Histone deletion mutants challenge the molecular clock hypothesis,"

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Michael J. Behe, "Histone deletion mutants challenge the molecular clock hypothesis," *Trends in Biochemical Science* 15: 374-376, October 1990.

Early in the development of the molecular clock hypothesis, it was discovered that not all proteins "ticked" at the same rate. When compared across a range of species, the fibrinopeptides, for instance, were much "faster clocks" (i.e., having a higher rate of amino acid substitution) than the very conservative, "slowly ticking" histones. These differences, writes Michael Behe (Chemistry, Lehigh University),

> required a modification to the clock hypothesis: the postulate of functional constraints. Thus, for example, histone H4 would diverge less rapidly than fibrinopeptides if a larger percentage of H4 amino acid residues were critical for the function of the molecule. (p. 374)

The problem with the notion of functional constraint, Behe argues, is an absence of experimental support:

> Although plausible, it has long been realized that no direct experimental evidence has been obtained 'showing rigorously that histone function is especially senstive to amino acid substitution or that fibrinopeptide function is especially insensitive to amino acid substitution.' (p. 374)

"Recent experiments," writes Behe, "now indicate that the key assumption of

functional constraints may not be valid."

Since the histones are so highly conserved — "the H4 sequence of the green pea differs from that of mammals by only two conservative substitutions in 102 residues" — one might expect that "few, if any, substitutions could be tolerated in the H4 sequence" (p. 374). However, experiments (reported in detail by Behe) have shown that large parts of the histone molecule may be deleted without significantly affecting the viability of the organism (in this instance, yeast) — results which, Behe argues, should trouble defenders of the molecular clock hypothesis:

> *[The experimental] results pose a profound dilemma for the molecular clock hypothesis: although the theory needs the postulate of functional constraints to explain the different degrees of divergence in different protein classes, how can one speak of 'functional constraints' in histones when large portions of H2A, H2B and H4 are dispensable for yeast viability? And if functional constraints do not govern the accumulation of mutations in histones, how can they be invoked with any confidence for other proteins? (p. 375)*

The resolution of the dilemma, Behe contends, must "as far as possible be grounded in quantitative, reproducible experiments, rather than in simple correlations with time that are its current basis" (p. 375). Otherwise, he concludes:

> *[T]he time-sequence correlation may end up as a curiosity, like the tracking of stock market prices with hemline heights, where correlation does not imply a causal relationship.*