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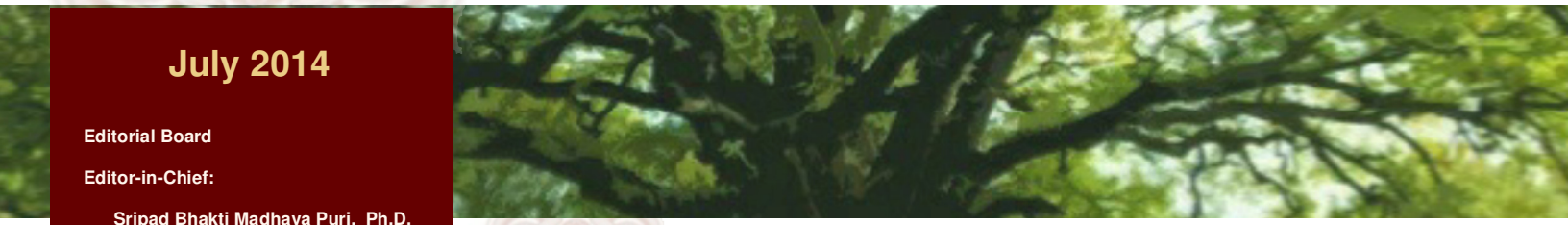

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Genetics, Epigenetics, Paragenetics Getting Closer to Life

Bhakti Madhava Puri, Ph.D.

Genetics

Gregor Mendel (1822-1884) was the first to explain that certain 'traits' were inherited in plants from one generation to the next. These would later become known as genes. Frederich Miescher in 1869 analyzed a substance from the nucleus of cells, which he therefore called nuclein. Further study of nuclein revealed that it contained elements like hydrogen, oxygen, nitrogen and phosphorous, with a specific ratio of nitrogen to phosphorous. Then in 1878 Albrecht Kossel determined that nuclein contained nucleic acid, from which he isolated five nucleobases (nitrogen compounds now referred to by the letters C, G, A, T, U representing cytosine, guanine, adenine, thymine, and uracil). It was also discovered that ribose, a sugar was present in the nuclein compound. What Miescher had isolated from the cell nucleus was actually what would latter be identified as DNA (Deoxy-ribo-Nucleic-Acid).

In 1888 the term chromosome was first suggested by von Waldeyer (1836-1921) to describe the carriers of these traits located in the nuclein. The name refers to the way they were identified using dyes, combining the Greek words chrome (color) and soma (body). Then in 1909 Wilhelm Johannsen coined the term 'gene' to refer to these traits. He also distinguished what he called the genotype to describe the genetic constitution of an organism, and the phenotype to describe the rest of the organism. Phoebus Levene in 1919 identified the nucleobase, sugar and phosphate that made up a unit called a nucleotide, which later X-ray diffraction patterns showed were regularly occurring in the strand of DNA.

Linus Pauling (1901 – 1994) proposed that the DNA structure was a triple helix in 1952, but this proved to be electrostatically unstable. The next year in 1953, James Watson (1928 - present) and Francis Crick (1916 – 2004) made their case for a double stranded DNA, following the discovery of Rosalind Franklin (1920 -1958). This is the model we use today.

While this chemical and structural analysis of genes proved to be of great importance in the study of the constituents of organisms, it missed the even more important role played by the living condition from which they were abstracted. The attempt to interpret only the molecular constituents of an organism, and the

chemical reactions associated with them is insufficient for describing the living or *in vivo* activity that actually occurs in a thriving organism. Take away the life of an organism and all the chemical reactions that were systematically occurring stop, despite all the same chemicals being present. In other words, it is not just a matter of chemical reactions producing life.

The hypothetical DNA theory, established by the historical study of DNA isolated and crystallized from an organism's nucleus, only gives us a chemical picture of what is going on in an organism. The actuality of the living organism's functionality is vastly underdetermined by such chemical descriptions. In order to determine how genes are functioning in their living environment, selected mutations by x-radiation or other means is used to establish what a particular gene is doing or not doing. The conception of genes established by this type of investigation was summarized in a paper by L. J.. Stadler in 1954, in which he gave what is appropriately called the operational definition of a gene [1].

Stadler writes:

> [O]perationally, the gene can be defined only as the smallest segment of the gene-string that can be shown to be consistently associated with the occurrence of a specific genetic effect.
>
> (1) It cannot be defined as a single molecule, because we have no experimental operations that can be applied in actual cases to determine whether or not a given gene is a single molecule"; (2) "it cannot be defined as an indivisible unit, because, although our definition provides that we will recognize as separate genes any determiners actually separated by crossing over or translocation, there is no experimental operation that can prove that further separation is impossible"; and (3) for similar reasons, it cannot be defined as the unit of reproduction or the unit of action of the gene-string, nor can it be shown to be delimited from neighboring genes by definite boundaries.
>
> The operational definition merely represents the properties of the actual gene, so far as they may be established from experimental evidence by present methods. The inferences from this evidence provide a tentative model of the hypothetical gene, a model that will be somewhat different in the minds of different students of the problem and will be further modified in the light of further investigation.

Further investigation came with the molecular structure of DNA being established along with a host of other discoveries brought about by molecular biologists. The complexities of the basic function of protein formation so vital to a cell was as much increased by such analysis, as simplified or made clearer for understanding. There are billions and trillions of atoms in a cell, all working together to keep it alive. Such a well organized system is not maintained by chemical reactions alone. R. A. Jorgenson writes [2]:

> "In modern terms, knowing the complete sequence of a chromosome does not allow us to precisely determine all of the many interdependent elements of a gene, including all those elements in *cis* that are necessary for the normal operation of a given gene that is associated with a specific genetic effect."

Epigenetics – between genotype and phenotype

C. H. Waddington (1905 - 1975) first proposed the term "epigenetics" in 1942 to describe the region between the gene and the whole organism (phenotype) [3]. Today, what is called the epigenome refers to all the chromosomal modifications, DNA modifications, chromatin protein modifications and their complexes. It is the epigenome that determines both the expression of the genes and their inheritance. R. A. Jorgenson reports [4], "Many of these modifications appear to be "programmable" and to be "read out" to

influence chromosomal functions." Nobel laureate Barbara McClintock stated this revolutionary proposal more clearly in her Nobel lecture [5], "to determine the extent of knowledge the cell has of itself, and how it utilizes this knowledge in a 'thoughtful' manner when challenged."

	Chromatin	Chromosome
Definition	In the nucleus, the DNA double helix is packaged by special proteins (histones) to form a complex called chromatin. The chromatin undergoes further condensation to form the chromosome.	A compact structure of nucleic acids and protein found in the nucleus of most living cells, carrying genetic information in the form of genes.
Structure	Composed of nucleosomes-a complex of DNA and proteins (called histones). Represent DNA folded on nucleoproteins by a magnitude of 50. The chromatin fiber is app. 10 nm in diameter.	Chromosomes are condensed Chromatin Fibers. They are a higher order of DNA organization, where DNA is condensed at least by 10,000 times onto itself.
Appearance	Chromatin Fibers are Long and thin. They are uncoiled structures found inside the nucleus.	Chromosomes are compact, thick and ribbon-like. These are coiled structures seen prominently during cell division.
Pairs	Chromatin is unpaired.	Chromosome is paired.
Metabolic activity	Permissive to DNA replication, RNA synthesis (transcription) and recombination events.	Refractory to these processes.
Presence	Found throughout the cell cycle.	Distinctly visible during cell division (metaphase, anaphase) as highly condensed structures upto several thousand nm.
Visualization	Electron microscope (beads on string appearance)	Light microscope (classic four-arm structure when duplicated)

The difference between chromatin and chromosome. [6]

Paragenetics

In 1960 R. A. Brinks suggested that chromosomes possess a paragenetic function in addition to their genetic function [7]. The physical nature of the paragenetic function is characterized by the variety of forms or states of chromatin that can reside at any genetic locus. While the genetic function is stable, the paragenetic function is labile and programmable in ontogeny. It is this latter function that allows organisms to transfer informational macromolecules (RNA and proteins) in a systematic and regulated manner over what is known as the "RNA information superhighway." Given this capacity, organisms may be able to store information at numerous genetic loci in the form of paragenetic chromatin states, which can be reprogrammed during ontogeny or environmental stress [8]. This reprogrammable system could operate over the whole organism as a storage device, allowing it to make informed 'decisions' during growth and development, or in response to the environment. Such processing capacity could be considered a form of 'intelligence,' which also could be passed on to future generations.

The study of the flow of information within and between cells and organisms represents the cutting edge of modern biological research. While physical correlates of cognitive behavior in living organisms are being discovered, it does not spell reduction to such correlates. The electronic activity within the physical components of a radio, for example, may be minutely determined, but ultimately it is not merely the electrical activity that produces the intelligent speech that is heard. Only the intelligent person whose voice is being broadcast through the radio can explain that. Without the broadcaster, the radio would sit silently even though fully functional. An organism without its living agency also appears to be devoid of metabolic activity although all the chemical components are fully present.

How to connect life to matter will be the ultimate challenge that has to be met. This will prove to be a philosophical problem we hope to address in the near future.

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