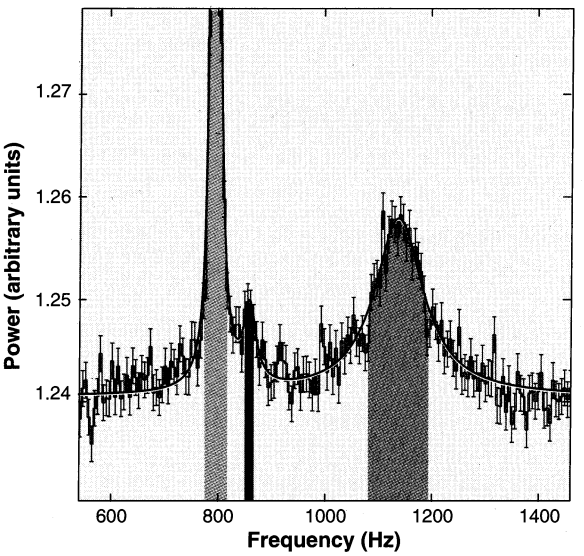
quent observations (*6*) have shown, however, that the red frequencies are sometimes two and sometimes four times the precession frequencies predicted by general relativity. The symmetry of the system makes it likely that the observed frequency should be double the theoretical, but a quadrupled frequency is difficult to explain. Several other models for the QPO peaks have been proposed; the issue remains to be resolved (*3*).

Another kilohertz QPO (colored purple in the second figure) has recently been discovered for several sources alongside the familiar blue and green QPO peaks through the use of new data analysis techniques (*10*). It has been suggested (*10*) that the new peak is produced by the same mechanism as the low-frequency red peak. If the two peaks have a common origin, the purple peak should be a beat frequency between the red and blue peaks. In this case, blue plus red should equal purple, but there is a mismatch of about 20 Hz. This suggests that the red and purple peaks are either independent or are caused by similar phenomena at different radii in the disk (*10*).

The frequency difference between the purple and blue peaks is constant in time, suggesting that the purple feature is a beat corresponding to another beat with unknown frequency. In this case, another beat should appear on the other side of the blue peak. This was not seen in two of the sources that were studied but was observed in a third source (*10*), strengthening the case for interpreting the new peak as a beat. It remains unclear, however, how the beats are produced and why the lower lobe is absent in two of the sources. It has been suggested in the popular press (but not in a refereed publication) that frame dragging may again be responsible. This seems unlikely, because the theoretical frame-dragging rate (*11*) for 4U 1728-34 should be no more than 20 hertz, whereas the purple-minus-blue frequency is 65 hertz.

The new data are intriguing but also raise many questions. The beat features have so far only appeared in low-luminosity sources. Do they also appear in high-luminosity sources? Black hole candidate sources show QPOs that may be similar to the blue and red peaks (although they appear at lower frequencies). Does a beat feature appear in these spectra? And is the peak separation between the purple and blue sources really constant? More data will help answer some of these questions, but it will be difficult for theorists to provide an explanation for the QPO phenomena. It is clear, however, that the x-rays originate from a region with a strong gravitational field and that in these neutron star systems general relativity will be an important effect, which is rare in astronomy.



Mysterious peaks II. An additional peak has appeared between the green and the blue peaks (*10*). This spectrum of 4U 1728-34 was measured at a different time than the first figure, and the frequencies of the QPOs will therefore not match exactly.

References and Notes

1. "Imagine the Universe" has lots of information about neutron stars. See http://imagine.gsfc.nasa.gov/.
2. The Web site for the RXTE satellite is http://guinan.gsfc.nasa.gov/docs/xte/. See also http://guinan.gsfc.nasa.gov/docs/xte/learning_center/.
3. M. Van Der Klis, *Annu. Rev. Astron. Astrophys.*, in press.
4. L. Bildsten, T. Strohmayer, *Phys. Today* **52** (no. 4), 40 (1999).
5. The most common type of neutron star observed is a pulsar, which emits constant, steady pulses, as opposed to the intermittent pulses seen in the stars discussed here. The fastest pulsars, called millisecond pulsars, are believed to be spun up to their fast speeds by the accretion of material from an orbiting companion in an x-ray binary system. It is thus very important that the RXTE observations have shown neutron stars in x-ray binaries to have spin periods similar to the millisecond pulsars. A "missing link" neutron star with characteristics typical of both the accreting x-ray binaries and the millisecond pulsars has also recently been observed [R. Wijnands and M. Van Der Klis, *Nature* **394**, 344 (1998)].
6. E. C. Ford, M. Van Der Klis, *Astrophys. J.* **506**, L39 (1998).
7. M. C. Miller, F. K. Lamb, D. Psaltis, *Astrophys. J.* **508**, 791 (1998).
8. S. van Straaten *et al.*, *Astrophys. J.* **540**, 1049 (2000).
9. L. Stella, M. Vietri, *Astrophys. J.* **492**, L59 (1998).
10. P. G. Jonker, M. Mendez, M. van der Klis, *Astrophys. J.* **540**, L29 (2000).
11. S. M. Morsink, L. Stella, *Astrophys. J.* **513**, 827 (1999).

PERSPECTIVES: AIDS

Boosting Immunity to HIV—Can the Virus Help?

Brigitte Autran and Guislaine Carcelain

The human immunodeficiency virus (HIV), the cause of AIDS, invades certain types of host immune cells, in particular $CD4^+$ T helper 1 (T_H1) lymphocytes that are progressively eliminated as the virus replicates. These $CD4^+$ T cells, along with $CD8^+$ cytotoxic T lymphocytes, are essential for mounting a coordinated immune attack against HIV. In the absence of antiretroviral drug therapy, the intensity and diversity of $CD4^+$ and $CD8^+$ T cell responses against HIV increase as the amount of virus in the blood (viral load) decreases during primary HIV infection (*1*, *2*). Treating newly infected HIV patients with antiretroviral triple drug therapy (HAART) provides a rapid reduction in the initial burst of virus replication and helps to preserve the HIV-specific $CD4^+$ T_H1 cell population from rapid elimination (*2*); unfortunately, this strategy also lessens the intensity of the HIV-specific $CD8^+$ cytotoxic T cell response (*3*). This calls into question the actual benefit of early therapeutic intervention, which does not completely eradicate the virus and leaves the patient with an incomplete antiviral immune response. In an effort to solve this dilemma, researchers have interrupted drug treatment during primary (acute) HIV infection. Although the benefits of such therapeutic manipulations remain controversial, anecdotal evidence from patients who have had drug therapy interrupted suggests that periodic and transient increases in the viral load restimulate the waning HIV-specific $CD8^+$ cytotoxic T cell response (*4*, *5*). Now, in a recent issue of *Nature*, Walker and co-workers (*6*) report that administering HAART to patients within 72 hours of diagnosing HIV infection, and then discontinuing treatment after 1 to 2 years, helps to establish durable immune control of the virus.

Walker and colleagues treated eight acutely infected HIV patients with HAART, and then, after complete suppression of the viral load for at least a year, interrupted drug therapy. Before treatment was stopped, the $CD4^+$ T_H1 (but not $CD8^+$ cytotoxic T cell) response to HIV could be detected in all eight patients. After discontinuing treatment, the virus rebounded and

CREDIT: ADAPTED FROM (*10*)

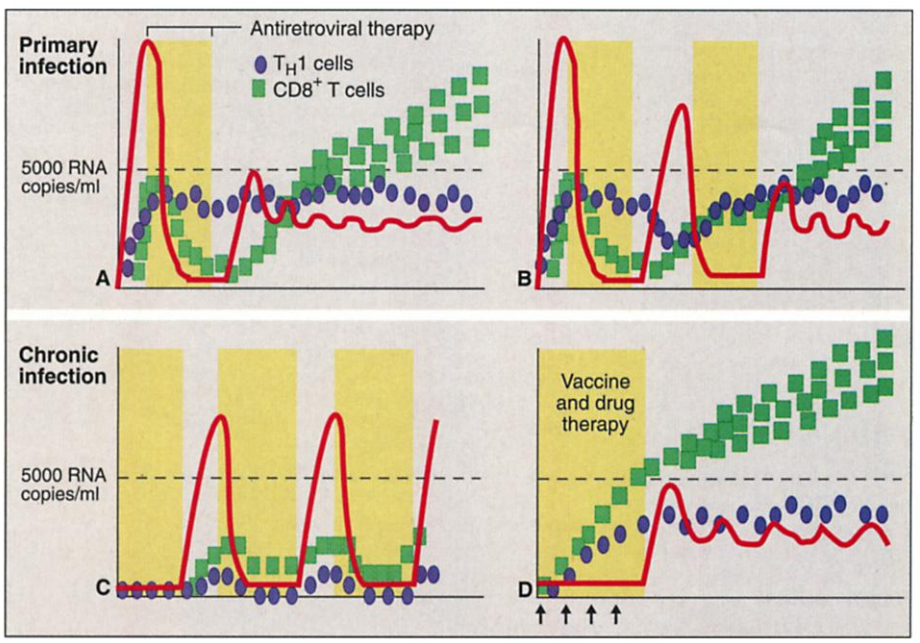
The authors are at the Laboratoire d'Immunologie Cellulaire et Tissulaire, Hôpital Pitié-Salpêtrière, Paris 75013, France. E-mail: brigitte.autran@psl.ap-hop-paris.fr

boosted the numbers of virus-specific cytotoxic $CD8^+$ lymphocytes in all patients (see the figure). In three cases, the amount of virus rapidly reached a low steady state—below 10,000 copies of viral RNA per milliliter (ml) of plasma, the level at which drug therapy would have to be reinstated. In the other five cases, the intensity of the initial virus rebound led to a transient decrease in the T_H1 cell response and drug therapy was immediately reintroduced. The subsequent reduction of HIV in these patients allowed the T_H1 cells to return to baseline levels. A second interruption in drug treatment then caused a weaker rebound of virus to a viral load below 5000 RNA copies/ml of plasma, and did not result in a decrease in the T_H1 response (see the figure). In addition, it boosted and broadened the HIV-specific $CD8^+$ cytotoxic T cell response, eventually leading to a low, steady-state viral load. Altogether, five out of eight patients remained off therapy for 6.5 months (median), with their viral loads remaining below 500 RNA copies/ml of plasma. This encouraging finding contrasts with the viral load in untreated HIV patients in the Multicenter AIDS Cohort Study (*7*), whose viral loads remained consistently above 5000 copies/ml.

What can we learn from the observations of Walker and colleagues? First, gentle or progressive exposure of the immune system to HIV, instead of abrupt and intense stimulation, might better facilitate the generation of protective immune responses. It is already known that a short exposure to the virus is sufficient for HIV-specific T_H1 cells to be generated and maintained for long periods (*2*). The new findings confirm that virus-specific T_H1 cells—in the absence of a stronger or more prolonged exposure to HIV—are not capable of stimulating an intense, broad, and durable $CD8^+$ cytotoxic response. Indeed, lessons from animal models infected with lymphocytic choriomeningitis virus show that the magnitude of the effector $CD8^+$ T cell response to an acute viral infection is proportional to the initial burst of virus replication, and determines the intensity of the memory T cell response, which in turn controls the virus at steady-state levels (*8*). Therefore, a tight, dynamic equilibrium between the virus, $CD4^+$ T_H1 cells, and $CD8^+$ cytotoxic T cells must be reached to establish efficient immune control. Walker and co-workers demonstrate that a low, quasi-steady state viral load can be achieved when HAART is discontinued during primary HIV infection. In most of their patients, however, the initial immune responses were too weak to ensure immediate protection after discontinuation of drug therapy. Thus, the immune response had to be boosted by the rising viral load that followed discontinuation of drug therapy.

Despite the encouraging findings of the Walker study, several important questions remain unanswered. Which factors of the host immune system govern the kinetics of establishing protective immunity, and how durable will this protection be? How many treatment interruptions will acutely infected patients require to achieve a steady-state viral load, and will these treatment manipulations be manageable in real life? Although there are no definitive answers to these questions as yet, and the number of patients in the Walker study is small, the results suggest that appropriate therapeutic intervention in patients during the earliest days of HIV infection should help to induce some immune control of HIV.

One intriguing question is whether the apparent benefits of interrupted therapy can be extrapolated to any stage of HIV infection—anecdotal data suggest that this is not the case. It is already known that patients with chronic HIV infection relapse 2 to 3 weeks after a single interruption to drug therapy and require the immediate resumption of treatment (see the figure) (*9*, *10*). In these patients, the HIV-specific $CD8^+$ T cell response can be boosted by interrupting drug therapy, but the immune response is limited compared with the broad repertoire of $CD8^+$ cytotoxic T cells observed in the Walker study patients with primary HIV infection (*11*, *12*). This lack of cytotoxic T cell diversity might reflect the existence of an immune footprint or "antigenic sin" as proposed for B cell immunity—a footprint of immune responses is established during exposure to a virus and is automatically triggered against the same antigens when the immune system encounters the virus again. Alternatively, the lack of cytotoxic T cell diversification in chronic HIV infection might also reflect the crippled HIV-specific T_H1 response, which can barely be detected in these patients (*2*). Although they can be restimulated when exposed again to the virus, these weak HIV-specific $CD4^+$ T_H1 cells cannot provide efficient help to $CD8^+$ cells. They are thus rapidly eliminated in the face



Therapy interrupted. Immune responses to HIV after interrupted drug therapy in patients with primary or chronic HIV infection. Rapid introduction of antiretroviral drug therapy (yellow areas) during the earliest phase of primary infection reduces the initial virus burst (pink line) and allows numbers of HIV-specific T_H1 cells (blue dots) to be maintained, but does not allow a strong HIV-specific $CD8^+$ cytotoxic T cell response (turquoise squares). Discontinuation of drug treatment allows the virus to rebound to levels just below the virus peak. (**A**) The plasma viral load rapidly reaches a steady state below 5000 RNA copies/ml (dashed line) after a single interruption to drug treatment. (**B**) If the intensity of the initial virus rebound is too great, there is a transient decrease in T_H1 cells and drug therapy must be reintroduced. The subsequent reduction in virus restores T_H1 cells to baseline levels. A second interruption in drug therapy results in a weaker viral rebound (with the viral load remaining below 5000 RNA copies/ml), no deleterious effects on T_H1 cells, and stimulation of HIV-specific cytotoxic $CD8^+$ T cells. Eventually, the virus is maintained at low steady-state levels. (**C**) In chronically infected HIV patients, treatment interruption is rapidly followed by a strong rebound in virus, which only weakly and transiently stimulates both T_H1 and $CD8^+$ cytotoxic T cells, even when repeated (*11*). (**D**) Boosting immunity to HIV with vaccines (rather than with the virus itself) before interrupting drug treatment (arrows) may allow the virus to be maintained in a low steady state both in primary and in chronic HIV infection.

of vigorous and poorly controlled virus production after each treatment interruption (*11*). So far, there is no evidence for virus control in chronic HIV infection after structured treatment interruptions. Therefore, any attempts to apply the observations of Walker and co-workers to chronically infected HIV patients should be discouraged until there is conclusive evidence of efficacy.

The encouraging results obtained in patients with a primary HIV infection support the rationale for combining interrupted drug therapy with immunological interventions such as immunization. Indeed, the heavy cost and toxicity of the current drug regimens frequently lead to unsupervised cessation of treatment. To quickly obtain a low, steady-state viral load when treatment is withdrawn, we should ideally restore strong and diverse T_H1 and cytotoxic T cell responses against HIV before, and not after, the virus rebounds. In addition, we should not be content with a deleterious immunogen such as HIV itself; instead, nonpathogenic antigenic formulations (such as those in candidate vaccines) should be administered to patients even though their immunogenicity might still be limited. Several clinical trials, involving about 200 acutely infected and 500 chronically infected patients, are currently combining antiretroviral drug regimens with immunization using various HIV immunogens. The response of these patients to cessation of drug treatment after the completion of therapeutic immunization may provide us with the best large-scale evidence yet that, when given a fighting chance, the immune system can indeed control HIV.

References

1. R. A. Koup *et al., J. Virol.* **68**, 4650 (1994).
2. E. S. Rosenberg *et al., Science* **278**,1447 (1997).
3. M. Dalod *et al., J. Infect. Dis.* **178**, 61 (1998).
4. G. M. Ortiz *et al., J. Clin. Invest.* **104**, R13 (1999).
5. J. Lisziewicz *et al., N. Engl. J. Med.* **340**, 1683 (1999).
6. E. S. Rosenberg *et al., Nature* **407**, 523 (2000).
7. R. H. Lyles *et al., J. Infect. Dis.* **181**, 872 (2000).
8. K. Murali-Krishna *et al., Immunity* **8**, 177 (1998).
9. A. U. Neumann *et al., AIDS* **13**, 677 (1999).
10. L. Ruiz *et al., AIDS* **14**, 397 (2000).
11. G. Carcelain *et al., J. Virol.*, in press.
12. L. Mollet *et al., J. Immunol.* **165**, 1692 (2000).

PERSPECTIVES: EVOLUTION AND SOCIAL SCIENCE

A Tale of Two Selves

Karl Sigmund and Martin A. Nowak

Our urban life-style, with its intensity and bustle, is often compared to life within a colony of social insects. But the similarities are superficial: Most humans working in large teams are not related, whereas insects in a colony are usually very closely related. The recent trend toward globalization, epitomized by a worldwide market and universal communications network, hints at the emergence of a superorganism composed of all members of the human race, but not based on genetic ties.

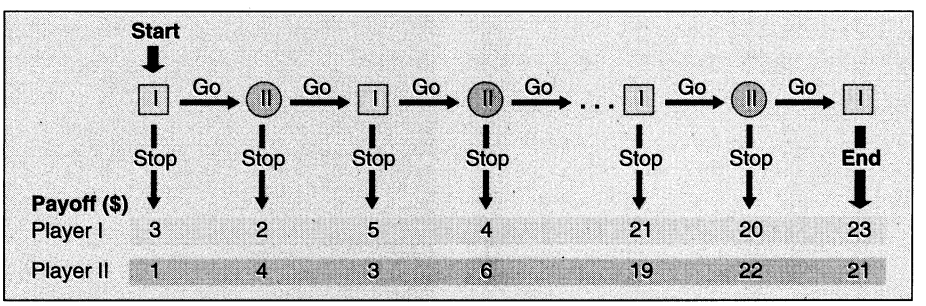
Enhanced online at www.sciencemag.org/cgi/content/full/290/5493/949

Modern human societies, with their economies revolving around stock markets and bond trading, are highly complex, yet theorists interested in the evolution of human cooperation and communication prefer to study the simplest aspects of human society, such as cooperation within a household. This became clear at a meeting held this summer in the picturesque Austrian town of Steyr (*1*). The meeting brought together scientists from two vastly different backgrounds: the evolutionary biologists, including those studying human as well as animal behavior, and the social scientists, including anthropologists and economists.

Interestingly, both of these groups—representative of our two selves—assume that the societies that they study are composed of selfish individuals, and each group has coined its own definition of selfishness. Economists think of the selfish individual as someone who uses rational behavior to achieve personal preferences or goals (*Homo economicus*), whereas biologists view selfishness in terms of selfish genes that when selected maximize their chance of being passed on to the next generation.

The symposium opened with an address by John Maynard Smith (University of Sussex, UK), a founding father of the field of evolutionary biology, who described some of the major transitions in evolution (*2*). He proposed that the emergence of cooperation and communication among our hominid ancestors was but the last (at least so far) evolutionary flourish following in the footsteps of earlier evolutionary leaps in which competing entities joined forces to form a stronger, larger unit upon which natural selection could work—the fates of genes are linked together in chromosomes; ancient bacteria become the building blocks of eukaryotic cells; there is coordination among different cell types in a complex multicellular organism; individuals, be they termites or humans, unite in colonies or societies.

In each of these cases, the individual building blocks have to work toward a common goal rather than for their own immediate benefit, and so the temptation to defect looms large. In fact, societies—whether they be cellular, insect, or human—are composed of would-be mutineers. As David Haig (Harvard University, USA) pointed out when describ-



The centipede game. You and a coplayer are sitting on opposite sides of a table. On your side of the table are two stacks of money, one smaller than the other. You can either STOP the game by taking the larger stack, leaving the smaller one for your coplayer, or GO to the next round by pushing both stacks to your coplayer's side of the table. In this case, the experimenter adds $1 to each stack. It is now the other player who can STOP the game and pocket the larger stack, leaving the smaller one for you, or alternatively GO to the next round by pushing both stacks to your side, in which case each stack increases by $1 again. But the rules require that the stacks cross the middle-line at the most 20 times. At the beginning of the game, one stack contains $3 and the other stack $1. If you and your coplayer opt for GO as long as you can, you will end up with $23 and your coplayer with $21. But, in the last round, your coplayer has two options: to push the stacks toward you or alternatively to pocket the larger stack (which contains $22), leaving you with the smaller stack (only $20). If you suspect that your coplayer will pocket the larger stack in the final round, then you should not push the stacks toward your coplayer in the penultimate round, but rather should take the larger stack for yourself ($21). Arguing backwards, you can quickly see that you should never choose GO, but should choose STOP right away. But this leaves you with only $3! In actual experiments, people rarely adopt this "rational" but counterproductive stance.

K. Sigmund is at the Institut für Mathematik, University of Vienna and International Institute for Applied Systems Analysis, Laxenburg, Austria. M. A. Nowak is at the Institute for Advanced Study, Princeton, NJ 08540, USA. E-mail: karl.sigmund@univie.ac.at and nowak@ias.edu