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Response: Liu *et al.* point out the inherent difficulties in determining quasispecies diversity, particularly under circumstances where the sample size of target molecules is low. We agree that this might in fact contribute to the discrepancies in the literature regarding the levels of viral diversity in HIV-infected slow versus fast progressors.

As pointed out by Liu *et al.*, the sample size may play a critical role in evaluation of HIV quasispecies diversity. It is conceivable in reports of long-term nonprogressors that

viral diversity was underestimated. Such technical constraints should be kept in mind when results are interpreted concerning patient populations with extremely low viral burdens.

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Gene Therapy Chronology

Eliot Marshall states in his response to Robert J. Levine (Letters, 24 May, p. 1085) that I "told Levine in June 1995 that [I] did not foresee any possibility of a human trial," although this is clearly contradicted by Levine's statement "that the [New York Times] story was premature and exaggerated . . . but that as soon as [Durning] could foresee any possibility of extending [his] work to involve human subjects, [he] would contact [me] promptly."

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Marshall's response also questions the process of the protocol review. To put the chronology straight, the project had only commenced in April, and in June we did not have long-term expression data or sufficient animal safety data to be confident that we could move toward a clinical intervention. A primate study began on 2 November 1995, and by late November, at the time of the protocol submission to Yale, we had clear evidence of the safety and efficacy of gene transfer in rodents and preliminary data on primate safety and therefore felt it appropriate to submit the protocol. As I was leaving Yale to take up a full-time position in New Zealand on 1 January 1996, I spoke to Nelson Wivel, director of the U.S. Recombinant DNA Advisory Committee (RAC), and also to the Food and Drug Administration about the most appropriate process for regulatory review. After my discussions with Wivel, he wrote on 30 October 1995

I indicated to [During] that it would be far better for him to develop the protocol and submit it for review in New Zealand at an appropriate time when that country's guidelines are in place.

In summary . . . the principal investigator has every intention of complying with recombinant DNA guidelines in New Zealand, and there is a clear indication that the safety practices to be employed abroad are to be consistent with the NIH guidelines.

Although this was a Phase 1 study in which the primary outcome measures were safety and tolerability, it was based on a therapeutic rationale, and we had some expectations (although uncertain) that a clinical benefit might result. Both the primary outcome measures and any (bonus)

therapeutic effect would be more readily determined if the disease process had not progressed too far. Moreover, the risks of the surgical intervention would be greater if the disease was more advanced. An ethical decision based on the changing risk-benefit ratio justified an early intervention. The protocol was vigorously reviewed by several scientific and ethical committees before surgery.

Matthew During

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Death in Athens

In Random Samples of 14 June (p: 1591), the item about the Ebola virus and the Plague of Athens contains the statement that "up to 300,000 Athenians—one in every three—were felled during a Spartan siege by a mystery disease. . . ." This would put the total population of ancient Athens at almost 1 million people. Morens and Littman (1) estimate that the total population of Athens at that time was between 250,000 and 300,000. They estimate that the total number of Athenians who died of the "Thucydides syndrome" was some 26% (about one in four) of the total population, or 65,000 to 78,000 people.

Richard Ellis

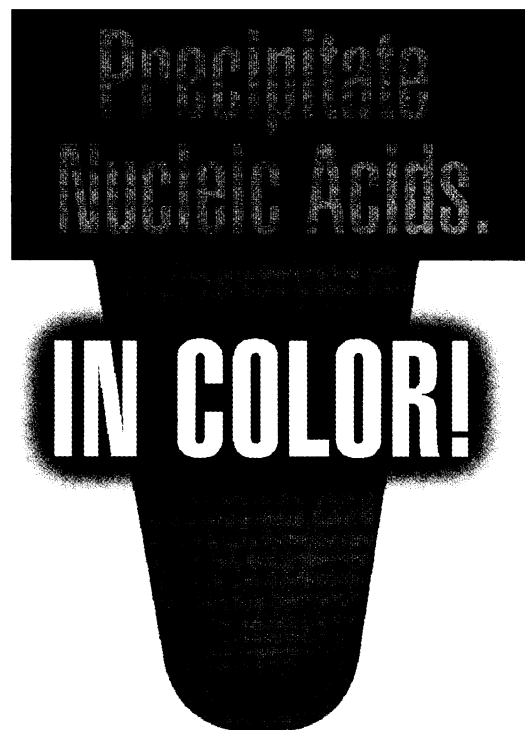
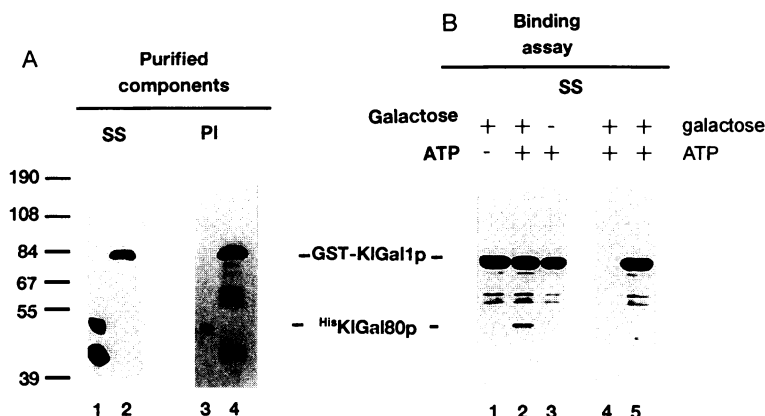
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Corrections and Clarifications

Figure 4 (p. 1664) in the report "Activation of Gal4p by galactose-dependent interaction of galactokinase and Gal80p" by F. T. Zenke *et al.* (14 June, p. 1662) was printed incorrectly. The correct figure appears below.



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