clustered in one of the three exons: the proportion of nucleotide sites that are polymorphic in this exon is three and a half times that in the other exons and between two and four times that in the introns[3]. Thus, Dover would need to postulate that conversion influenced both flanking regions, both introns and two exons, but not the third exon! Hudson *et al.* have a more parsimonious interpretation.

Furthermore, the theoretical foundation for some of Dover's claim is lacking. Dover offers no support at all for his claim that unbiased conversion will decrease the polymorphism at a locus but not affect its rate of divergence. Because unbiased conversion amounts to an additional mechanism of drift, one might expect that it would increase the rate of divergence between species. Until we see a formal model, we will remain unconvinced that unbiased conversion has any effect on intraspecific nucleotide polymorphism beyond that attributable to drift.

Do Dover's 'turnover mechanisms' have any potential at all to explain the *Adh* data? Slippage, unequal crossing over and transposition all generate length mutations. Thus none of them can explain the *Adh* data where aligned nucleotide sequences were used to determine divergence, and length variations were excluded from the measure of polymorphism. These mechanisms have no special significance to tests of this sort. They act simply to increase the mutation rate, and thus cannot increase divergence between species without also increasing polymorphism within species. They cannot generate discrepancies from the neutral model as long as we are careful to count the result of a single mutational event as no more than one change (this is most easily done by excluding length mutations, as Hudson *et al.* did).

Unbiased conversion is just a mechanism of drift, but biased conversion is another matter. It is natural selection at the level of the gene and, like other selective forces, can increase or decrease either polymorphism or divergence, or both. For example, the rate of divergence would be decreased if the currently fixed allele had the ability to convert other alleles. This amounts to the gene being constrained by selection: new alleles are at a disadvantage, polymorphism is reduced, and there is no departure from the neutral model. As we noted[2], departures can arise from the fixation of a new selectively favoured allele, whether it is by biased conversion or selection at the phenotypic level. Here polymorphism is reduced while overall divergence is unaffected.

More relevant to the excess polymorphism of the *Adh* locus is the possibility that a system of balanced, biased conversion among three or more alleles might allow an accumulation of neutral polymorphism on each allele. This possibility is consistent with the conclusion of Hudson *et al.* that the excess variation in one exon of the *Adh* locus suggests a selectively maintained polymorphism in the area. The only viable explanation for the *Adh* data that we can construct from Dover's turnover mechanism is essentially the one proposed by Hudson *et al.*.

What can we conclude about Dover's general point, that we need to consider turnover mechanisms as a force in molecular evolution which is distinct from natural selection and neutral drift? Where they are unique events, slippage, unequal crossing over and transposition are simply mechanisms of mutation. Biased conversion, or any given mutation that occurs repeatedly, is a form of natural selection at the gene level (which may or may not be opposed by selection at higher levels). Unbiased conversion is a mechanism of drift. In short, the effects of turnover mechanisms may be understood within the contexts of natural selection and neutral drift. To the extent that they are special at all, it is only because they provide a means to transfer information between members of a repeated gene family. All mutations may not be equally likely, and they may differ in their forward and backward rates, but these possibilities are already incorporated into existing population-genetics models[4]. We are reminded of Maynard Smith's concluding statement to the book edited by Dover and Flavell[5]: "people have been thinking about evolution for a long time, and . . . some of their conclusions may be worthy of attention."

There is no mysterious third force. The *Adh* data will ultimately be explained with reference to natural selection and neutral drift. We need to determine the relative roles of these two forces, and the test developed by Hudson *et al.*, which was the subject of our original report, goes a considerable way towards that goal.

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Is there a role for herpesvirus in AIDS?

SIR—Latchman[1] has challenged the significance of our original observation[2] on herpes simplex virus (HSV)-induced human immunodeficiency virus (HIV) *trans*-activation[2]. He argues: first that the observed transcriptional activation of HIV is nonspecific, as others have shown that HSV infection can activate heterologous genes; second that the activation is limited to the transfected gene and does not generally apply to endogenous genes, as a transfected, but not an endogenous, beta-globin gene can be *trans*-activated; and third that the system used may not be relevant to the regulation of expression of the proviral HIV genome, because transcription of other viral genes is significantly suppressed by HSV infection.

Although valuable, Latchman's reasoning is incomplete and we would like to add three comments. First, the *trans*-activation of HIV-LTR by HSV infection is specific in that none of the heterologous promoters were activated within the same experiment. Furthermore, in our most recent studies[3], we have localized a 73-base-pair sequence from the HIV-LTR which can confer HSV responsiveness to a heterologous gene that was previously unresponsive to HSV infection. Second, the HIV genome is not an endogenous gene, therefore the differential activation of a transfected gene and endogenous genes is irrelevant for this system. There is no evidence for site-specific retroviral integration in infected cells, and thus the integration of provirus into the cellular chromatin upon either infection or transfection will be a random event. Third, Latchman states that the "studies involving cells latently infected with HIV itself will be necessary to confirm the provocative suggestion of Mosca *et al.*". We have addressed this statement directly by constructing a permanent SW480 colon carcinoma[4] cell line containing HIV proviral DNA. This cell line has a low constitutive level of reverse-transcriptase activity which is augmented 14-fold by HSV-1, 12-fold by transfection with the combination of HSV IE175 (ICP-4) and IE110 (ICP-0) genes, and 13-fold by transfection with the HIV-1 *tatIII* gene. These data indicate that infection with HSV is able to enhance the replication of infectious HIV.

In addition to our results, recent data of Quinn *et al.*[5] suggest that individuals with previous herpesvirus infections are particularly susceptible to either HIV infection or disease progression. Thus, it is becoming increasingly clear that herpesviruses have a role in HIV infection.

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