GENE AND CHROMOSOME THEORY*

By Dr. H. J. Muller

THE treatment of gene and chromosome theory was on a far more analytical plane than ever before. Thus, the multiform variations of behaviour of chromosomes at meiosis, and the rules governing these variations, were shown by Darlington to trace back to variations in two primary factors: the region (centric or telic) in which pairing begins, and the time limit set to the pairing process; normally, these must be adapted to each other, so that a mixing of two systems tends to disturb the balance.

Regarding the mechanism whereby structural changes in chromosomes come about, a series of experiments by the present author and co-workers was reported, substantiating and extending, for Drosophila, the earlier conclusions of Stadler, of McClintock and of Sax on plant material, and of Muller and Belgovsky on Drosophila, to the effect that the manifold kinds of structural changes capable of surviving indefinitely are all caused by two distinct primary processes, succeeding one another. These are: (1) breakage of the chromonema at two or more points, followed (2) (though not until after the spermatozoon stage is passed) by two-by-two junction between the adhesive broken ends, giving a new linear order. Distant breakages, giving gross changes, were shown to result from separate individual ionizations, but nearby ones, giving minute rearrangements, to result from one and the same ionization by a spreading of its effect. The reports and demonstrations of a large series of separate investigators—Bauer, Fabergé, Demerec, Camara, Catcheside, Oliver and Belgovsky—in one way or another agreed with or led to one or more of the same conclusions, although some investigators had until then held contrary views. Further light was thrown on chromosome structure and on the changes to which it is subject, in a special evening lecture by Metz, recounting his notable findings in Sciara.

A considerable group of papers analysed the special, though not absolutely distinctive, properties of heterochromatic regions of chromosomes. In this connexion, further illustrations were given of the high breakability of these regions by Kaufmann, Camara, Prokofyeva and Sidorov, and of their somatic variability (correlated in related cells) in respect to manner of chromatin staining, manner of aggregation of chromonemata and gene functioning. It was noted that all these properties extend, although to a degree diminishing with distance, beyond the originally heterochromatic regions into regions lying near to them in the chromonema, by a kind of 'position effect' (Schultz, Prokofyeva, Panshin, Khvostova), and the important new point was brought out that the variations in staining—which, as proved by Caspersson and Schultz's studies of ultra-violet absorption spectra, fairly represent nucleic acid distribution—and the variations in gene activity are correlated with one another. Evidence was also adduced, by Prokofyeva and by Kaufmann, that small interstitial regions having some degree of heterochromaticity are scattered rather widely throughout the chromatin, and often coincide with regions that apparently originated relatively recently as duplications (which suggests that genes may become heterochromatic by a kind of denaturizing degeneration).

Analysing the mechanism of gene mutation on the basis of a great series of experiments, Timoféeff-Ressovsky brought out its causation (1) by individual atomic activations, apparently resulting from the accidental peaks of kinetic energy of thermal origin, as well as (2) by individual ionizations, resulting from radiation. The dependence on single ionizations was further strengthened by Rai-Choudhuri's finding that even radiation of intensities so low as 0·01 r./min. (a hundred times lower than the lowest previously used in such work) is so effective, ion for ion, as radiation of higher intensities. At the same time, the generality of the gene mutation effect of radiation was strengthened in another important way, by its definite extension to mammals (mice), in experiments of P. Hertwig.

* Although the Russian geneticists had withdrawn and most of the Germans had left before the time for their addresses, their abstracts had already been submitted, and in this Section the policy was followed of reading all such papers *in absentia*. They are accordingly included in this report, although only the papers of official members will be printed in the *Proceedings*. Also included here are papers given in joint meetings of this and the next Section.

In earlier work, no dependence of the frequency of the gene mutations upon the closeness of spacing of the ions within the radiation-paths could be detected, but newer work by Timoféeff-Ressovsky and his collaborators, reported at the meeting, suggested that a perceptible influence of this kind might be found by the use of the extremely closely spaced ions resulting from some neutron radiation. If so, it should be possible to estimate the 'sensitive volume' for a gene mutation, that is, the amount of contiguous space occupied by material so constituted that one ionization, occurring anywhere within it, is capable of producing some one or more of a given series of alleles. Similar work, utilizing the frequency of chromosome breakage instead of that of gene mutations, was reported by Marshak. In this connexion, however, it should be noted that if, as seems likely, only a small proportion of the ionizations occurring within the region in question actually resulted in the effect looked for, this method would tend to lose its efficacy. Moreover, we have no basis for identifying the volume or area in question with that of the gene or chromonema itself.

In addition to the seemingly simple thermal effect of van t'Hoff type, above-mentioned, there were shown—by Plough, Timoféeff-Ressovsky, Kerkis and Zuitin—to be decided increases in mutation frequency attending the abnormal physiological states of organisms subjected to temperature changes too rapid or too extreme for the organisms to adjust to them. This makes the search for special chemical influences affecting gene mutations seem more promising, despite certain negative results reported by Auerbach with carcinogenic substances. The sensitivity, as well as the intricacy, of the chemical complexes conditioning mutation was further evidenced by the strong dependence of the general mutation frequency upon the genetic complex present, as reported by Plough and by Tiniakov, and more especially by observations of Rhoades and of Harland showing certain enormous and highly specific mutational effects on particular genes, not previously known as 'mutable genes', by other particular genes and gene-combinations.

The series of papers dealing with the production of mutations by ultra-violet light showed the notable progress made in this field since the last congress. It was shown by Stadler that the curve representing the effectiveness of different wave-lengths in producing gene mutations and deficiencies in maize pollen begins at about 313 mμ and rises to a peak at 254 mμ, declining thereafter. This is suggestively similar to the absorption spectrum of nucleic acid and quite different from that of protein. Both Hollaender, working on fungus spores, and Knapp and Schreiber, on spermatozoids of Sphærocarpus, reported results substantially similar to this, although their peaks of mutational effect (as well as of directly lethal effect) were at 265 mμ, which corresponds more exactly to the absorption peak for thymonucleic acid. In Hollaender's work, however, there was also a secondary peak, at 238 mμ; and another peculiarity in his results (one suggesting differential sensitivity of different spore-stages) was a falling off in the mutation frequency of surviving individuals at very high doses.

In Stadler's work, a basis was found for drawing qualitative distinctions between several different classes of radiation effects. Thus, the frequency of abortive embryos at different wave-lengths, unlike that of gene mutations and deficiencies, failed to follow the nucleic acid curve, as it showed too high frequencies for the shorter wave-lengths. While these abortive embryos may after all represent some kind of non-genetic effect, the same cannot be said of sectional rearrangements of chromosomes (translocations). Stadler found that the latter were not produced by ultra-violet light, or were produced with a markedly lower frequency than by X-rays of the same gene mutation-producing strength.

This result, which was corroborated for Drosophila sperm by experiments carried out by Muller and Mackenzie, gives some ground for supposing that ultra-violet does not act by breaking the chromosomes, and that therefore gene mutations may not consist merely of linear rearrangements of ultra-small size, involving 'intragenic' breakage and reunion. The latter idea, which is not yet actually refuted, would have tended to make the concept of the segmentation of the chromosomes into discrete 'genes' a mere matter of verbal convenience. Possibly connected with the same series of problems was Stadler's further finding that the gene mutations produced by ultra-violet are far oftener 'fractionals'—that is, confined to one of the chromatids derived from a given treated chromosome—than are those produced by X-rays.

For the first time in the history of genetics congresses a session was included on virus and protein studies in relation to the problem of the gene. A peculiar case of non-chromosomal, probably virus, 'inheritance' in Drosophila, was reported by L'Héritier and Teissier. As was brought out by McKinney, by Gowen and by Kausche, viruses, now known to be crystallizable nucleoproteins, have the distinctive combination of properties characteristic of genes, namely, mutation and (despite mutation) self-duplication, thus substantiating the concept (Muller, 1921, 1926) that viruses represent relatively free genes, and that the gene constitutes the basis of life.

An illuminating account was given by Astbury of his and other modern studies of the chemical structure of viruses and other proteins, with especial consideration of those features which might help to explain the gene's property of mutable self-duplication. He, as well as Caspersson and Schultz (who reported an increase of nucleic acid during periods of growth, both for chromosomes and for cytoplasm), directed attention to the role which nucleic acid may have in this process. The significant fact was reported by Astbury that the nucleic acid spacings are of the same magnitude as those within the protein (polypeptide) chain, a feature which would allow the nucleic acid to unite in parallel with the protein and so perhaps to serve as an intermediary in its synthesis. The paper of Mazia also was of interest in this connexion, since it showed that in salivary chromosomes the framework is not disintegrated by digestion either by pepsin or by nuclease, though it is by trypsin; hence it probably consists of protamine or histone chains, bound together laterally in some other way than by nucleic acid cross-connexions. Other chemical studies of nuclear material were reported by Gulick, which among other things cast doubt on the presence of iron in chromosomes, thus bringing their composition closer to that of the virus.

Our present knowledge of the internal structure of the tobacco mosaic virus particles, as disclosed by the pioneer X-ray diffraction studies of Bernal, Crowfoot *et al.*, was described by D. Crowfoot as well as by Astbury. It was shown that in these rods, which are 15 mμ thick and at least ten times as long, the smallest possible chemical unit—that associated with one nucleotide—must contain about fifty-four amino-acid radicals, although there may be a geometrical sub-unit as small as one eighth of this volume (that is, about 1 mμ each way). But these units (or sub-units) are grouped according to a regular pattern into larger aggregates, about 7 mμ long, and the latter in turn are grouped in a regular way to form the aggregate of high order—the virus rod itself. The globular protein insulin, as well as the fibrous proteins, all show elementary units of about the same size, but the mode of aggregation varies both with the protein and with the conditions (*p*H, amount of water, etc.) under which it is being kept. Thus this type of analysis is already bridging the gap between the structures of the chemist and those of the microbiologist and geneticist.

A series of special conferences were held on problems of the gene, presided over chiefly by J. B. S. Haldane. These were very well attended. At these gene conferences' many of the reports of those unable to attend were read, and many of the above and related questions concerning gene and virus structure and gene mutation were subjected to animated and searching discussion.

CYTOLOGY

By Dr. C. D. Darlington

PERHAPS the most significant feature of the cytological discussions was the difficulty of separating them, except in an arbitrary way, from the discussions of experimental breeding This was due to three general trends. First there was an increasing use of the direct study of meiosis as a basic of genetic prediction and as a means of testing the reproductive methods of particular species. The work of White and Koller with sex chromosomes and of Huskins and Newcombe with the relations of chromatids at chiasmata were examples of the one, the studies of Levan on Allium, of Cleland on Œnothera, and of Janaki on Saccharum were examples of the other.

The second trend was the increasing application