SYMPOSIUM ON NUCLEIC ACIDS AND NUCLEOPROTEINS

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CHAIRMAN’S INTRODUCTION

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This symposium on nucleic acids and nucleoproteins was arranged because the sensitive probing point of really significant research in several important areas of biology and medicine seems to be leading directly to these materials and there is a pressing need for a greater general appreciation of the importance of the nucleoproteins and nucleic acids. For a long time the genetic material of all living things has been regarded as nucleoprotein in nature. Then the viruses, the smallest structures possessing many of the properties of living agents, were found to be nucleoprotein in nature, with many viruses being comprised solely of nucleoprotein, and some of these being crystallizable. Some of the most potent anticancer and mutagenic agents have been found to be analogues of components of nucleic acids.
In the enzymatic synthesis *in vitro* of deoxyribonucleic acid it has been found necessary to have present in the system a small amount of nucleic acid, presumably to act as a primer and to provide the pattern for the newly synthesized nucleic acid.* Nucleoprotein particles from cells have been found to provide the structural framework for the addition of activated amino acids in the synthesis *in vitro* of peptides. Thus nucleoproteins and more probably the nucleic acids seem to be the key material in the transfer of genetic information from parent to progeny, in mutation and hence in the evolutionary process, in the transformation of a normal cell into a malignant cell, in nucleic acid synthesis, and in protein synthesis.

To some the symposium this morning may seem to be unduly concerned with work on tobacco mosaic virus, hence a word of explanation may be in order. Tobacco mosaic virus and its strains would appear to represent the materials par excellence for launching an experimental attack on the basic problems just mentioned. This viral nucleoprotein and its strains can be obtained without undue effort in gram lots in preparations that are almost completely homogeneous—chemically, physically, and genetically. These viral nucleoproteins are highly organized rods 15 by 300 mμ in size and are composed of 5 per cent ribose nucleic acid and 95 per cent protein. The latter is, in turn, composed of about 2,100 sub-units of about 18,000 molecular weight arranged in helical fashion, and the nucleic acid appears to be a single elongated molecule of about 2 million molecular weight intermeshed in a helical pattern within the protein. These components can be separated to yield a protein preparation and a nucleic acid preparation and the latter has been found to retain the characteristic virus infectivity. Under certain conditions the protein and nucleic acid components can be reconstituted to form the original rod 15 by 300 mμ in size possessing full virus activity.

The very important fact that inoculation of a susceptible host with the nucleic acid preparation alone induces the formation of additional molecules of its own kind as well as the formation of a highly specific protein with which it eventually combines offers a direct experimental approach to the synthesis of polynucleotides and polypeptides and their interrelationships. If the chemical and genetic significance of the general association of nucleic acid and protein is ever to be elucidated, the tobacco mosaic virus system is probably the least complex we are likely to find for its study. Already much is known about the sequence of the 164 amino acids which make up the sub-unit of the protein component of this virus, and it seems reasonable to expect that we will be able to write out the exact amino acid sequence of this structure in the near future.

It is already known that the different strains of tobacco mosaic virus contain protein components which differ. While the amino acid sequence that is characteristic of a given strain is not known in such great detail as obtains in the case of the parent tobacco mosaic virus, it is known, for example, that a sub-unit from a given strain may characteristically contain a different amino acid at a given location. Thus there is ample reason to believe that every viral strain has an amino acid sequence that is uniquely characteristic for that strain. Since nucleic acid preparations alone are infectious, it is also reasonable to suppose that the nucleic acid of every viral strain has a polynucleotide sequence that is characteristic of that strain and that in each case a given polynucleotide sequence governs the corresponding polypeptide sequence. This conception provides a unique opportunity to probe
into the possible point-to-point structural relationships that may exist between the polynucleotide and polypeptide during the synthetic processes within the cell. Furthermore analogues such as fluorouracil, a compound possessing antitumor activity, can be incorporated into tobacco mosaic virus nucleic acid to a substantial extent and any resulting biological effects as well as any effect on the amino acid sequence within the progeny nucleoprotein can be studied. Tobacco mosaic virus thus provides a most favorable experimental material for these very important and very basic studies. It is unfortunate that polynucleotide chemistry is not nearly so advanced as is polypeptide chemistry and that the eventual solution of problems involving polynucleotide sequence may be some years in the future. However, as you will learn this morning, the pattern has been set and in time we confidently may expect to know the polynucleotide sequence that is characteristic of a replicating system, and something concerning the detailed structural changes involved in mutation and whether or not these can be controlled or perhaps even directed. We may also expect to learn something about the aberration in polynucleotide sequence that most probably is responsible for the transformation of a normal cell into a malignant cell. I trust, therefore, that this morning you will listen to the papers, some of which may appear rather detailed, with this larger view in mind. Work of this type and its extensions into the future are destined to permeate all of biology and medicine and eventually solve some of the most perplexing problems facing mankind.

*The presentation which was made by Howard K. Schachman of work with Arthur Kornberg entitled "Studies on the Enzymatic Synthesis of Deoxyribonucleic Acid" is not included among the following papers but some of this work has already been published in the Proceedings of the National Academy of Sciences [44, 633-647 (1958)].

ULTRACENTRIFUGAL FRACTIONATION AND IRON DISTRIBUTION IN INFECTIOUS NUCLEATES FROM TOBACCO MOSAIC VIRUS*

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Although the infectious materials prepared from tobacco mosaic virus, TMV, by Fraenkel-Conrat, Singer, and Williams1 and by Gierer and Schramm2 are generally considered to be salts of ribonucleic acid or ribonucleates, there has been neither agreement as to the molecular weight of the infectious component nor satisfactory explanations provided for their relatively low infectivity. With respect to the first question the authors first mentioned found that the infectivity was not sedimented under conditions (105,000 × g for 2 hr at about 0°C) where sedimentation might be expected for a particle of the order of 2 × 10^6 molecular weight. Accordingly they estimated that the infectious nucleate was of the order of 2 × 10^8 in molecular weight. Gierer,3 on the contrary, has suggested on the basis of sedimentation velocity and infectivity studies that infectivity was associated only with nucleate particles of the size present in the original TMV rods, namely about 2 × 10^8. Partial agreement with the latter conclusion has come from the work of Hop-