King J L & Jukes T H. Non-Darwinian evolution. *Science* 164:788-98, 1969.
[Donner Laboratory and Space Sciences Laboratory, Univ. California, Berkeley, CA]

Most evolutionary change at the DNA level is driven by mutation and drift, natural selection serving mainly to retard rates by screening out harmful changes. Total DNA and the most rapidly evolving proteins change at a rate ten times greater than average proteins; thus at least 90 percent of mutations resulting in amino acid changes are eliminated by natural selection. Genes and portions of genes most important to function are evolutionarily conserved. [The *SCI*® indicates that this paper has been cited in over 510 publications since 1969.]

Jack L. King
Department of Biology
University of California
Santa Barbara, CA 93106

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"Tom Jukes came to me for help with the idea, which he had mentioned in his 1966 book, that most of the changes that have occurred in evolution at the level of protein sequences might be meaningless noise rather than adaptive change.[1] I found it easy to calculate that the rate of neutral evolutionary change per species per generation should be equal to the rate of selectively neutral mutations per gamete, regardless of population size.

"Before we had finished our manuscript, Motoo Kimura published the same idea in *Nature*.[2] His paper was much shorter than ours but mathematically much more sophisticated. For instance, he showed that selective neutrality did not have to be absolute; any gene with an advantage or disadvantage less than the reciprocal of the population size would be effectively neutral.

"We decided to go ahead. We buttressed the idea with observations, data, and testable predictions. For example, we predicted that in mammals, synonymous third-position changes in codons, and DNA changes in noncoding regions, would turn out to be about ten times more common than changes in other codon positions (and so

they are). We estimated that the human genome contained about 40,000 genes, with structural genes accounting for only about one percent of DNA. I held out for the provocative title, which indeed managed to provoke everyone. We were able to cite Kimura in our revision, and began what was to be a lengthy period of friendly and productive exchanges.

"*Science* rejected our manuscript. One referee said that we had merely set up and demolished a straw man and that the idea was obviously true and therefore trivial. The other said the idea was obviously false. We appealed; meanwhile our colleague, Jim Crow, was able to present most of our findings to the 1968 Genetics Congress.

"*Science*'s next set of referees recommended publication. Even so, one referee objected to our suggesting that most allozyme polymorphisms were also probably neutral, so that passage had to be deleted.

"'Non-Darwinian evolution' inflamed evolutionary biologists to action: most of the citations are reports of experiments that optimistically purported to have proved King and Jukes wrong at last. Selectionists felt that natural populations had enormous amounts of phenotypic variation of adaptive significance, due to polymorphism; neutralists felt that patterns of molecular change indicated neutrality. Both sides assumed that selectively neutral genes would not be expressed in the phenotype, and that adaptive change was due to a different class of genes—beneficial alleles—which were directly affected by natural selection. The controversy continued unresolved for a decade, apparently because both sides were essentially correct in the matters they were arguing about while both were mistaken in the ideas they held in common. Eventually, Kimura himself showed that the genes that determine polygenic variation may often, under stabilizing selection, have such small individual net advantages or disadvantages as to be effectively neutral.[3] Such genes determine phenotypic variation, and may bring about adaptation, by their massed effects, while their individual fates are subject only to mutation and drift. The neutral theory is now part of the accepted framework of evolutionary genetics."

[Jack L. King died on June 29, 1983.]

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1. Jukes T H. *Molecules and evolution.* New York: Columbia University Press, 1966. p. 9.
2. Kimura M. Evolutionary rate at the molecular level. *Nature* 217:624-6, 1968.
   [The *SCI* indicates that this paper has been cited in over 400 publications since 1968.]
3. ————. Possibility of extensive neutral evolution under stabilizing selection, with special reference to nonrandom usage of synonymous codons. *Proc. Nat. Acad. Sci. US* 78:5773-7, 1981.