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The Evolution of Genetic Intelligence

David S. Thaler

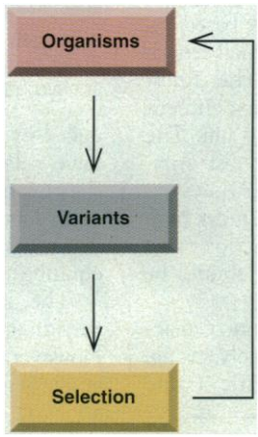
In 1988 Cairns and his colleagues (*1*) published a scientific paper that provoked heated discussion, even among philosophers (*2*). They suggested that mutations arise more frequently when the organism is under selective pressure for that mutation, in apparent contradiction to the conventional idea that mutations arise without regard for their utility. In this proposal, the environment not only selects among preexisting variants, it also interacts with the organism in a sophisticated way to generate the variation on which selection acts. This phenomenon of mutagenesis under selection has been variously called "Cairnsian," "selection-induced," "adaptive," "post-plating," "late-arising," or "selection-promoted" mutation and has been much polemicized. A paper by Harris and co-workers in this week's *Science* (*3*) helps to move beyond the polemic that has obscured our study of the molecular mechanisms that generate variation.

In their classic works, Luria and Delbruck (*4*) and Lederberg and Lederberg (*5*) studied mutation in the context of lethal selection—in which only preexisting mutants have a chance to survive. In contrast, the experiments of Cairns and of others inspired by him are designed to detect the frequencies and types of mutations arising under conditions of nonlethal selection, in which the organism has a chance to react to the selective conditions. These conditions do not kill counterselected cells but prevent an increase in their number (for example, in the paper by Harris and co-workers in this issue, cells mutant for *lacZ*, the gene for the lactose-utilizing enzyme, are plated onto medium with lactose as the only carbon source). The frequencies, timing, and types of mutations arising under selective conditions are then compared with those that occur during nonselective growth.

The most biting criticism directed at the Cairnsian school has been that, under conditions selective for the appearance of scorable mutants, there is enough "normal" growth to account for the mutants, assuming only that selection-induced mutations are created similarly to those of nonselective growth (*6*). This "growth-on-the-plate" argument, however, is not an adequate explanation of the results, because the types of mutations arising under selection seem to be distinct from those that occur during nonselective growth (*7*). For example, transposon excisions are seen only under stressed conditions, and the ratio of recombination to point reversion is different under selection. In addition, distinct sets of genes are required in the two conditions—strong evidence that different pathways of mutagenesis operate during mutation under selection. Cairns and Foster (*8*) found that the DNA recombinase gene *recA* is required for mutagenesis only during selection. Cairns has pointed out that this requirement for *recA* (*9*) indicates that there is a specialized pathway for mutagenesis under selective conditions.

The work by Harris and co-workers in this issue of *Science* (*3*) confirms the necessity for *recA* in selection-promoted mutagenesis and strengthens the conclusion by using a deletion allele of *recA*. They also find that the *recB* recombination gene is required for selection-induced appearance of mutants and that a *recD* null mutation increases mutagenesis only under the selective conditions. (RecD is an inhibitory subunit of the recombination complex.) The $recA^+$ and $recB^+$ alleles are required for the *recD* (null)–stimulated mutation. These requirements for mutation occurring under selection are the same as those for homologous recombination via the wild-type (RecBCD) recombination pathway of *Escherichia coli*. The absence of effect of *recJ* and *recQ* genes implies that an alternative *E. coli* recombination pathway called RecF does not participate in the formation of selection-induced mutants. Because *recA* participates in processes other than recombination, the reported involvement of other RecBCD pathway genes provides important new support for the idea that mechanisms that underlie homologous recombination also underlie mutation during selection.

Numerous models, all of which account for the necessity of the homologous recombination machinery, have been invoked to account for the apparently Lamarkian evolution seen under selective conditions. These proposals include reverse-transcribed mRNA interacting with the host genome (*1*), heteroallelic interactions (*7*) analogous to cassette switching (*10*), immunoglobulin diversity generation (*11*) or heterochromatic interactions (*12*), and gene amplification (*8*, *13*). The "toe-in-the-water" proposal invokes transcripts as replication primers when growth is the consequence of a revertant transcript (*13*). Homologous interactions may be



A conventional view of evolution. The environment functions only at the selection step.

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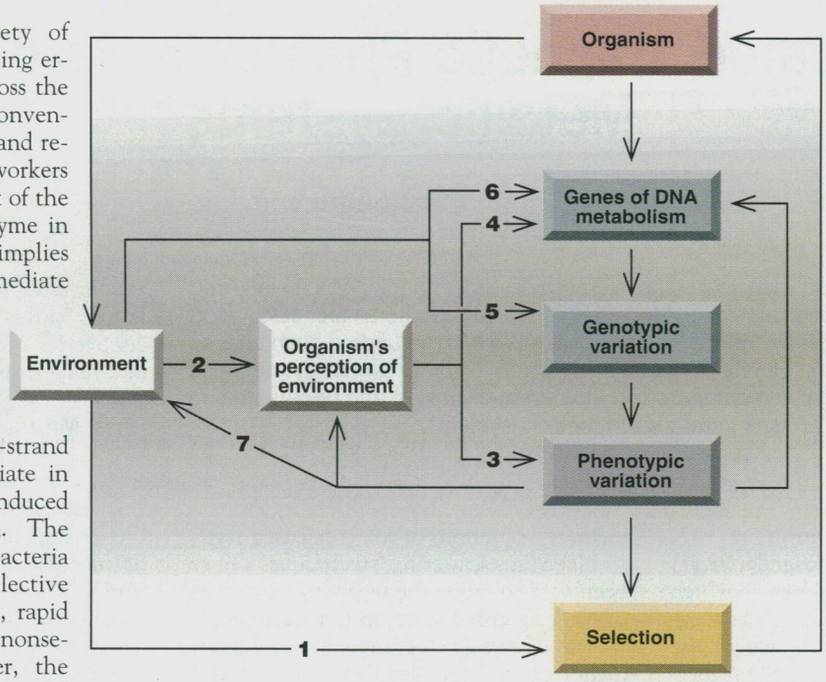
mutagenic through a variety of mechanisms (*14*, *15*), including error-prone gap filling, that cross the conceptual border between conventional concepts of mutation and recombination. Harris and co-workers believe that the involvement of the RecBCD recombination enzyme in selection-induced mutation implies a particular molecular intermediate in selection-induced mutation: Because RecBCD has so far been documented to load onto DNA only at double-strand breaks, the authors suggest that double-strand breaks may be an intermediate in the formation of selection-induced mutations in their system. The growth that occurs when bacteria are living under nonlethal selective conditions is not the robust, rapid doubling that occurs during nonselective growth (*16*). Rather, the cells are in poorly characterized states of stress and starvation. Is this state specialized for the generation of mutations (*17*), perhaps particularly in the genes deficient in the starving bacteria? Along these lines, it would be of interest to know whether starving cells have mutations in genes of DNA metabolism, such as *recD*, that might preadapt cells for mutation under selection.



A more complete view of evolution. The environment functions at three stages. (**1**) The environment is the proximate agent of selection. (**2**) The environment is perceived by the organism. (**3**) Organisms use their perception of the environment to modify their physiology, as in operon induction. (**4**) Organisms use their perception of the environment to modify their genetic metabolism, as in the SOS pathways. (**5**) The environment directly impinges on the DNA via such agents as radiation and chemical mutagens. (**6**) The environment interacts with DNA via the genes of DNA metabolism. (**7**) The organism modifies environmental interaction with the genome as in metabolic activation or detoxification.

In bacteria, the prototype for differentiated states specialized for genetic change is the DNA damage repair response, SOS (*18*), in which changes occur that help not only to repair damaged DNA but also to increase the mutation rate of undamaged DNA. SOS not only enhances the absolute rate of genetic change, it also alters the spectrum of the resulting mutations. Similarly, phage mu is induced from the lysogenic state under conditions of nutritional, and perhaps other, stress. This system offers a means to understand stressed states that are differentiated for genetic change (*19*–*21*).

Related phenomena may in fact be widespread. Thus, there may be many differentiated states analogous to SOS that are induced by stressors and serve to accelerate and specify genetic change (*14*, *22*, *23*). In yeast, meiosis is induced by starvation (*24*). Cancer cells, which are predisposed to change rapidly, may be in a regulated state of high mutation. Sequential clonal selection in oncogenesis (*25*) could select for alterations in DNA metabolism and perhaps other changes analogous to those in starving bacteria (*26*).

The generation of genetic variation is in large part controlled by the genes and physiology of DNA metabolism. The environment interacts with DNA metabolism through a variety of routes (see figure), and therefore the components exist for feedback between the generators of genetic diversity and the environment that selects among variants. The efficacy of such a feedback loop could be tested and refined through many cycles of selection. Particular genes of DNA metabolism will be selected because they will often be coinherited with other alleles that they played a role in generating. Transcriptional focusing (*27*), in which actively transcribed genes are mutated more frequently than silent genes, could allow regulation of genetic change to be as tightly coupled to the organism's perception of its environment as is gene expression.

Mutation rate is sometimes portrayed as a tradeoff between fidelity, economy, and the occasional need to generate variation. Locus-specific variation, particularly if sensitive to the environment, offers a way out of this tradeoff (*28*). Natural selection acts beyond particular alleles. It also favors genetic metabolism that generates alleles with a high probability of passing the tests of environmental selection. If environmental influences affecting the generation of variation can become coherent with those affecting subsequent selection, then the conditions are ripe for the evolutionary bootstrapping of genetic intelligence (see figure) (*29*, *30*).

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