REVIEWS

SYNTHESIS AND STRUCTURE OF MACROMOLECULES. Cold Spring Harbor Symposium on Quantitative Biology, Vol. 28 (1963). Cold Spring Harbor, Long Island, New York. Pp. 610+xx.

Molecular biology is concerned especially with the basic questions of how the genetic DNA is replicated, how it determines the structures of other macromolecules, especially proteins, and how the rates of formation of proteins, and their enzymic activities once formed, are regulated. This impressive volume provides something approaching a complete account of the state of these enquiries in the summer of 1963. It contains over 600 substantial double-column pages and no fewer than 74 individual papers and it is impossible to mention more than a minority of them.

The very first paper, by Ris and Chandler, stands alone in dealing with the genetic material of higher organisms. The authors, having established their credentials by producing a beautiful electron micrograph of the complete genome of a *lambda* bacteriophage particle (one looped molecule of DNA) go on to present some much more complex pictures of chromosomes of various animals. These latter provide some of the clearest evidence so far for the compound nature of higher organism chromosomes; in the newt *Triturus*, for example, there seem to be at least four parallel molecules of double-stranded DNA in each chromosome. This paper, almost unrelated to anything else in the symposium, seems to have evoked little response. Indeed, current molecular genetical theory has little to say on the problem of how a chromosome can be multistranded and still act as a unit of mutation and of semiconservative replication; but the questions raised by the observations of Ris and others cannot be neglected for much longer.

Cairns, by means of extremely elegant autoradiography, provides direct evidence for the semiconservative sequential replication of the *E. coli* genome, while Sueoka and Nagata, working respectively with *Bacillus subtilis* and *E. coli*, also show sequential replication through ingenious techniques for timing the duplication of genetic markers. Cairns's observations imply that the two new strands of opposite polarity which are formed during duplication of a DNA molecule must grow in the same direction; that is, that one must grow by addition of nucleotides to the end of the chain with the free 5′-carbon atom, while the other adds nucleotides to the end with the free 3′-carbon. The latest information on the isolated DNA polymerase, contributed here by Kornberg's group, is that it adds nucleotides only to a free 3′-hydroxyl end, and so the *in vitro* system accounts at most for only half of the process of DNA synthesis *in vivo*.

The following section deals with the synthesis of RNA both by means of the DNA-directed enzyme, RNA polymerase, which appears to be universally present in living cells, and by various RNA-directed polymerases, which so far have only been detected in cells infected with RNA viruses. Thus there are now well established enzymatic processes both for transcribing DNA base sequences into RNA base sequences, and for replicating RNA itself as genetic material.

Messenger RNA is the subject of numerous papers, several authors

using the DNA-RNA hybridisation technique of Spiegelman and Hall to identify RNA complementary in base sequence to DNA. Perhaps the most convincing demonstration of the reality of messenger is that of Attardi *et al.*, from the Institut Pasteur, who used transducing λ phage as a source of the *gal* segment of the *E. coli* chromosome through which to identify the complementary RNA species; it turns out that the putative messenger is only present in significant amounts under conditions (presence of galactose) where the *gal* genes are active. It would be even more satisfactory if a natural messenger could be shown to deliver its message to the protein-synthesising machinery in an *in vitro* system. Spiegelman and Doi appear to have demonstrated that the RNA of the RNA bacteriophage MSØ$_2$ will induce the formation of the phage coat protein in a cell-free system, but this is rather a special case, with the genetic RNA acting as its own messenger.

Work on artificial messengers, in the form of synthetic polynucleotides of controlled composition, seems now to have been pushed almost to the limit of what is possible by present methods. Both Nirenberg and his group, and Speyer, Ochoa and their collaborators have identified coding triplets for all the protein amino acids; the coding assignments made by the two groups agree, with very few exceptions, and most amino acids are coded for by two or three different triplets, a result which agrees with the expectation, on genetic grounds, that the code is likely to be highly degenerate with rather few " nonsense " triplets. Weinstein's results with mammalian cells and *Chlamydomonas* suggest that the genetic code may be the same in all organisms. The high hopes engendered by Nirenberg's discovery, only three years ago, of the stimulation of phenylalanine incorporation by polyuridylic acid have been amply justified, but experience has also shown that results obtained with *in vitro* systems with synthetic polynucleotides, should not be taken too literally as necessarily representing in detail what happens in the intact cell.

Transfer RNA, as the key to the translation of RNA base sequence into protein amino acid sequence, naturally comes in for a good deal of attention. Transfer RNA molecules, which are only about 80 nucleotides long and are apparently of a limited number of separable types, each specific for one amino acid, are especially attractive objects for structural study at the present time. Papers by Holley, Ingram and Cantoni show how much progress has already been made towards the solution of their structures. When a few of them have been fully analysed the reasons for their specificity for particular RNA coding sequences on the one hand, and for particular amino acid activating enzymes on the other, should be much clearer.

Much has been added in the last year to knowledge of the way in which ribosomes participate in protein synthesis. The papers by Gilbert and by Rich *et al.*, with their emphasis on the importance of polyribosomal aggregates, make this subject seem much clearer than it has ever been before, though much about ribosomes remain mysterious.

With the synthesis of completed polypeptide chains the process of genetic information transfer is generally thought to have been completed, but one still has to explain how the specific folding and aggregation of polypeptide chains into complete protein molecules is accomplished. Conformational changes induced in enzyme proteins by the binding of small molecules are dealt with in a substantial section devoted to " allosteric " effects; such changes are now recognised as of major importance in

the regulation of the enzyme activities of proteins. An adjacent section deals with inter-allelic complementation, which from being a mere oddity and a hindrance to tidy genetic nomenclature, is now seen as exemplifying a type of interaction between polypeptide chains which is of very general significance for the explanation of protein structure.

This symposium saw the launching of at least two new ideas, both likely to be widely influential. The first is the *replicon* model of Jacob, Brenner and Cuzin. The replicon is seen as a unit of DNA replication, with a *replicator* segment at which replication is initiated, and another gene controlling the formation of an *initiator*, perhaps an enzyme. According to this model only DNA segments possessing a replicator segment are able to replicate automonously, and this explains the difference between autonomously replicating episomes and non-replicating DNA fragments. The analogy with the *operon-operator-regulator* model (also from the Pasteur Institute) for regulation of gene action is obvious, and the replicon model has the same sort of instant appeal, though the evidence in its favour is not yet compelling.

The second new idea, put forward in a fascinating paper by Ames and Hartman, is that of sites within messenger molecules which cause " modulations " in the translation process. There is very clear evidence now that many mutations within one gene of an operon can affect, in a quantitative way, the activities of all the genes in the operon to the " left "—that is, of all genes whose messages are thought to be translated *after* that of the gene primarily affected. These results will affect all our future thinking on functional relationships between adjacent genes.

Finally one must mention the paper on conditional lethal mutants in bacteriophage T_4 by two groups of workers headed respectively by Edgar and Epstein. Purely as a piece of formal genetics this work is a considerable landmark. The almost complete analysis of a genome, even of a virus, into a definite number of known genes, is a spectacular achievement. This paper also introduces the electron microscope as an instrument for the routine scoring of mutant phenotypes.

The arguments against publishing the proceedings of symposia are well known, and to some extent are supported by this volume. When all the papers are invited, and when manuscripts are often extracted with difficulty from authors at or after the last possible moment, editorial screening is apt to be minimal. The papers tend to suffer from the common defects of written-up oral presentations, often combining a high density of experimental results and a rather wide-ranging account of a variety of investigations with a complete absence of any concise summary. Most of the papers are not easy to read and most of the material has been, or will be, published in the regular journals, often in more readily assimilable form. In spite of such criticisms this publication, like its predecessors, fully justifies itself by the distinction and importance of the bulk of the work which it represents, and by the convenience of having all of it in one place. The possession of this one volume will save the owner much hunting through the literature and many visits to the library.

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