https://doi.org/10.29321/MAJ.10.A04084

Evolution in the Concept of "Gene" and its Structure-A Review *

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The shape of our knowledge regarding certain aspects of life is being changed to-day as it was changed in the past by the work of Mendel, Darwin and Pasteur.' This is a situation not merely in Biology, but in Physics and Chemistry and other branches of knowledge as well. Starting with Mendel the concept of the gene has undergone evolution comparable to the concept of atom in physics and chemistry with many transformations, contradictions, paradoxes and reconstructions. But most geneticists have, however, been so far content to employ the gene concept as perhaps the last member of the series, organism-cell-nucleus-chromosome-gene and mainly as a useful tool in research and to define it, if at all, in terms of its effects (19). The concept of atom also was long employed by physicists and chemists with conspicuous success when far less was known about its actual nature than is known today. Formerly, the deepest properties of life were interpreted on biological basis and today - they are being related to a physical and chemical basis. So is the "gene"

For the sake of convenience the subject may be dealt with in three phases :

(a) Concept of the gene before 1938 (early).

(b) Around 1938 (twenty years back).

(c) The "gene" of today.

(a) Starting from the spadework done by his predecesors, Gregor Mendel (1865) discovered and enunciated the fundamental principles of inheritance of characters which are applicable both to plants and animals. He supposed that there is "something" in the germ plasm of the pure parent which represents the character. These "somethings" were named by him as "elements" which were later on variously termed as "factors" or "gene". Thus he introduced a new comcept that an organism is a composite of a large number of independently behaving unit characters.

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* The manuscript of this article was written during 1958—'59 when the writer was ICA—TCM—U. S. A. Participant.

Sutton (1902) drew pointed attention to the fact that the behaviour of Mendelian factors in heredity and that of chromosomes were parallel, resulting in the study of heredity not only by observations on chromosomal changes. Thus the chromosome theory of heredity was established which was confirmed by the researches of Morgan and his followers.

Meanwhile Johannsen's pure-line theory was pronounced. It was he who gave the name "genes" to Mendelian somethings. (5,23). He suggested that the genotype was the sum total of all the genes. His pure-line theory established the conservative nature of the genes and their stability. But he did not define the positions and structure of the genes. He assumed that the whole hereditary substance consisted of particles analogous to those whose differences made the direct inference of genes possible. He also assumed that they were units of recombination and mutation (an important genetic phenomenon first discovered by De Vries in 1901). In 1909 meiosis, chiasmata and crossing-over were studied in detail by Jannsens. Morgan (11, 15) enunciated his linkage theory and showed that the genes located on the same chromosomes are linked. Then the gene became the unit of crossing-over. But later work has entirely vindicated this concept.

Attempts were then made to correlate the genetical behaviour with changes in the structure of the chromosomes. In 1919 Castle (4) spoke of the whole chromosomes as one molecule and Belling in 1928 (2) thought of the genes as cytologically visible and countable chromomeres separated from one another, at least at interphase by relatively long fibers of a nongenetic material. The chromosomes showed particulate inheritance. Pairing between identical chromosomes and structural changes like inversion were noticed on the salivary gland chromosomes. But, the particle as a unit of variation was also invalidated. For a reliable criterion of a genetic particle crossing-over was not satisfactory because it could be suppressed by structural hybridity. Mutation was found useless as it could be stimulated by structural change. The chromomere also was not satisfactory, if it varied during development.

It was then thought that there might be some solution if the mutations of the gene could be controlled. In this connection, the discovery by Muller (1927) and Stadler (1928) that x-rays could be used to increase considerably the very low spontaneous mutation rate is of significance and many mutations were produced and studied in various laboratories.

In this connection Muller (16, 17) himself states, "with reference to the transmutating action of x-rays it is found that the mutation does not usually involve a permanent alteration of all the gene substance present at a given chromosome locus at the time of treatment, but either affects in this way only a portion of that substance, or else occurs subsequently as an after-effect in only one or two or more descendant genes derived from the treated one."

Another important phenomenon, during this progress, was discovered by Sturtevant (22) (1925). This is position effect. It was found that genes when translocated to new positions behaved differently. They not only react with the external environment but also with their immediate neighbours in bringing about the phenotypic effects. Subsequent work revealed that the gene, even if it is of a particulate nature, is not an isolated unit operating simply in conjunction with other genes; it is actively influenced by them. (10, 11) Goldschmidt strongly supports this, and hypothesises that the whole chromosome or even the entire chromosome complement behaves as a unit. He has even doubted the existence of individual genes or wished at any rate that the classical theory of the corpuscular gene must be discarded.

Mean while, chemists and biochemists started investigations on the hereditary material. The investigation started even in 1874 with Meischer (8).

(b) The over all picture of "gene" under combined illumination from the diverse slants of cytology, genetics, biochemistry and portions of the evolutionary field of study around 1938 was stated as follows (8) (Gulick 1938).

1. The actual material and structure of the genes are unknown, but the matrix in which or on which they are located and from which they must derive their substance is a combination of nucleic acid with special proteins characterised by nitrogen-rich amino acids.

2. It is uncertain as yet whether each gene consists of a single, huge molecule, or whether it consists of a limited cluster of molecules. Certain lines of inference point toward a single molecule.

3. The genes constitute but a small fraction of the mass of the chromosomes in which they are located.

4. The genes are ultra microscopic.

5. If the genes have a protein constitution (as is very probable) they may reasonably be pictured as having an internal lamellar structure such as is shown by x-ray studies to be wide spread among the proteins.

6. The chain of genes is carried in the chromonema, held in its alignment by chemical bonds arranged in a non-polar pattern, i. e., the gene molecules are basic proteins held in the chromonema by longitudinal nucleic acid molecules, or they are nucleoproteins, some of whose nucleic acids straddle from gene to gene, or they are nucleoproteins alternating with a basic protein filling substance, to which they are bound on both sides by their nucleic acid valencies.

7. The total number of genes is moderately large.

8. A great part of their individual pecularities and some at least, of their mutations, are qualitative rather than quantitative.

9. Genetic peculiarities due to quantity differences (reduplication) are frequent and important in the higher plants.

10. Each gene has two types of action. The first is autocatalytic, whereby it conditions the formation of further molecules having the same peculiarities as its own.

11. The second activity is an enzyme-like control over the formation of active substances that gives them a sort of long distance control over cytoplasmic happenings.

12. As a part of the evolutionary process, a gene must be credited with a liability for undergoing chemical alteration to produce a new gene substance with a slightly different molecular constitution, capable of autocatalysing itself including the new item in its constitution.

13. Quantitative changes in the gene equipment also occur by "mutation".

14. The two processes of gene reduplication and single gene mutation, taken together, provide a possible mechanism by which a complex genetic machinery may be evolved out of simple antecedents.

15. In the evolution of organisms, genes play a part not merely by supplying mutations among which natural selection must select, but further more by setting up barriers of mutual sterility possible through various kinds of translocations (producing semi-sterilities etc.) or through serological mutations or by releasing conditional lethals or making non-viable combinations.

16. Because they are subject to the biological type of evolutionary process, we must still view the genes from the evolutionary standpoint as essentially living units (Are genes living? It was understood that it was scientifically good sense to consider them living). Very possibly they may be the smallest ultimate units that function according to biological categories.

17. Every effect said to be produced by a gene is really brought about by reciproral action of a gene with the rest of the cell, and in spite of the particularistic machinery the outcome always carries a totalitarian complexion.

The discovery of the means of sexual breeding in yeast by Winge and in paramoecium by Sonneborn (24), both in 1936, opened the field of microbial genetics.

(c) In the former part of 1940s cytologists and geneticists began to define gene. The current theory then was (19) "Gene is any small portion of a chromosome having an effect upon character development differing from that of the neighboring portions. Any change in this portion affecting its influence, whether change be a loss, gain, or rearrangement represents a mutation. In other words, genes are not all elements of the same nature, even though their effects are generally comparable. In this search for further light on the nature of the gene, few developments are more suggestive than the increasingly close association of genetics, protein chemistry and virus research. It seems that genes, proteins and viruses have much in common". See also (13).

Till then the garden pea, maize, the jimson weed, the fruit fly (Drosophila), the mouse and to some extent man have been some of the organisms that contributed important knowledge of classical genetics. One can call it as almost Drosophila genetics, on which tremendous work was done. In 1940 by Beadle and Tatum another new organism, the red bread mold, *Neurospora crassa* was selected for genetical work. Side by side, many geneticists began to work with bacteria, bacteriophages, and viruses. The biochemical approach to solve the riddle began to increase by leaps and bounds. The electron microscope, the X-Ray microscope, the polarisation microscope, the spectrophotometer have been some of the more powerful instruments in the hands of the investigator with which many more secrets of nature are revealed and concepts changed.

But, till recently the gene has been considered to be an elementary biological unit, occupying a definite position in a chromosome (locus), and transmitted in fact from one generation to another and it has been widely believed that the process of crossing over does not alter individual genes.

Different geneticists, working with various organisms and with different criteria of characterisation, have arrived at somewhat divergent concepts of the nature of genes and their action. The following have been some of the important concepts (20).

1. A gene is a unit of chromosomal structure not subdivisible by chromosomal breaking or crossing over.

2. A gene is a unit in mutation.

3. A gene is a unit of biochemical action.

Accordingly the definitions of the gene are (1) it is the ultimate unit of recombination (2) it is the ultimate unit of mutation (3) it is a unit of physiological activity and (4) it is the ultimate unit of self-reproduction (23).

Even as recently as 1954 Dr. L. J. Stadler (21) while emphasizing the need for more intensive study of the mutations of specific genes selected as best suited to detailed genetic analysis says, "The term 'gene' as used in current genetic literature means sometimes the operational gene and sometimes the hypothetical gene and sometimes, it must be confessed, a curious conglomeration of the two".

Calvin F. Konzak (12) (1957) brings about a compromise between Stadler and Goldschmidt, saying :

"In accordance with a modern concept of mutation types, such cytological changes as deficiencies, duplications, inversions, or translocations – if resulting in a detectable hereditary change in the morphology or physiology of the organism - must be classified as mutations along with those where no such chromosomal structural alteration can be discerned. The term chromosome alteration might be retained for the mere rearrangement of chromosome material, if accompanied by no detectable genetic consequence, but there seems little justification for calling one kind of change genic and another extragenic. Even the most subtle chemical change in the genetic material must involve similar phenomena, i. e., the addition, substitution, translocation, inversion, or removal of atoms or molecules.

Hence, such different philosophies of genetics as expressed by Stadler, on the one hand, who maintained the classical concept of the gene as a discrete particle, and Goldschmidt on the other, who developed a view of genetic substance based on position effect phenomena, are in reality not incompatible. Rather, the evidence concerning the nature of mutations seemed to confirm the view that mutations are not due to a single phenomenon, but to a series of often quite diverse phenomena.

The gene is no longer imagined in the classical interpretation as the smallest unit of heredity. It may now be subdivided into smaller functional units in higher plants as well as in the lower organisms, phage and bacteria. "*Yet, a gene is a very convenient unit for describing a hereditary function associated with a locus or segment of chromosome*". (See also 18).

Therefore, till recently the gene is more a concept of function and behavior than it is of structure. Regarding the size of the gene and its stability also there are divergent opinions. As such, no definition of a gene seems to satisfy all experimental situations. For other important views regarding the properties of a gene refer 25, 26, 27, 28.

As a result of various investigations about the biochemical basis of heredity and as a result of various genetical studies on bacteria, viruses and bacteriophages, after the Brookhaven Symposium in Biology (1956) an entirely new picture of gene, particularly about its structure and chemical nature, is placed before us (9). Evidence has accumulated that can be interpeted to mean that the gene is divisible by intragenic crossing-over. Some important points in the present view are :—

1. The gene is defined as a localized unit of nucleic acid with a specific function, in higher forms closely associated with proteins. The function is presumed to consist in the determination of the specificity of a non-genic macro-molecule such as a protein.

2. The primary genetic material in all living systems appears to be nucleic acid-desoxyribonucleic acid (DNA with adenine, thymine, guanine, cytosine) in all cellular forms and some viruses, and ribonucleic acid (RNA with adenine, guanine, cytosine, uracil) in some plant and animal viruses. Genetic information consists in specific sequences of bases in DNA or RNA.

3. In phages the genetic material appeared to be of one continuous Watson-Crick double helix (?) of DNA built up of possibly 200,000 base pairs (adenine—thymine; guanine—cytosine). The

double helix of DNA of phages is presumed to be replicated by separation of complementary poly-nucleotide chains, each of which then serves as a template for the synthesis of partners. The mechanism by which DNA is replicated in higher forms is presumably fundamentally the same as in phages. The DNA of a phage consists of many genes.

4. In cellular forms primary genetic information can be assumed to be carried by DNA intimately associated with protein in the chromosomes.

5. It is at present tenable to assume that conventional crossing-over is always intergenic.

6. Gene mutation in all organisms is presumed to consist in alteration of nucleic acid structure through base substitution, inversion of intergenic segments, duplication of intragenic segments of one or more bases or deletion of bases. Intragenic mutations of the above kind may occur at many levels, called "sites" within a single gene.

7. Recombination of genetic material from DNA of different parental phages occurs by a process that gives only one genetic recombinant per event.

8. Genes of cellular forms may function by a process in which genetic information is transferred from DNA to RNA segment, which then serve as templates for construction of micromolecules such as proteins.

9. Many genes seem to have as their function the transfer of specificity to an enzyme. In a number of instances it appears that the total specificity of an enzyme, of which substrate specificity is only a part, is derived from a single gene.

10. The absolute amount of DNA per chromosome is remarkably constant from cell to cell within individuals of the same species. About DNA replication-mechanisms there are no definite conclusions as yet, but Stent (6) classifies the schemes into conservative, semi-conservative and dispersive mechanisms on the basis of distribution of the parental material.

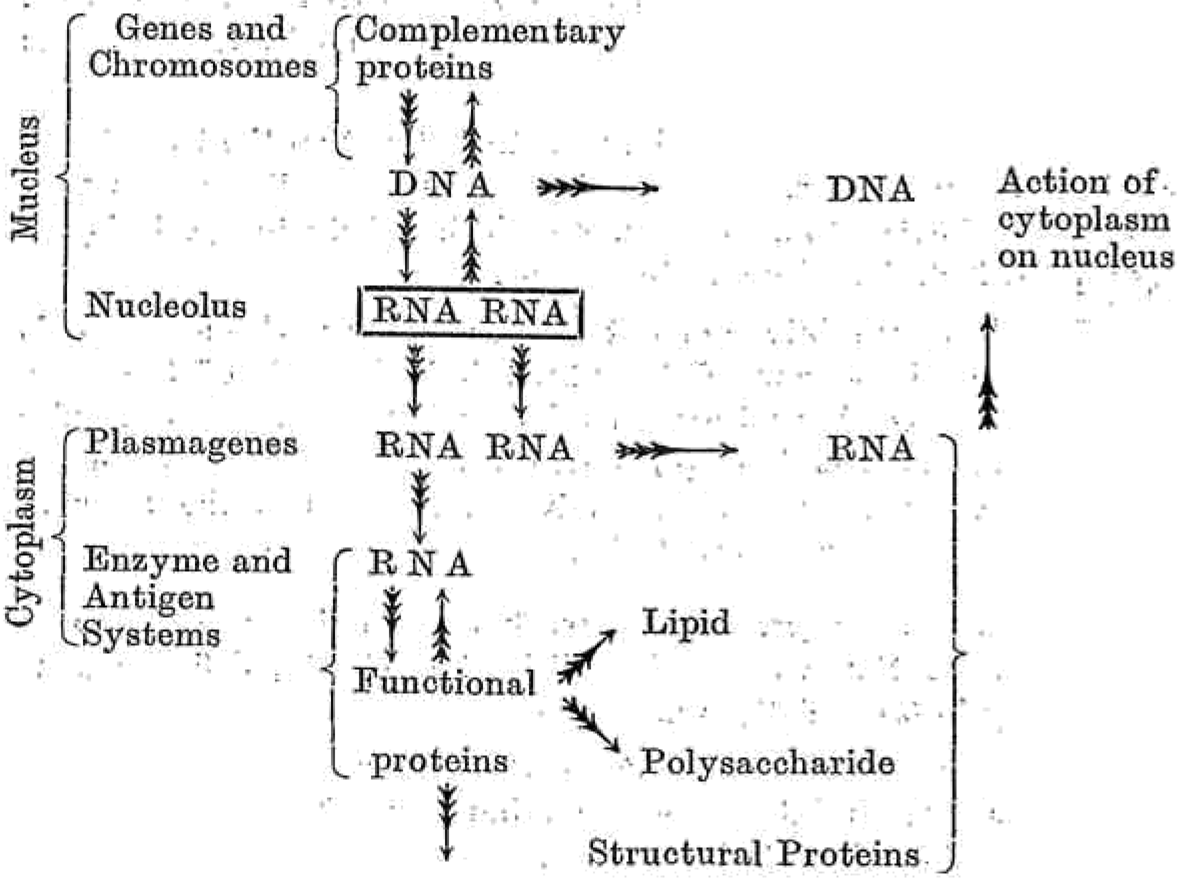
Meanwhile, Benzer, with his work on the linear sequence of genetic units in the *Escherichia coli* bacteriophages, defines a gene operationally in *three* distinct new terms (3).

(1) The smallest element in the unidimensional array of genetic units that is interchangeable, but not divisible by genetic recombination is to be called the *recon*.

(2) The smallest element that, when altered, can give rise to a mutant form of organism is to be called the *muton.*

(3) The same functional unit to which the mutant belongs is to be called the *cistron.*

It is not out of place here to mention that side by side certain cytoplasmic units are discovered about a decade back which, like the nuclear genes are believed to be self-duplicating and capable of determining hereditary characteristics. The plastids are shown to have hereditary characteristics of their own which to a degree are independent of those of the genes. Other units as found in various cases are termed differently as particles, plasmagenes, chrondriosomes and organellae respectively and thus particle genetics is also developed. All these particles having genetic influences were formerly termed as "plasmon" collectively. All genetic particles are, it seems, proteins combined with nucleic acids. Larger particles seem to be combined with DNA and smaller particles with RNA. They are the smaller viruses and plasmagenes. Again, there are some particles which can diffuse from cell to cell. These are the "proviruses". Taking all these into account a genetic balance between the nucleus and cytoplasm as shown below seems to exist (5) as given by Darlington.



Considering the presumptions and not conclusions that are existing now regarding the concept of gene and its structure, the words of Bentley Glass may be quoted here "............it is still very clear that geneticists and biochemists are for the most part talking different languages that remain mutually unintelligible, while the biophysicists and crystallo-graphers add to the babel with a third. The microbiologists are trying valiantly in this commotion to dispel semantic confusion, even at the risk of generating yet another terminology. Benzer's notable new terms, the muton, recon and cistron, will undoubtedly become widely used because they so neatly distinguish the several operational concepts into which our one time unit of heredity, the gene, has dissolved" (9).

Thus, it appears that the unit 'gene' in usage so far, before it is properly and precisely understood, is being divided into further simple units and fragments and in this reduction to absolute molecular realities the problem of the gene is not yet completely solved. The demonstration that active, infective particles of tobacco mosaic virus may be constituted from its inactive, non-infective protein and nucleic acid constituents - gives hope and appears to be a step in this direction (7).

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