consequences can flow from this practical choice of means.

Mechanisms of directed variation in general can be expected to be similar to the yeast example. To evolve, such a mechanism must have been used many times in the ancestral lineage of any modern cell, and must still be used frequently enough for selection to be effective against mutation at the loci underlying the mechanism. A directed locus must therefore have been mutated many times, and must still be regularly mutated. A locus subjected to so much change is likely to qualify as heritable soma rather than germ plasm, as any mutation is likely to be 'overwritten' fairly rapidly by directed mutation.

E. coli may be professional mutators, routinely modifying their DNA to switch between metabolic states. The immune systems of vertebrates contain cells that create antibodies using high rates of somatic mutation[3], thus effectively segregating their 'scratchpad DNA' from their germ plasm DNA in a way unavailable to unicellular organisms. It seems likely that whatever mechanism underlies the *E. coli* results of Cairns *et al.*, the cases will be logically parallel, and have the same evolutionary status.

I have suggested elsewhere[4] that the centrosome may contain inherited and potentially immortal information that is not encoded by nucleic acids. If this were true, then the conventional identification of DNA with germ plasm would have to be modified on the dual grounds that not quite all chromosomal DNA is germ plasm, and not quite all germ plasm is DNA.

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SIR—In their article, Cairns *et al.*[1] present results and an interpretation which have already aroused considerable interest and controversy. It is a guiding principle in science that a radical new interpretation (in this case, one invoking the inheritance of acquired characteristics) should only be considered if simpler explanations based on existing knowledge are inadequate. In the same issue, Stahl[2] invites readers to devise their own explanation, and puts forward one of his own. We present here an even simpler possibility for some, but not necessarily all, of the observations of Cairns *et al.*, which is in keeping with current knowledge of the genetics and molecular biology of *E. coli*.

Whereas replication of DNA is known to be highly accurate (in the range of 10^{-9}–10^{-10} errors per base per generation[3]), the accuracy of transcription and translation is far less. Several studies have shown that the error levels are of the order of 10^{-4} for RNA bases during transcription[4] and as high as 10^{-3} random errors per amino-acid residue during translation[5]. From studies on the *lac⁻amber* mutations in the gene for β-galactosidase (one of the genes studied by Cairns *et al.*) it is clear that the mutants still contain measurable residual enzyme activity[4,6] and that some growth in the presence of lactose is to be expected. It should be noted that in this situation the cells which are most error-prone will grow fastest and that any introduction of extra random noise in the pathways of information transfer will increase the probability of mutations from *lac⁻* to *lac⁺* (ref. 7).

The *lac⁻amber* cells attempting to grow in the presence of lactose will be severely limited for energy and biosynthetic substrates. We would argue that such limitations could introduce additional random noise into the information transfer process and, together with the basal error levels, may be responsible for at least some of the effects that Cairns *et al.* discuss. The accuracy of DNA[3], RNA[8] and protein[5] synthesis at any particular site depends on the pool sizes of the correct and related but incorrect substrates and on the availability of energy for repairing wrong insertions. If the relative concentrations of the correct substrate for a particular site in protein or nucleic-acid synthesis are reduced, the error frequency rises. As errors increase a feedback mechanism may be set up and, as described in the general error theory[7], give rise to an increased number of mutations.

As we mentioned, this proposal may not explain all the results reported by Cairns *et al.* but it will account for a significant deviation from the Luria and Delbruck distribution of mutants in a population. To decide how much an error feedback contributes to the appearance of late mutants, one needs much more and more detailed data on the non-randomness of the mutations. Although Cairns *et al.* make non-randomness the central theme of their arguments, it seems fair to say that the data on this is perhaps the least satisfactory part of their presentation. It would seem important to know the relative frequencies of *lac⁺* and *val^R* mutants in their strain. In particular the reversion frequency of *lac⁻amber* can vary greatly with the site of the nonsense codon, which they do not specify. If the nonsense codon is in a part of the enzyme where the nature of the amino acid inserted in its place does not affect activity, mutations in many transferRNAs will give *lac⁺* mutants. Should this lead to a markedly higher frequency of *lac⁺* than *val^R* mutants, one may need to detail the mutant numbers and statistical analysis (not given) to demonstrate non-randomness.

In general, under conditions where the disabled strain will grow but only very poorly, there is first likely to be weak phenotypic suppression and later mutation, but this will not happen when the mutation would not be selected. If this is correct, it will account for observed deviations from Luria and Delbruck expectations. The involvement of errors could be tested by manipulating translational or transcriptional accuracy.

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SIR—The interesting paper by Cairns *et al.*[1] provided presumptive evidence for bacterial mutations occurring adaptively rather than randomly with respect to selection. However, their main evidence, on mutation to lactose fermentation, may have a more conventional interpretation.

The authors assume that there is no natural selection in their cultures. If one relaxes this implausible assumption the expectation of a Poisson distribution of mutant frequencies no longer holds; the direction of change in the expectation is the same as that found.

The most likely source of most of the selection against *Lac⁺* revertants is periodic selection[2]. This refers to positive selection for fitter variants arising in a population. These variants are more likely to arise in bacteria with the majority genotype, with the result that rarer alleles will be eliminated as the fitter variants take over the population.

The data presented by Cairns *et al.* can be explained if *Lac⁺* mutations accumulate at the rate seen in lactose agar for about half a day between the latest wave of periodic selection for a fitter variant and the time of plating on lactose agar. Whether this actually happened or not I do not know, but in this case it still needs to be shown that the apparent unicorn is not a goat after all.

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