## SYMPOSIUM ON VARIATION—VIII***

# NEW TRENDS IN THE MOLECULAR BASIS FOR VARIATION

KEVIN L. ANDERSON*

**Received 2 October 1990; Revised 26 December 1990**

**Abstract**

*All biological variation is a result of the genetic information contained on the chromosome of the cell. For evolutionary change (horizontal change) to occur, there must be a change in this genetic information. The discovery of introns and exons on the chromosome of "higher" eukaryotic cells has suggested these cells may contain far more genetic information than previously realized. Despite evolutionary suggestions that introns allow for greater variation that ultimately leads to evolutionary change, the cell is actually less capable of undergoing such a change. The potential ramifications for evolutionary change are devastating.*

### Introduction

The evolutionary model requires that biological variation be an ongoing, accumulative process leading to the formation of new phyla. However, despite pressures claimed to be exerted by "natural selection," any variation that occurs within the organism must originate from the genetic information contained on the cell's DNA. For evolutionary change ("macroevolution") to occur, there must be a change in the information content of that DNA, a mutation. While this has been known for years, it still seems to be "down played" in discussions regarding biological change. In part, this reflects a general lack of understanding of molecular biology, but it also reflects the realization that molecular biology is not responsive to a "vital force," that it is deaf to the call of natural selection. Regardless of whether the mechanism is an accumulation of hidden "neutral" mutations, the sudden appearance of massive mutations, or the gradual effects of minor mutations, the workings of the DNA molecule are governed strictly by chemical laws. These laws dictate that all mutations of the DNA sequence are a result of completely blind and random chemistry.

Mutations, therefore, are random, and their subsequent effect is random. Even simple statistical calculations reveal that random shuffling is a poor problem solver. There is little credibility given to the view that random mistakes in a computer program will eventually produce a more sophisticated algorithm. At a Wistar symposium? [5] Eden (1967) and Schutzenberger (1967) attempted to explain that random mechanisms will not produce the type of "upward" genetic change demanded by evolution. This view was met with great resistance, especially from those more interested in viewing evolutionary change as a natural force than a molecular alteration of the chromosome. As our understanding of the molecular biology of cells increases, we are presented with even more staggering complexity than was realized just a few years ago. Understanding these molecular processes points clearly to the inability of the cell to undergo evolutionary change.

*Kevin L. Anderson, Ph.D., 3313 York Drive, Champaign, IL 61821.

**Editor's Note: For detailed reviews of this symposium see Armstrong, H. 1968. Article review. *CRSQ* 5:35-37 and Williams, E. L. 1968. Book review. *CRSQ* 5:123-126.

***Parts I-VII are in *CRSQ* 27:144-153; 28:18-27.

### The Central Dogma

It is well established that the genetic information in a cell is contained in the chromosome. The chromosome is comprised of deoxyribonucleic acid (DNA), which is a polymer of nucleotide molecules. The sequence in which these nucleotides are linked dictates the type of genetic information carried by the DNA, which determines the genetic characteristics of the cell. Francis Crick (1958) proposed a pathway for the flow of genetic information that he referred to as the central dogma (Figure 1). He concluded that DNA served as a template for RNA formation. The RNA then dictated the sequence of amino acids within a protein.


**Figure 1. The central dogma as described by Frances Crick. The arrows indicate the flow of genetic information. The DNA molecule serves as a template for its own replication. The DNA molecule also serves as the template for RNA formation. It is now known that the DNA is subdivided into smaller units termed genes, the translation of which results in a mRNA molecule that encodes a protein. There is now evidence that RNA may serve as a template for DNA of complementary sequence, so the arrow may not be unidirectional.**

Proteins act as "workers" inside the cell, constructing and dismantling, transporting and communicating—activities that give the cell its specific functions and characteristics. Thus, the DNA sequence controls the types of proteins made in the cell, causing the cells of a human to differ from that of a frog. Therefore, biological change (such as the frog becoming a human) must involve a mutational alteration of the DNA sequence, thereby providing the cell with a new store of genetic information. This new genetic information enables the cell to possess functions it did not previously possess.

### Exons and Introns

The genome of the eukaryotic cell is more complex than that of the prokaryotes, and much more complex than once thought. Gradually researchers have come to realize that much of the DNA of "higher" eukaryotes is never translated into proteins. Use of recombinant DNA methodology revealed only 5% of the *Drosophila* and less than 2% of the human genome code for proteins. Also, in complex eukaryotes, few genes are

a continuous sequence of nucleotides. Instead, the genes are interrupted by DNA sequences that are not themselves translated. These noncoding sequences are called introns (intervening DNA), and sequences that are translated to form a protein are called exons (i.e., they are expressed).

All exons and introns that occur between the start codon and stop codon of the gene are transcribed into precursor-messenger RNA (pre-mRNA). This results in the pre-mRNA containing more sequences than will ultimately be translated into a protein. The number and size of introns varies with each gene. For example, the chicken collagen gene contains over 50 introns (Wozney, et al., 1981) and the gene for chicken ovalbumin contains about three times as much introns as exons (Chambon, 1981). Before the pre-mRNA leaves the nucleus of the cell however, these introns are removed and the exons are spliced together to form mature mRNA (Figure 2). The mature mRNA is then translated into a protein. The arrangement in which these introns are spliced together determines the sequence of the gene, thus the amino acid composition of the protein. This directly determines the nature and function of the protein.

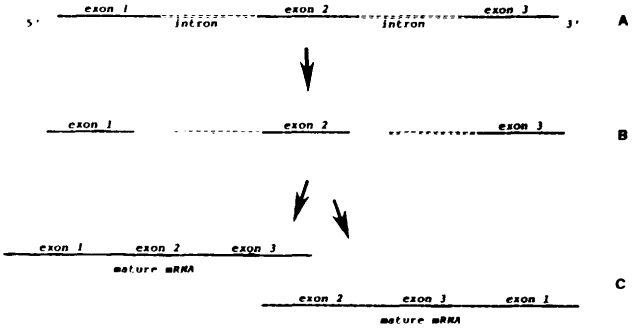


**Figure 2. Schematic of a eukaryotic pre-mRNA molecule (A) with intermittent introns and exons. Introns are first separated at the 5' end of the RNA (B) and then completely removed. They are then degraded, or perhaps function in coordinating activation and inactivation of other genes. Exons are then spliced together to give mature mRNA (C). The exons may splice in any combination (exactly what governs this combination is not clear). The mature mRNA is then translated into a protein. The type of protein formed depends upon the sequence in which the exons are spliced together.**

Originally it was thought that, even if the mRNA contained multiple start and stop codons, nothing beyond the first stop codon was translated because it automatically caused the ribosome to detach from the mRNA. This meant that one gene corresponded to a single RNA transcript that carried information for a single protein. However, the discovery of introns and exons has changed this perception. Most intron sequences do not appear to contain any specific function, but the existence of the splicing mechanism associated with introns apparently provides extra genetic flexibility for the cell. This flexibility is possible because different mRNA splicing patterns can generate a number of different proteins from the same RNA transcript. Thus, the same DNA sequence can code for several different proteins. For example, pattern changes of some transcripts have been found to occur during cell differentiation, thus the same DNA sequences code for different proteins (Andreadis, et al., 1987). How the variable recessing of identical RNA transcripts is controlled is not yet known.

The net result of RNA splicing is that it greatly expands the total number of genes in the cell. Thus, the DNA in a "higher" eukaryotic cell may contain far more information than once considered possible. This is illustrated by the *b* -globin gene of the mouse, rabbit, and human. The exons of this gene contain a very similar DNA sequence, but the introns vary in both length and sequence (Alberts, et al., 1983). Thus, the vast difference of the *b* -globin protein made by these three species appears to be a direct function of introns. While the exact significance of introns is still not clear, most evolutionists have attempted to "wave off" this new twist to cellular genetics. The general view is that such expanded genetic information allows for greater variation, and, as such, becomes a mechanism by which the cell can accelerate its evolutionary development. However, the potential ramifications for evolutionary change are devastating. Increasing the total genetic information of the chromosome also increases the total number of possible deleterious mutations. As Denton (1986) explains:

> If it turns out over the next few years that this [RNA splicing is being used to achieve a vast expansion in the total number of genes in the higher organisms, then it could well be that the total number of unique adaptive traits in, say, mammalian genomes is in the order of $10^{13}$ ($10^{10}$ genes, each containing $10^{3}$ significant bits of information). Which could pose what would seem to be an almost insurmountable 'numbers problem' for Darwinian theory—a problem of such dimension that it would render all other anti-Darwinian arguments superfluous (p. 332).

## References

Alberts, B., D. Bray, J. Lewis, M. Raff, K. Roberts and J. Watson. 1983. Molecular biology of the cell. Garland Publishers. New York.

Andreadis, A., M. E. Gallego and B. Nadal-Ginard. 1987. Generation of protein isoform diversity by alternative splicing: mechanistic and biological implications. *Annual Review of Cell Biology* 3:207-42.

Chambon, P. 1981. Split genes. *Scientific American* 244(5):60-71.

Crick, F. 1958. On protein synthesis. *Symposium of the Society of Experimental Biology* 12:548-55.

Denton, M. 1986. Evolution: a theory in crisis. Adler and Adler. Bethesda, MD.

Eden, M. 1967. Inadequacies of Neo-Darwinian evolution as a scientific theory in P. S. Moorhead and M. M. Kaplan (editors). Mathematical challenges to the neo-Darwinian interpretation of evolution. The Wistar Institute Symposium Monograph No. 5. The Wistar Institute Press. Philadelphia. pp. 5-19; 109-11.

Schutzenberger, M. P. 1967. Algorithms and the Neo-Darwinian theory of evolution in P. S. Moorhead and M. M. Kaplan (editors). Mathematical challenges to the neo-Darwinian interpretation of evolution. The Wistar Institute Symposium Monograph No. 5. The Wistar Institute Press. Philadelphia. pp. 73-80; 121.

Wozney, J., D. Hanahon, V. Tate, H. Doedtkes and P. Doty. 1981. Structure of the pro alpha (2) (I) collagen gene. *Nature* 294: 129-35.

## QUOTE

. . . one might say that the frailty of natural selection seems to be regarded as a *trade secret.*

Book review of *Ever Since Darwin: Reflections on Natural History* by Stephen J. Gould. 1978. *Systematic Zoology* 27:26.