

The General Nature of the Gene Concept*

By PROF. R. RUGGLES GATES, F.R.S.

THE conception of the gene has resulted from two lines of biological evidence: (1) The amazing stability of the germ plasm, as expressed in the facts of heredity; (2) its occasional instability, as shown by the occurrence of mutations. That external forces, such as X-rays, impinging upon the germinal material should produce changes, is not surprising but inevitable. That the resulting effects are inherited, however, shows that the organism is incapable of regulating against changes in this particular part of its cell structure.

It appears that these phenomena of stability and inherited change can only be understood by recognising that some substances or structures in the chromosomes must maintain in general their spatial relationships and chemical nature, not only from one generation of organisms to another, but also with only minor changes through thousands, and in some cases even millions, of years. However protoplasm grows, these substances must be self-reproducing, with a permanence equal to that of the species itself, for when they change the species changes.

While emphasising these conclusions, which seem inevitable from the modern genetical work, I do not wish to minimise the importance of the cytoplasm. It has been shown, for example, by the investigations of embryologists (for example, Conklin, Lillie) that the visibly differentiated substances in various animal eggs can be displaced and rearranged by centrifuging, without affecting the development, yet if the fundamental hyaline ground substance of the egg-cell is disturbed, distortions of development will be produced. This and the facts of egg polarity argue strongly for a more or less determinate spatial arrangement of the cytoplasmic materials, at least in many animal egg-cells. It has also been shown by reciprocal crossing of plant species that some species are differentiated only as regards their nuclear content, while in others the cytoplasm differs as well.

The spatial arrangement of the genic materials within the chromosomes is therefore not different in principle from that shown to exist in the cytoplasm of certain animal eggs. The main difference is that the chromosome is a thread-shaped structure and is believed to be differentiated only along its length, that is, its differentiation is regarded as one-dimensional rather than three-dimensional.

In what sense do genes exist? The gene is probably the last in the long series of representative particles beginning with Darwin's 'gemmules' and the 'pangens' of de Vries, which were formulated to account for the phenomena of heredity. With advancing knowledge, such conceptions have

tended to lose their formal character as ultimate particles reproducing by fission, and to become more physiological and more closely related to the known structure and activities of the cell. They lost their morphological nature when the conception of the unit character was given up many years ago. Bridges's conception of genic balance is essentially physiological. As Sir Frederick Gowland Hopkins has said of all organic units, "The characteristic of a living unit . . . is that it is heterogeneous. . . . The special attribute of such systems from a chemical point of view is that these reactions are organised". What is the nature of the organisation which leads us to the conception of the gene?

In 1915, I first pointed out that a gene represents a *difference*—a fact so obvious that its importance is in danger of being overlooked. Johannsen, who invented the term 'gene', afterwards (1923) expressed the same point of view. Our actual knowledge of genes, apart from speculation, is derived entirely from their differential effects in development and from the phenomena of linkage and crossing-over. The visible difference in the developed organism is the product of an initial germinal difference which must have arisen at some time through a mutation. The great majority of biologists will agree in locating the genic materials in the chromosomes. In the endeavour to get a more intimate picture of the nature of the gene, we must therefore explore the structure of the chromosome. It is also necessary to remember that, like everything else in the organic world, the genes, as well as the chromosomes, must have had an evolutionary history.

There have been two main theories of chromosome structure. According to one theory, the core of the chromosome contains a continuous thread or chromonema, which takes on a spiral form in various stages of mitosis. Cytologists have brought strong evidence for the existence of chromonemata in plant cells. The investigations, particularly of Sharp and Kaufmann in the United States and of Hedayetullah (1931) and Perry (1932) in my laboratory, have given a clear and definite picture of the chromosome during the cycle of mitosis. These accounts agree in finding the chromosome to be a double structure throughout the mitotic cycle, containing two chromonemata which are spirally twisted about each other in anaphase, telophase and prophase, each chromonema splitting before the chromosome halves separate in metaphase. There is also much wider evidence for the existence of a chromonema as a continuous thread embedded in the matrix of the chromosome. The genes must then be contained in this thread, and they must undergo duplication into two series before these are separated by the longitudinal fission of the chromonemata. The duplication of

* From a paper read on September 12 at a joint discussion of Sections D (Zoology), I (Physiology) and K (Botany) at the Leicester meeting of the British Association on "The Nature of the Gene".

the chromonemata must then be the fundamental process on which the phenomena of heredity depend.

Another theory of chromosome structure which has been much in vogue in recent years and has found perhaps its strongest support in animal cells is that of the chromomeres. According to this view, the chromosomes in prophase and telophase are made up of granules or chromomeres strung together on a fine connecting thread. Various attempts have naturally been made to identify these discrete chromomeres with the genes. They are perhaps most clearly demonstrated in such work as that of Wenrich on grasshoppers. The chromomeres in cytological preparations, however, differ greatly in size, and their number appears to be smaller than present estimates of the number of genes. Bridges has spoken of them as the houses in which the genes live. If this is the case, it would appear that whole families or even villages of genes must live in one house. Belling (1928) endeavoured to count the number of chromomeres in certain plant nuclei and has arrived at 1,400-2,500.

In a posthumous paper recently published, as well as in earlier papers, Dr. Belling strongly supports the chromomere theory, from observations of smear preparations of pollen mother cells in various lilies. Not only does he deny that the chromosomes are split in telophase, but he also holds the novel view that the prophase split in the chromomeres is not accompanied by division of the thread connecting them. Instead, he thinks connecting threads are formed *de novo* between the new daughter chromomeres, thus linking them up into a new chromosome. The chief merit of such a view appears to be that it would obviate many of the serious difficulties which still exist with regard to all current theories of chiasmata and crossing-over. The fact that such diverse views can be held by competent cytologists, shows the extreme difficulty of crucial observation in this field.

Recent observations now in progress in my laboratory indicate that chromomeres may not exist, at least in plant cells. We are finding that, in some cases at any rate, the appearance of a string of beads or a moniliform thread, when critically analysed, is due to the presence of two spirally intertwined chromonemata, the nodes and internodes of which give the superficial appearance of a single chain of chromomeres. It is therefore desirable that a re-investigation, particularly of animal chromosomes, be undertaken, to make certain whether chromomeres actually exist or whether they will bear the general interpretation here suggested. In the meantime, it appears that the core of many plant chromosomes is a continuous structure, not broken up into visibly discrete bodies. As the imagination of many genetical investigators has been caught by the idea of discreteness both in the gene and within the visible chromosome, it is well to emphasise this point.

The absolute discreteness of the genes within the chromonemata does not appear to be an essential part of the gene theory. It is well known that many of the Protozoa have numerous chromosomes which undergo longitudinal fission and exhibit the usual features of the chromosomes in higher organisms. Are we to suppose that these chromosomes are as highly differentiated along their lengths as the evidence of crossing-over leads us to believe they must be in higher plants and animals? I find it impossible to accept such a view, which would be virtually a denial of evolution except in the embryological sense. The alternative is to assume that, when the mitotic mechanism first evolved in the Protista, the chromosomes were perhaps differentiated from each other but each was uniform along its length. From this point of view the mitotic mechanism would be a striking example corresponding with Berg's idea of *nomogenesis*.

The development of the mitotic figure may be regarded as one of the main evolutionary achievements of unicellular organisms. We may reasonably suppose that it appeared there in its simplest form and that the chromosomes in these groups of organisms remained more or less longitudinally homogeneous. We may then think of the evolution of higher plants and animals as having taken place through internal differentiation of the chromosomes, combined with adhesion of the products of cell division into multicellular aggregates. Thus would gradually arise the condition which has been postulated for higher organisms as a result of experiments in crossing-over, that is, a set of chromosomes not homogeneous but longitudinally differentiated. According to this view, all the developments of evolution in multicellular groups were foreshadowed or at least made possible by the mitotic mechanism achieved by the Protista. Just as the simplest cell aggregates consist of undifferentiated cells, so their individual chromosomes are internally homogeneous, each containing a different type of genic material.

The current view of genes, as developed particularly in connexion with *Drosophila*, tacitly assumes that all genes are of the same kind. If the views here expressed have any validity, then it seems more reasonable to suppose that a portion of an original chromosome, not necessarily of minimum size, underwent a mutation. Later, a portion of this would undergo a different change, and so on until a series of genes or chemically different segments of various sizes would result. This would lead ultimately to some genes of minimum dimensions, although others might be larger, and segments of the original unchanged chromosome might remain. It would appear probable, however, that in this process the majority of genes would ere now have reached the minimum size. (I find that East in 1929 also emphasised the view that genes are probably of various sizes.)

Some workers have of course taken an entirely different view of the origin and history of genes, regarding them as the primordial bodies or organic

units from and by which protoplasm has since been constructed. Numerous comparisons have been drawn between genes on one hand and bacteriophage and virus particles on the other, based on their supposed similarity in size and action. While such comparisons are suggestive, the view of the genes as differentiated at a later stage of evolution within the originally homogeneous chromosomes seems on the whole more probable, and on this view there is no need to regard them as indivisible, discrete bodies of uniform size and nature.

Various estimates of gene size have been made in *Drosophila*. One of the latest, by Gowen and Gay (1933), arrives at a minimum size of 10^{-18} cm.³, the number of loci in the nucleus being estimated at more than 14,000. This maximum size would only allow space for about fifteen protein molecules. There is at present a large margin of error in such estimates. From measurements of sperm-heads and chromosome lengths, these authors draw the interesting conclusion that the chromosomes are all arranged end-to-end in the *Drosophila* spermhead.

The view of gene origin within the chromosomes as sketched above appears to be supported by the fact that the genes are now known not to be uniformly distributed in the chromosomes. The Y-chromosome has long been recognised as nearly empty of genes, but later work of Dobzhansky (1933) and others shows that one third or more of the length of the X-chromosome at the right or proximal end near the spindle fibre attachment is also inert. In this region only one mutation, 'bobbed bristles', is known to occur, and crossing-over apparently does not take place. Possibly these inert or 'empty' segments may represent an earlier unmutated condition of the chromosomes. The bulk of the chromosome is probably composed of thymonucleic acid, but it does not necessarily follow that the genes embedded in the chromonema axis are derivatives of that substance.

Although Belling believed that each chromomere contains a visible gene, yet the bulk of evidence leads to the conclusion that the genes are ultra-microscopic, and Bridges (1932) has recently expressed the view that they are unimolecular. It has been more usual to picture them as definitely organised bodies containing a score or a few hundred molecules and reproducing either organically by fission or chemically by duplication. The idea that each gene is a single molecule, while avoiding the possibility of its divisibility, appears to add difficulties of another kind. It is difficult to see why a tenuous chain of single unlike molecules should persist in the core of the chromosome, as it would be necessary to assume. Chemical forces alone could scarcely be expected to hold such a chain together, even if we rely upon the properties of the carbon atom. On the other hand, whatever physical forces give the chromosome its unity as a structure, might also be concerned (1) in organising each group of like or unlike molecules into a gene, and (2) in maintaining their axial arrangement in the chromosome. Could one

molecule exert its catalytic effect while maintaining its position undisturbed in the chromonema? And could it duplicate itself when the row of genes divided? The mere asking of such questions shows that we do not know whether genes should be regarded as organic or inorganic groupings, and it indicates also that the time-honoured phenomena of growth and reproduction formerly associated with such bodies are in some danger of being lost, although it must equally be said that they have not yet been eliminated.

The 'scute' series of genes in *Drosophila* has become increasingly difficult to interpret on the prevalent conception of the gene as a body which can never be fractionated but can only undergo change (mutation) as a whole. On the other hand, the theory of step allelomorphism as developed by Dubinin (1932) and others is entirely in harmony with the view of gene evolution which I have outlined above. On the assumption that genes are indivisible in all circumstances, it has been necessary to make them smaller and smaller, until the limit is now reached in the single molecule. But surely, if the atom itself can be disrupted by suitable forces, it is not unreasonable to suppose that something of a similar kind may happen to a group of molecules constituting a gene.

The genetic study of variegations in plants has also led to the view that the genes involved are compound structures, the somatic segregation of which results in the variegated condition. The studies of Emerson on the varieties of maize with variegated pericarp, of Baur on *Antirrhinum*, Eyster on maize and *Verbena*, Demerec on *Delphinium* and *Drosophila* are notable in this connexion. Eyster (1928) adopts the hypothesis that the genes causing variegation are compound structures composed of a constant number of 'genomeres' which may or may not be of the same chemical or physical nature. Demerec (1931), however, explains the variegation in *Delphinium* as a result of highly mutable genes. It remains to be seen whether the divisibility of the gene in somatic tissues or the high mutability of such genes will supply the explanation.

We prefer to think of genes as differentiations of many kinds and sizes which have arisen in the core of the chromosome during its evolution, making it a nest of catalytic substances, most of them having specific effects mainly on the development of particular organs. By different processes of translocation in the nucleus, genes tend to become shifted from their original positions. The result is that genes affecting quite different organs come to occupy adjacent positions in the chromosomes. It seems quite likely that, from a historical point of view, mutation has been a much more orderly process than might be supposed from the present disorderly arrangement of the genes in *Drosophila*. The fact that the genes have been scrambled in this way seems to show that mere position within the chromosome is of little or no significance.