirs. To develop such therapies and monitor their effects, investigators will undoubtedly require a new generation of viral-load tests—ones that can accurately measure the virus hiding in resting cells. Fortunately, efforts to create those urgently needed assays are under way.

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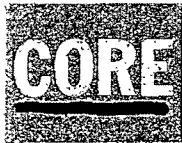
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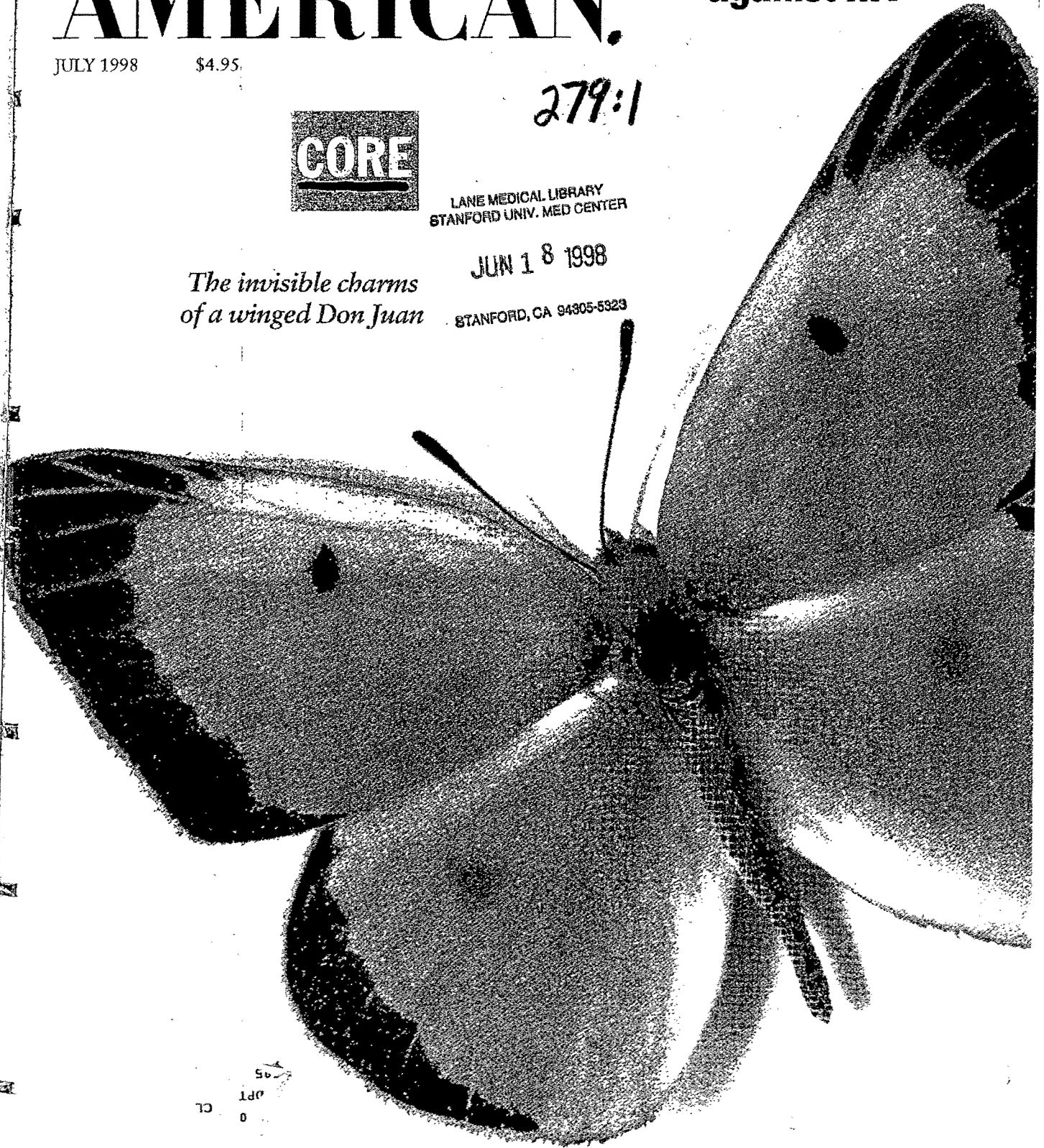
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*The invisible charms
of a winged Don Juan*

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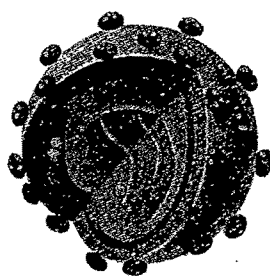
Black market in CFCs.... America's Cup racers sail into the lab.... Computers that feel your pain.... Richter-scale models.... Fusion plasma spirals.

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SPECIAL REPORT

81 Defeating AIDS: What Will It Take?

Infections with HIV, the human immunodeficiency virus that causes AIDS, continue to sweep the world. Cures and vaccines remain elusive, although the search goes on. The good news is that safer behaviors and—for those with access to proper care—better drug treatments and tests can save or extend lives. These leading investigators describe the state of the fight against HIV today and the prospects for winning tomorrow.



82 HIV 1998: The Global Picture

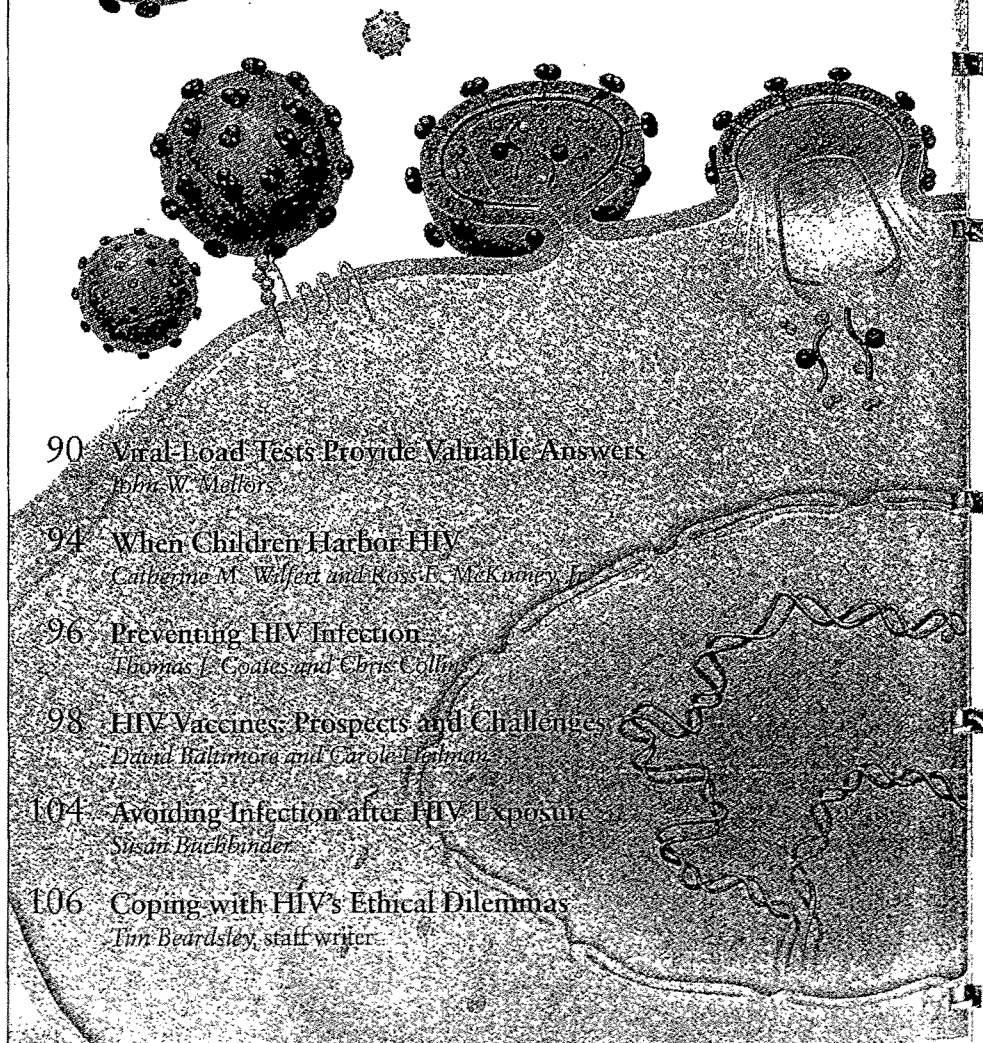
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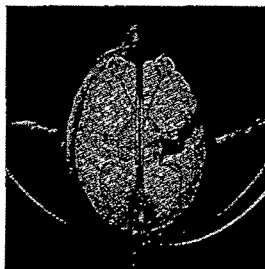
NASA's Pathfinder spacecraft and the intrepid Sojourner robot confirmed that the Red Planet was once wetter and warmer. Equally important, they proved new space-exploration concepts for the future, including the scientific worth of low-cost unmanned probes to the planets.



50 The Split Brain Revisited

Michael S. Gazzaniga

Three decades ago this author and his colleagues learned that when the hemispheres of the brain are disconnected, each functions alone but with different abilities. Since then, further research on split brains has revealed much more about the asymmetries of the brain and the operation of the mind.



56 The Single-Atom Laser

Michael S. Feld and Kyungwon An

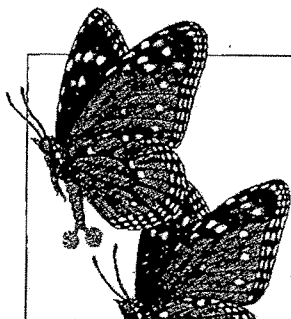
Conventional lasers need millions of atoms in a column of gas or a crystalline rod to generate a coherent beam of light. New quantum-mechanical lasers coax radiation from atoms one by one. What this tiny beam illuminates best are the closely guarded secrets of how light and matter interact.



64 Mating Strategies in Butterflies

Ronald L. Rutowski

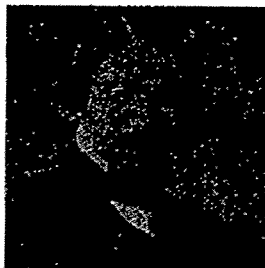
On their wings, in colors visible and invisible to the human eye, butterflies advertise their reproductive eligibility: "Single Male Yellow Lepidopteran—young, successful, healthy—seeks same in amorous female." But wing displays are only part of a mating ritual for weeding out the unfit.



70 Léon Foucault

William Tobin

This French physicist is best remembered for his famous pendulum experiment of 1851, which proved directly that the earth spins. Yet Foucault also clinched the case against the particle theory of light, invented the gyroscope, perfected the reflecting telescope and measured the distance to the sun.



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THE AMATEUR SCIENTIST

Recreational divers lend a fin to marine biologists.

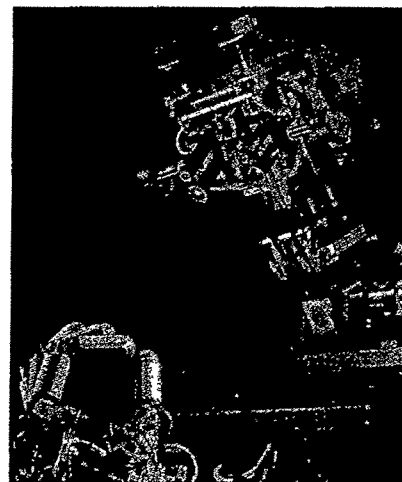
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About the Cover

Males of the Orange Sulphur butterfly *Colias eurytheme* are brightly colored, but unlike those of the females, their wings also strongly reflect attractive patterns in the ultraviolet end of the spectrum. Photograph by Dan Wagner.

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