10. 137 (1963)]. Analysis of variance was used to compare neuronal responses for each trial type within the cue and delay conditions. The source of significant variance was then determined by the Tukey HSD test. All delay-related and stimulus-specific neuronal responses were based on significant comparisons. Care of the monkeys was in accordance with the Yale University Animal Care Committee.

8. On PDR trials, neuron 787 responded during the delay period (26 spikes per second) after a pattern that required a rightward saccade and was significantly less responsive (12.5 spikes per second) after the other pattern, and after spatial cues (11 and 10 spikes per second) on SDR trials. Spontaneous activity was 8.4 spikes per second.

9. The delay period activity of neuron 627 on SDR trials was 13.5 spikes per second after spatial cues requiring saccades (13° to the right, significantly greater than the delay activity (2.9 spikes per second) for leftward-going saccades, and the delay activity (4.2 and 0.9 spikes per second) on PDR trials. Spontaneous activity was 1.9 spikes per second.

10. The picture fixation task required the monkey to fixate while stimuli (subtending 10°) were presented in foveal vision for 1 s, and juice was delivered 0.5 s after stimulus offset; directional saccades were not required. This task utilized a library of 280 stimuli, grouped into 40 sets of seven images (five objects, one color field, and one face). The stimuli were digitized photographs of laboratory objects; each color field was of uniform hue, generated by mixing red-green-blue values with graphics software.

11. Neuron 787: a total of 30 objects was presented (294 trials), of which 22 elicited a response (range, 37.6 to 14.3 spikes per second, mean, 24 spikes per second; spontaneous activity, 8.4 spikes per second); the other 8 objects failed to elicit any change in firing rate. The neuron (Figs. 1B and 2A) was unresponsive on SDR trials (80 trials) when the monkey had to remember and respond to the locations of 8 spatial cues; the average response to these 8 cues was 6.1 spikes per second.


13. The responses of neuron 566 to faces ranged from 99 to 30.6 (mean, 64) spikes per second for 12 face stimuli presented, significantly greater than the responses to 14 objects ranging from 23 to 6.2 (mean, 16.4) spikes per second; data were obtained on 240 trials of the picture task. The neuron was unresponsive (mean, 11.8 spikes per second) in the eight-location SDR task (80 trials). Spontaneous activity was 16.2 spikes per second.

14. Neuron 532 fired during the delay period over which the monkey was required to remember one particular face (11.8 spikes per second), a response significantly greater than the responses to another face (5.9 spikes per second) and to the two patterns (6.1 and 5.9 spikes per second). Spontaneous activity was 5.3 spikes per second.


19. Stimulus-selective neuronal activity in the inferior convexity did not depend on directional eye movements, but we have recorded dorso-lateral prefrontal neurons with conditional responses to foveal stimuli when the stimuli required a specific movement in the PDR task.


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**TECHNICAL COMMENTS**

**Unusual Mutational Mechanisms and Evolution**

R. E. Lenski and J. E. Mittler argue that studies purporting to demonstrate directed mutation lack certain controls and do not account adequately for population dynamics (1). In addition, none of the novel, even unorthodox, mechanisms invoked to explain the directed mutation hypothesis is supported by secure evidence, and some of the ideas have proved untenable (1-5). In concluding that no evidence has been presented to deny the classical tenet that mutation and selection are independent, Lenski and Mittler point out that mutation rates may vary both between and within genomes, and they raise the possibility that variable mutation rates may be an evolved response that specifically promotes increased genetic variation under stress. We lean favorably toward this suggestion and wish to expand the proposition with reference to the evolution of genetic mechanisms.

Central to the directed mutation debate is a means of explaining the increased frequency of altered phenotypes, which those who support the hypothesis have said arises "specifically when (and even because) it is advantageous" (1). We suggest that an increase in the frequency of altered phenotypes could occur as the result of an increase in the frequency of gene expression mediated by two classical mechanisms, namely, alterations in DNA sequence and alterations in DNA topology. Mechanisms facilitating alterations in the frequency of gene expression include reiterative oligonucleotide sequence motifs, which introduce frameshifts and affect translation (6); homopolymeric tracts, which, because of the likelihood of insertions or deletions occurring within regions of reiterated bases, affect transcription (7); and differential inhibition of site-specific methylation, which induces extrinsic alterations in DNA conformation (8). These are but a few examples, possibly the tip of the iceberg, of documented mechanisms with potential for mediating high-frequency changes in DNA sequence, or DNA confirmation. We wish to emphasize that, in addition to being compatible with neo-Darwinian theory, these mechanisms contribute an intrinsically stochastic component to the regulation of gene expression, the potential outcome of which is polymorphism, that is, population heterogeneity. Far from being directed, such phenotypic variations arise from mechanisms that are blind.

In an in-press article we have placed considerable emphasis on the potential importance of polymorphism within bacterial populations generated through genetically based stochastic mechanisms (9). We also outlined evidence suggesting a role for stress in regulation of the frequency of altered gene expression.

Mechanisms capable of generating random variation might provide a satisfying solution to the problem of responding to unpredictable environmental change. It is likely that evolution has favored a balance between biological memory (as stored within a sequence of nucleotides) and probabilistic mechanisms ("contingency behavior") that enables an optimal response to situations that cannot be anticipated.

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3. F. W. Stahl, ibid., p. 112.

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The article by Lenski and Mittler (1) prompted us to reevaluate our data about the conjugal transposable element Tn916 (2). Our data suggest that control of
Unusual mutational mechanisms and evolution

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