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FUNDAMENTAL UNITS IN BIOLOGY[1]

By Professor H. S. JENNINGS

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BIOLOGY has long sought to follow the example of physics by finding fundamental units, through the properties and combinations of which the phenomena of biology are produced, as the phenomena of physics are produced through the properties and combinations of its fundamental units. The history of biology yields long lists of the names and properties attributed to these supposed units. But till the recent rise of biological genetics, all these units remained hypothetical. Their existence and their properties were assumed, in order to explain the phenomena observed; they themselves were not observed.

But with the investigations of genetics in the last three decades, materials that have been claimed as the fundamental units of biology, and that at least in part fill the rôle of such, have emerged into the class of things that are observational. They are seen, at least as groups, under the microscope. Their location in the organism has been precisely determined, their arrangement and order discovered. Their properties and behavior have been to a great extent concretely investigated, their rôle in the life of organisms in large measure brought to light, though their physico-chemical nature remains as yet uncertain.

These are the materials known to biological science as *genes*. They yield in interest perhaps to no other units known to science, since a group of these develops into a living organism; into a human being, with all its powers; its consciousness and its intelligence.

Though these materials fulfil the conception of fundamental units as nearly as anything that is likely to be found in biology, they differ in many and important ways from the hypothetical units earlier postulated. The application to them of the phrase "fundamental units," with its connotation of fixity and simplicity and uniformity, brings with it the possibility of serious misconception. I should like to present a picture of their concrete properties and behavior such as may dispel these misconceptions. Whether, in view of the picture that emerges, it is to be held that biology has

[1] Address at the Mark Hopkins Centenary, Williams College, October 10, 1936.

indeed discovered fundamental units, I shall not undertake to decide. I shall first try to present the picture that arises through the study of genes in genetics and cytology. I shall at the end touch upon certain attempts to interpret them in terms of known physico-chemical phenomena.

Genes, as every one knows, are found within the nuclei of cells. They are grouped in coordinated systems which constitute the well-known structures called chromosomes. Single separate genes are not observed or known; seemingly the single gene can not exist by itself; certainly it can not long persist. But the chromosomes are known to be differentiated into separable parts—parts that can be disjoined and recombined into new groupings. It is in this possibility of separation and recombination that they show their unitary character. In view of this separability and varied power of recombination, taken in connection with the picture presented under the microscope, the genes are not uncommonly conceived as essentially separate particles, secondarily united into chains that form the chromosomes. The correctness of this conception is perhaps becoming questionable. I shall, however, present the known properties and relations of the genes in terms of this prevailing conception, later bringing out the possible necessity of a reinterpretation.

Looking upon the genes as separable units, it is certain that the number of genes in the single cell is very large. In a higher animal it is certainly not less than a thousand, and careful estimates of the number have run as high as fourteen thousand. The entire group of genes is present in the nucleus of the single cell with which every individual begins life. As the cell divides, producing the many cells of the body, every gene divides, its products passing to all the cells. Thus every cell of the developed body contains the entire set of many genes, though to this there are some exceptions. The development of the individual is brought about through the interaction of these many genes; the nature and characteristics of the individual that is produced depends on the particular combination of genes that is present in the original cell, as well as upon the conditions to which they are subjected.

The genes are known to be arranged serially within the nucleus, as are beads on a string. The string of genes is seen under the microscope as the thread-like chromosome. At certain periods such a thread is seen to bear at intervals minute particles forming a series. These particles, known to the cytologist as chromomeres, have the positions and arrangement which on other and quite independent grounds the genes are known to have. It has seemed possible that they are indeed the genes; or that at least they contain the single genes.

The genes are not a series of identical particles. On the contrary, each gene differs from every other gene in the series. Thus a thousand or more diverse types of genes exists in the single cell. It is by the complex interaction of these many different agents that development is brought about and the organism produced. The single gene, not by itself capable of development, supplies to the great complex of physiological processes some necessary ingredient or agent, without which development can not occur. Thus the single cell that is ready to develop may be compared in constitution to an enormously complex formula from which is to be produced some organic product. If each ingredient in such a formula is conceived to be concentrated in a minute particle, and all the diverse particles are strung in serial order on a filament, the resulting structure seems comparable to the system of genes in the cell nucleus.

The system thus formed is uniform and orderly. Each different type of material, each gene, has its precise place in the system, so that different gene types can be located, their serial numbers given. Many of them have been named. Detailed maps of the relative positions of many of the different genes in the system have been made for certain organisms.

With very rare exceptions, each one of the great number of genes present in the system is necessary to the life and development of the organism. If the elaborate system is made imperfect by the loss of any single one of the many known gene types, the organism does not develop; it can not live. To this, exceptions are very rare.

Thus the gene is not a unit in the sense that it can live and develop by itself. On the contrary, it depends for its life and functioning on the presence and cooperative action of a great system that includes hundreds or thousands of gene types with different properties. It is in the fact that they can be separated and recombined that the genes behave as units. But as we shall try to indicate later, it is possible that they are not properly to be considered self-contained units, but only as coordinated parts of complex structures acting as organic wholes.

Different organisms have diverse sets of genes, the different genes of the set having different properties and behavior from those of other species. Thus the number of diverse types of genes that occur in the organic world is practically infinitely great. Within the same species the different individuals have many genes in common; that is, they have genes of the same descent, and of the same properties and behavior. But such individuals of the same species usually differ in some of their genes, few or many. Two such individuals may have gene systems that are identical in

properties in all their genes except a single one; or they may differ in two or in any number.

The individuals thus differing with respect to certain genes show correspondingly different characteristics, structural or physiological. A blue-eyed individual may differ from a black-eyed one in but a single gene. There are many diversities between individuals that thus result from a difference in single genes.

But for every gene in one of the differing individuals of the species, there is a corresponding gene in the other individual; a gene corresponding in location within the chromosome system, and in properties. Making allowance for sex differences, every individual of the species has the same number of genes, arranged in the chromosomes in the same order, the genes that occupy corresponding positions having identical or similar properties and functions.

But two genes occupying corresponding positions in the two individuals, although they have similar properties, similar functions, may differ to some extent in their properties; differ somewhat in the way they perform their common function. One may produce blue eyes, another brown eyes, a third gray eyes. One may tend to produce a strong individual, another a weak one. The number and degree of such diversities in the action of corresponding genes is very great, among the many individuals of the species taken as a whole.

Thus there are two types of diversities among the genes of a given species, such as man:

(1) In the single individual the many different genes in the long series differ in their physiological action, in their functions, in the effects that they produce in development. One gene has its primary function in producing the color of the eye, another in determining the physiological properties of the blood; a third affects primarily the rate of growth; and so on for the hundreds or thousands of different genes. The entire group must work in coordination, if the individual is to live and develop. We must thus distinguish a great number of diverse genes in the same individual.

(2) In different individuals of the same species, as we have seen, the genes at corresponding locations, although they have the same general functions, may differ in the way they perform these functions; they differ to some degree in their properties. Some examples of the given gene may be weak or imperfect, others may be strong and perfect. One may produce blue eyes, another black eyes. One may give rise to a certain blood type, another to another blood type. These corresponding genes, differing in different individuals, are known as alleles or allelomorphs; they are derived by modification from a single gene type. Thus a given gene type, occupying a certain definite position in the chromosome, may have many diverse modifications or alleles, present in different individuals. This adds greatly to the number of diverse gene types present in the species.

The grouping of the genes into chromosomes differs greatly in different species. In the individuals of the same species or variety the grouping into chromosomes is as a rule the same. Yet in some cases there are diversities in the order of the genes in the chromosomes, among individuals of the same species. Such diversities in the order of the genes commonly make but little difference in the characteristics of the organism. Yet if the order of the genes is artificially altered, as may be done by the use of radiations, in many cases development and characteristics *are* altered; they are usually made in some respects abnormal. The ground for this change of characteristics with change of relative position of the genes is not yet clear. It may be the result of injury to the genes brought about at the time their relative positions are altered; or possibly the relative position has itself some effect on the functioning of the genes. This is a matter that is now under active investigation. If the gene system is artificially broken up, so that it no longer contains the full ordered set, development and life cease.

A further feature of the system of genes is of great practical importance. In some of the lower organisms the genes within the cell form a single chain or linear system, each gene in the chain differing from every other. But in all higher organisms, two cells unite at the beginning of individual life to form a single cell. The cells so formed—the fertilized egg cells—have double chains of genes, one chain derived from each of the two cells that have united. Each of the two chains contains the full set of genes, so that all the different gene types are in pairs. This is the state of the case in the cells of all the higher plants and animals and in many of the lower ones.

The two systems present in the same cell, but derived from different parents, may differ in the properties of some of their corresponding genes; that is, they carry different alleles of certain genes. One member of a certain pair of genes may thus tend to produce an effect somewhat different from that produced by the other member. One of the two may be weak or defective; in that case the remaining normal gene performs the function for both. The doubleness of the genes thus acts as an insurance factor; if one gene of the pair does not play the proper rôle, the other gene takes over that rôle. The doubleness of the gene system is what gives rise to the most characteristic and perplexing features of heredity; it is the basis of the numerical proportions seen in the Mendelian rules or laws.

Our knowledge of the diversities among genes and of their functions in determining the characteristics of

organisms comes from the fact that at reproduction new combinations of genes are formed. The single parent cell, containing two complete sets of genes, divides into germ cells, each of which contains but one complete set of genes. Now, in preparation for this division into germ cells, the two sets of genes in the parent cell unite in pairs, the two corresponding genes forming the united pairs. After this union the two again separate, and in so doing there is often an exchange of some of the genes between the two systems. Now when the division into germ cells occurs there are produced in the different germ cells combinations of genes differing from the combinations that existed in the parents. By the union of such germ cells at fertilization, many diverse combinations of genes are produced. By study of the individuals that develop from these germ cells, the effects of altering the gene combinations can be discovered. This is the method by which all our knowledge of these things has been obtained.

Such analyses of the results of changing the gene combinations have been carried far; they constitute the experimental study of Mendelian inheritance. An elaborate technique has been devised—each step of which requires a generation of the organism studied. This technique is a powerful instrument. By its aid the results of changing any one of the known genes are determined; or the results of changing two, or many. It is to this that our detailed knowledge of the properties and effects of the different genes is due.

Thus the genes combined into particular systems may be separated and recombined into new systems; thus the single gene may be removed from one combination and transferred to another. It is in this respect that the genes act as units. But the gene, when removed from one system, must, in order to produce development, find its proper place in another complete system. In the development of the organism and the production of its characteristics the genes do not act as units, but as coordinated materials interacting to produce a harmonious result.

Moreover, the single gene does not represent or produce any single part or characteristic of the organism. The single gene does indeed, in many or most cases, have its most conspicuous effect on a certain feature of the organism, as the eye or the blood. But the single gene is known to affect also many other features; and to have a constitutional effect on the organism as a whole. Further, it is known that every feature of the organism is affected by many different genes. Any part or characteristic is built up by the coordinated action of many genes. The genes must be conceived to produce organic materials which interact in a long series of reactions that ultimately produce the developed organism.

The genes affect development and characteristics through interaction with the cytoplasm in which they are imbedded, this cytoplasm constituting the remainder of the cells. Cytoplasm is absorbed into the nucleus; here it comes under the direct action of the genes and is modified by them. It is given off from the nucleus in modified condition. In the single cell different portions of the cytoplasm become thus differently modified. By division of the cells, some receive cytoplasm of one type, others of another type. By continuation of this process, the details of which are yet obscure, the different types of cells and of tissues are produced. Each different type of cell seemingly still contains the entire set of genes. Thus the different types of cells within the single organism differ in their cytoplasm, not in their genes. The differentiations of the body therefore have their seat in the cytoplasm, but they are produced under the action of the genes, and are diverse with different genes.

Thus the cytoplasm plays a great and essential rôle in development and the production of characteristics. This being so, the question is asked: Is there ground for considering the cytoplasm less fundamental than the genes? And is the conception of *units* applicable to the cytoplasm? Is it not misleading to designate the genes as the fundamental units of biology, in view of the existence and functioning of the cytoplasm?

There is some ground for the criticism implied in these questions. The cytoplasm is as essential to life and development as are the genes; and this means a limitation of the conception that the phenomena of biology are the result of the properties and combinations of the genes as fundamental units. The important thing is that the rôle of genes and of cytoplasm is different in kind. So far as experimentation shows, the seat of diversity among different individuals is almost exclusively in the genes. The diversities of inherited characteristics are due to diversities among the genes. Only in rare instances and in slight degree are there known cases in which diversities of cytoplasm cause diversities among the individuals of a species, and thus affect heredity. Diversity of sex, diversity of structure, diversities in fundamental physiology—all these are abundantly produced by diversities among genes, hardly at all by diversities in cytoplasm. It is by changes in the genes through radiation or the like that inherited changes in characteristics are produced. In the relatively few cases in which diversity of characteristics results from diversity of cytoplasm, there are indications that the diversity of cytoplasm is originally due to diversity of genes, and is brought about by the action of different genes on the cytoplasm. The general picture leaves the impression that evolutionary changes in organisms are in the main or exclusively the consequences of alterations in the genes, not

of alterations in the cytoplasm. On the whole the cytoplasm appears to play a uniform and relatively passive rôle, as compared with the varied and active rôle of the genes. Even in the development of the individual, the genes appear to initiate and determine the nature of the differentiations that appear in the cytoplasm.

The action of the genes in development is not stereotyped and invariable. On the contrary, the genes are elaborately sensitive and responsive to the conditions which surround them; they change their action and effects in accordance with the conditions. Every cell of the developing body contains the same set of genes. Yet this same set produces in diverse parts of the body totally different structures and functions. Some of the cells produce nerve tissue, others muscle, others bone, others connective tissue, others mucous or serous membrane. Some produce eyes, others wings, limbs, integument, brain, alimentary canal—all operating with the same set of genes. How in detail the genes so react or are so controlled as to give with the same set the many diverse parts and functions of the organism is as yet one of the darkest problems of biology. Some slight beginnings of knowledge of these matters have come through experimental embryology. By altering the conditions in certain parts of the developing organism, the gene system here may be induced to produce parts that normally it would not have produced. The single cell, with its gene system, appears capable of producing any part or function of the body, depending on the conditions to which it is subjected.

Turn now to certain other properties of genes. In reacting with the cytoplasm and with the conditions of the environment, the genes are not used up. Always a reserve portion of each gene remains and perpetuates the gene type by division. Each of the many different types of genes reproduces true to type. Each gene assimilates nutritive material, producing thus more of its own kind of substance. Then this material divides, and by a continuation of the process many genes of this type are produced, scattered through all the cells of the body. This distinctive assimilation and reproduction of its own kind of material by each type of gene is the fundamental phenomenon of heredity. The distinctive gene type is maintained, even though the conditions to which the gene has been subjected may have altered greatly its activities and products. The gene shows a high degree of resistance to change in its fundamental nature. This is the ground for the usual lack of inheritance of acquired characters.

But paradoxically, one of the most remarkable and important properties of the gene is that it may become altered, modified; and that it may assimilate and reproduce in this altered state, giving rise to additional genes of the altered type. On this fundamental property of genes rests the process of organic evolution. By transformation of the genes, the organisms they produce are transformed. By reproduction of the genes in their transformed condition, the transformed organisms are perpetuated, later forming the foundation for further transformations.

Until recently nothing was known as to the effective agents inducing such transmissible changes in genes. At the present time certain agents are known that bring about such changes; but our knowledge is negligible when confronted with the changes shown in organic evolution. Certain radiations may alter the genes without killing them. But these altered genes bring about injuries and weakness in the individual that carries them. The weakened and injured genes assimilate and reproduce in their damaged condition, giving rise to organisms that are weakened, deformed or abnormal; and this inheritance of the defective condition continues for generations or indefinitely. Similarly weakened or damaged genes are producible by subjecting the developing organism to abnormally high temperatures. Whether radiations and high temperatures may ever cause inherited gene modifications that increase vitality or are beneficial to the organism is a question on which the evidence is not yet clear. Certainly the overwhelming majority of the gene changes so induced are harmful; it may be doubted whether any such changes not harmful have been produced.

But in organic evolution, transmissible gene changes that increase the fitness of the organism for life and development have certainly occurred on a grand scale. We know as yet little or nothing as to how these changes are produced.

Our account thus far has presented the main features of the genes so far as they have been discovered through investigations in genetics and development. Such investigations are the main sources of knowledge of genes. But through them the genes are known mainly, though not exclusively, in an indirect way, through the effects which they produce. Our presentation has dealt mainly with such effects, and with conditions that are postulated as necessary for the production of such effects.

Can we approach the genes more closely and directly, forming an idea of what they are as material bodies in space; as they would be described in chemistry or physics? Such knowledge of the genes is as yet largely hypothetical. We may, I believe, expect great changes in this matter: changes that may revolutionize our interpretations; they may come soon.

Some investigators of the genes believe that they must be considered single molecules of a complex character. Others hold, on the basis of size relations, that the single gene probably consists of a number of

molecules. It is sometimes suggested that one such gene, whether unimolecular or multimolecular, is lodged in each of the chromomeres which at certain stages are visible in the chromosomes. Naturally, though not necessarily, going with these ideas, is the conception that the genes are primary as compared with the chromosome; that the chromosome is a secondary aggregation of genes, which conceivably might be separate.

Another conception of the matter has been presented and has come into some prominence of late. It is a conception which would change in some fundamental respects the interpretation of the phenomena that I have described, though the phenomena themselves would of course remain. According to this conception, the chromosomes are the primary and unitary structures, while the genes are but differentiations in the length of the filamentous chromosomes. This idea has recently been ably worked out, from the standpoint of physical and organic chemistry, by Dr. Dorothy M. Wrinch.[2] According to this view, the chromosome is to be conceived as a structure constituted of two types of elements making a sort of warp and woof. The warp is a set of longitudinal filaments or bundles composed of "identical sequences of protein molecules in parallel"; the woof of a set of ring-like nucleic acid molecules surrounding the protein filaments and holding them together. The longitudinal protein bundles are held to consist of "polypeptide molecules placed end to end with suitable linkages." These molecules thus placed end to end are not identical, but are held to differ in a definite pattern, so as to form a linked chain of diverse molecules, indicated by Wrinch in the following formula:

$$A_1\ B_1\ C_1 \ldots X_1\ Y_1\ Z_1,\ A_2\ B_2\ C_2 \ldots$$
$$X_2\ Y_2\ Z_2,\ A_n\ B_n\ C_n \ldots X_n\ Y_n\ Z_n$$

These molecular diversities constitute the basis for the differentiations that give rise to the conception of genes. The nucleic acid rings form transverse darkly staining bands, distributed at irregular intervals along the length of the chromosome, their location and extent depending on whether the reaction of the protein molecules beneath them is prevailingly acid or basic.

Recently certain huge chromosomes—the salivary chromosomes of insects—have been minutely investigated. These show a banded structure such as agrees with the conception of Wrinch; and it has been proved that these bands have definite and constant relations to known genes. So far as they go they perhaps support the conception of the chromosome that I have just described.

According to this view of the matter, then, it is the chromosomes that are primary, the genes being but differentiated regions in them, which may be broken apart and recombined with the corresponding part of similar block taken from it at any other level. Any such block might be called a gene. This conception, if it finally prevails, will considerably alter the picture of the genes and their relations, and may serve as a guide to fruitful study of their properties and mode of operation. It would possibly incline us to answer in the negative the question whether biology has discovered fundamental units comparable to those of physics. But it will not materially alter the general picture of the relation of genes to development and heredity, as I have just tried to present it. Whether the genes are essentially separate units or only differentiations in the body of the chromosomes, they are structures which, when in appropriate combinations, give rise to living, conscious organisms; and which, by the changes that occur in them, give origin to the infinite variety of the organic world, and to the changes that we call organic evolution.

OBITUARY

WILLIAM BUCHANAN WHERRY[1]

1875–1936

BORN of missionaries in India, in 1875, raised in our Middle West, wanderer into the Philippines, Japan and Hawaii and dead in Cincinnati in the night of November first, 1936—such is the material sequence in the life of William Buchanan Wherry. Accompanying it, like a shadow, is the story of a soul.

The spirit spoke Hindoostani before it could lisp English—and never forgot that tongue. And forever after was it thus to speak more of the mystery of life and less of life's obviousnesses.

At fourteen he was catapulted into the rough surroundings of Chicago's offside; at seventeen made a student of the classics in conformist Pennsylvania, to learn there, non-conformity.

Then back—because more convenient—to the Middle West, where he was to walk with gods, sunk like himself in the mire of man's life on Halsted Street—Ludvig Hektoen, Frank Billings, Edwin Oakes Jordan. Whereafter he lived for a season with Theobald Smith. Now blessed with the hallowed oil of their approval, he entered the fight on his own, out where the frontiersman struggles 'gainst miasma, 'gainst pestilence and

[2] Dorothy M. Wrinch, *Protoplasma*, 25: pp. 550–569, 1936.

[1] Tribute read into the service at the funeral on the morning of November third in the auditorium of the Medical School of the University of Cincinnati.