Chromosome Behaviour in Terms of Protein Pattern

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CHROMOSOMES are molecular aggregates. An ultimate objective, both of cytology and of genetics, must therefore be to interpret their findings in terms of the molecular structure of chromosomes. If, as there seems reason to suppose, chromosomes consist substantially of aggregates of protein molecules in association with nucleic acid, the properties of such aggregates must inevitably determine the behaviour of chromosomes in general, the characteristics of individual chromosomes being attributable to the possession of individual protein patterns.

In view of recent advances in our knowledge of proteins[1], it is reasonable that an attempt should now be made to see how far the properties of chromosomes and the facts of genetics may be brought into relation with certain known facts of protein structure.

To this end a molecular model—however inadequate—must be constructed. The model consists of one or more two-dimensional sheets in the form of a long, worm-like, uni- or multi-molecular surface. The units which lie disposed, possibly helically, along the surface are homologous protein molecules of the classical type[2]—peptide linked amino acids—

. . . -NH-CO-CP-NH-CO-CQ-NH-CO-CR-NH- . . .

put end to end. In consequence, the specification of a chromosome will be in terms of the side chains . . . *P Q R* . . . belonging to molecules consisting of certain numbers of amino acid residues, and, in the most general case of n molecules, will consist of a linear sequence of n linear sequences

$$A_1B_1C_1 \ldots X_1Y_1Z_1A_2B_2C_2 \ldots X_nY_nZ_n.$$

Such an arrangement is in excellent accord with the structure recently proposed for clupein[3], the basic protein of herring sperm, since this structure is specified in terms of a sequence of side chains, namely,

. . . . *M A A M A A M A A* . . . .

with, in some cases,

. . . . *M A A A A M A A M A A A A*;

where *A* represents arginine and *M* some monoimino or monoamino-monocarboxylic acid. The specificity of a given chromosome may be regarded as an expression of its particular protein pattern. (The orderly arrangement of black and white notes on the keyboard of a piano provides a rough picture of what is meant.) Since arginine is known to be the major constituent in sperm of various species, an attractive hypothesis (as a first approximation) is to define chromosomes in such species as various sequences of *M* and *A*. Even if we maintain the ratio of 2 to 2·5 *A* molecules to one *M* molecule, as required by the chemical analysis of clupein, a considerable and presumably sufficient variety of sequences is available.

The end groups of the arginine side chains in the protein molecules[4] are completely ionised for pH < 9 and the four acidic groups in the molecules of nucleic acid[5] for pH > 4, and salt compounds will be formed. In the range pH 4 to pH7, nucleic acid has a variable *zwitterionisch* character, consequent upon the ionisation of the fifth acidic group (pK = 6·0) and of the amino groups in cytosine (pK = 4·2), in adenine (pK = 3·7), and in guanosine (pK = 2·3). The degree of ionisation of the end carboxyl and amino groups of the individual polypeptide chains (which in clupein are on the average 28 residues = 98 A. long[3]) is also variable in this range.

Cyclical changes in pH in this range are believed to occur during mitosis[6]: they would entail a cyclical variation in the degree of hydration of the molecular aggregate as a whole, which accords well with the swollen state of the chromosomes in early prophase[7,8], and with the severely dehydrated state of chromosomes at metaphase established by Belar in a classical experiment[9]. By analogy with keratin[10], the molecular aggregate may be regarded as being endowed with considerable powers of contraction, due to a number of different contractile factors. A cyclical change in pH suggests another technique of contraction, which in view of the facts of differential condensation (heteropycnosis)[11,12] is possibly the most important: for the change entails cyclical readjustments in the association of the protein chains with molecules present in the cytoplasm, in particular in the association with the molecules of nucleic acid. The *zwitterionisch* character[13] of molecules appears to provide a key to many cytological problems, notably to those concerned with the geometry[14] and dynamics[8,15] of chromosomes, which have recently been the subject of a number of cytological studies.

The model may also be studied in relation to the other essential properties of chromosome, namely, growth and division. The chromosome here pictured as a cylindrical mosaic or manifold—but with a radius running into thousands of angstroms—may add to its material by the wrapping round of new sheets, each new sheet being laid down over the old mosaic, as in the case of keratin[10]. Alternatively—and more probably—it may grow after the manner of a smectic crystal, such as a film of sodium oleate, where growth consists in other molecules slipping into their places and increasing the area[16]. The incorporation of sufficient new material would then lead to instability, the tendency to division being aggravated by a change in pH which gives the whole aggregate a larger net charge—and the molecular aggregate (now a charged shell) divides after the manner of a charged drop.

Our model is also of significance for genetics. Two chromosomes defined respectively by:—

$$A_1B_1C_1 \ldots . X_1Y_1Z_1A_2B_2C_2 \ldots . X_nY_nZ_n$$

$$A'_1B'_1C'_1 \ldots . X'_1Y'_1Z'_1A'_2B'_2C'_2 \ldots . X'_nY'_nZ'_n$$

will differ genetically if they differ in one or more members of their sequences. Genetics formally requires of a chromosome that it be specifiable as a sequence *a b c d . . . x y z* which is capable of certain types of behaviour, for example, fusion and fragmentation, represented respectively by:—

$$abcd \ldots p + qrstu \ldots xyz \rightleftharpoons abcd \ldots\ldots pqrstu \ldots\ldots xyz.$$

For the units *a b c* an upper limit of 200–300 A. has been suggested by H. J. Muller and A. A. Prokofyeva[17]. We therefore identify a genetic character with a sequence of n residues: since the length of an amino acid residue[18] is 3·5 A., the upper limit would allow n to be anything up to 86. With this identification,

the phenomena of fusion and fragmentation fall neatly into place on the basis of the classical researches of Fischer, which would translate them into the form :—

$$\ldots\text{-CO-CP-NH}_2 + \text{COOH-CQ-NH-}\ldots \rightleftharpoons \ldots\text{-CO-CP-NH-CO-CQ-NH-}\ldots + H_2O.$$

A detailed investigation will be published shortly, offering molecular interpretations of a number of genetic and cytological facts, including those relating to the nature of chromocentres, heterochromatin and euchromatin[19], the behaviour of the spindle attachment[8], the nature of chromomeres and of some of the forces between chromosomes[8]. The fundamental approach to the problem is clearly the study of the molecular structure of chromosomes by X-rays. Pending the necessary technical developments we must pursue our inquiries inductively. The central theme of the work—the chromosome as a crystal structure—gives unity and coherence to the task, the considerable body of knowledge of protein molecules in general, including those of globular type[20], providing a most admirable guide.

Happily, opportunities of testing the hypothesis are not wanting, those rendered possible by the new work on clupein[3] being specially attractive.

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Brood Diseases of Bees

THE eighteenth of the Rothamsted conferences was held at the Experimental Station on May 19, 1934, under the chairmanship of Sir John Russell, and was devoted to papers and discussions on the brood diseases of the hive bee. Its proceedings have now been published under the title of "Brood Diseases of Bees".*

Notwithstanding the extensive researches which have been conducted on foul brood diseases of bees, the present knowledge of the subject is still very incomplete. Practically no scientific work has been done in Great Britain on brood diseases since 1885, and such information that is at present available is derived chiefly from the results of investigations carried out in other countries. The advisability of studying this subject in England has been recognised for some years by the Rothamsted authorities, and the advisory committee connected with the apicultural branch of the Experimental Station strongly urged that action should be taken.

Sir John Russell, in his introduction to the published report on the Conference, explains how the means for carrying out the necessary work was obtained. A decisive move was made by the British Bee Keepers' Association, which secured from its constituent bodies subscriptions enabling it to guarantee a sum of £250 a year for three years. An equivalent amount has been voted by the Agricultural Research Council, and a capital sum of £250, for the special equipment needed, has been obtained through the generosity of private benefactors. Dr. J. C. G. Ledingham, and the managers of the Lister Institute, have offered the use of their laboratories for any special bacteriological work required. The actual investigations started in the present year when Dr. H. L. A. Tarr was appointed in charge of the work. The Conference, it may be added, was called at the outset of the investigations in order to review the whole subject.

In the printed report, Mr. D. Morland contributes an article on the distribution of foul brood diseases in England, which is based on replies received in response to a questionnaire. The information received indicates the need for a full survey of the incidence, varieties and means of control of brood diseases, rather than any feeling that the data obtained is at all complete or that informants were always correct in their diagnoses. Other contributors discuss the historical aspect of our knowledge of brood diseases and the subject of legislation with reference to bee diseases in other countries. The possible benefit to be derived from legislation, as a means of controlling the spread of brood diseases, suggests itself when the success attendant upon such methods in Switzerland, for example, be taken into account. In reviewing the present position of the scientific study of foul brood diseases, Dr. Tarr lays stress upon the confusion that at present exists as regards this subject. American foul brood, European foul brood, sacbrood and rarer infections are individually discussed. The concluding article by Mr. D. Morland is essentially practical and summarises our knowledge with regard to the symptoms, means of prevention and current methods of treatment of the various diseases in question.

The papers contained in this report provide an excellent summary of the present status of the whole subject: they indicate what is already known and

* Rothamsted Conferences, 18: Brood Diseases of Bees. (Secretary, Rothamsted Experimental Station, Harpenden, Herts.) 1*s.* 6*d.*