models will allow the incorporation of more complex sampling and population dynamic scenarios, the data presented in our report did not justify such additional considerations. Similarly, while more sequence data, from this and other loci, will be required before the full evolutionary history of Y chromosomes and of our species can be deciphered, our report was both an attempt to initiate this evolutionary reconstruction and an example of how the absence of variation represents an evolutionary signal in its own right.

Finally, we wish to clarify a point raised by Rogers *et al.* Although the most parsimonious tree that can be derived from our data does in fact place the chimpanzee-human split after the branching off of the gorilla lineage (supported by two characters), we were careful to state, in note 10 of the report, that the next shortest tree describes an unresolved trichotomy. When we calculated an expected mutation rate for this intron (note 11), we assumed such a trichotomy, and used independent estimates of branching times of 5MY for the chimpanzee-human, gorilla-human, and chimpanzee-gorilla splits (14MY for the splitting off of orangutan). We then averaged over all possible pairwise comparisons to obtain a mean mutation rate.

Given the small number of changes taking place along the branches and nodes of this gene tree, our data should not be used in a molecular clock form to estimate the age of the interspecific splits, as was done by Rogers *et al.* If one considers only the numbers of changes, the observed numbers (5, 10, and 11) for the human-chimpanzee, human-gorilla, and chimpanzee-gorilla comparisons, respectively, are not significantly different from the 8, 8, and 8 expected from a trichotomy ($\chi^2 = 2.75$).

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REFERENCES

1. R. L. Dorit, H. Akashi, W. Gilbert, *Science* **268**, 1183 (1995).
2. M. F. Hammer, *Nature* **378**, 376 (1995); L. S. Whitfield, J. E. Sulston, P. N. Goodfellow, *ibid.*, p. 379; S. A. Tishkoff *et al.*, *Science* **271**, 1380 (1996).

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Correlates of Protective Viruses Damaging to HIV Infection

Barton F. Haynes *et al.* (*1*) state correctly that concentrations of human immunodeficiency virus (HIV) are low and of cytotoxic T lymphocytes (CTLs) are high in people who are "nonprogressors." Therefore, they argue, our proposals—that HIV is essentially not a lytic virus and that immunosuppression may be caused by virus-specific $CD8^+$ T cell-mediated immunopathology that destroys infected antigen-presenting and T cells—do not apply. This is an incorrect conclusion drawn from our views, because the example of the nonprogressor with a low HIV load and high CTL response does fit into our balance-scheme between the two extremely rare cases that Haynes *et al.* quote from our proposal (*2*). If efficient CTL killing (plus neutralising antibody) eliminates HIV completely before it can be integrated into many cells, HIV negativity and immunity will result. If high CTL activity (plus antibody) controls infection early and efficiently, long-term nonprogression will result (with potential incubation times of more than 30 years). If the balance is in the middle, the average of 8 to 10 years necessary for development of the disease will result; if the growth of HIV is less, but still somewhat controlled, immunopathology will develop quicker to cause disease. The other extremely unbalanced state occurs when no T cell responses are available, or T cells become exhausted by too wide an infection, which probably is enhanced by the developing immunopression. This latter extreme situation would correspond to a "healthy" hepatitis B virus carrier state. The dynamic balance between virus and immunopathology depends on the discussed various host (human lymphocyte antigen, interferon, and so forth) and virus (escape mutants, susceptibility to interferon, and so forth) parameters; their combination differs from patient to patient, yielding the wide spectrum of disease patterns and disease kinetics. The view that disease is caused by immunopathology—that is, by the damaging effects of the protective immune response—has important implications for therapy and prevnetion. Accordingly, enhancement of an immune response that is beneficial when the HIV load is low, may be damaging and enhance disease when virus has already spread widely. Absence of evidence that HIV is directly lytic in vivo must encourage us to search for evidence, or absence, of an important role of immunopathology in AIDS pathogenesis.

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REFERENCES

1. B. F. Haynes, G. Pantaleo, A. S. Fauci, *Science* **271**, 324 (1996).
2. B. Odermatt, M. Eppler, T. P. Leist, H. Hengartner, R. M. Zinkernagel, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 8252 (1991); R. M. Zinkernagel and H. Hengartner, *Immunol. Today* **15**, 262 (1994).

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Response: The remark in our report (*1*) about CTLs was not meant to imply that the elegant and provocative hypothesis of Zinkernagel and Hengartner (*2*) was invalid. Rather, it was intended to point out that it is difficult to hypothesize that CTLs are either immunopathogenic or protective only on the basis of quantitative differences in the CTL response. For example, if one examines CTL responses in HIV-infected individuals in early stages of the disease, it is not unusual to observe high frequencies of HIV-specific cytotoxicity despite the fact that the vast majority of these individuals will ultimately progress in their disease. Quantitation of the CTL response early in the course of HIV disease does not seem to predict progression of disease. In contrast, qualitative differences in the CTL response as reflected by recognition of variable versus conserved epitopes, and the mobilization of a broader (as opposed to a more restricted) CTL repertoire, may determine whether a CTL response will be pathogenic or protective.

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REFERENCES

1. B. F. Haynes, G. Pantaleo, A. S. Fauci, *Science* **271**, 324 (1996).
2. R. M. Zinkernagel and H. Hengartner, *Immunol. Today* **15**, 262 (1994).

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