A SYMPOSIUM ON THE CHEMICAL BASIS OF HEREDITY. EDITED BY WILLIAM D. McELROY & BENTLEY GLASS

A Symposium on

THE CHEMICAL BASIS OF HEREDITY

Sponsored by

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Edited by

WILLIAM D. McELROY AND BENTLEY GLASS

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The Mechanism of Enzyme Action.

Amino Acid Metabolism.

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PREFACE

A Symposium on The Chemical Basis of Heredity was held at The Johns Hopkins University under the sponsorship of the McCollum-Pratt Institute on June 19-22, 1956. This volume consists of the papers and informal discussions presented at these meetings.

Biologists have long been concerned with the mechanism of duplication, and geneticists in particular have developed the concept that probably the only self-reproducing unit smaller than the cell is the gene. Chemical discoveries during the past ten years relating particularly to nucleic acid and chromosome structure, gene function, protein synthesis and enzyme action have provided a broad chemical and physico-chemical framework which makes speculation on the mechanism of duplication profitable. In the planning of the present symposium we attempted to bring together those geneticists, virologists, biochemists, physiologists, biophysicists, and physical chemists who have made important contributions to our understanding of the mechanism of self-reproduction with the hope that an exchange of ideas would be of value in eventually explaining "The Chemical Basis of Heredity".

In the planning of the Symposium the participants and members of the Institute contributed their time generously. It is a pleasure to acknowledge the important contributions of the following moderators: Dr. Bentley Glass (Part I), Dr. Boris Ephrussi (Part 2), Dr. S. Luria (Part 3), Dr. Roger Herriott (Part 4), Dr. Paul Doty (Part 5), Dr. Gerhard Schmidt (Part 6) and Dr. J. Lederberg (Part 7).

It is also a pleasure to acknowledge the important assistance of the Atomic Energy Commission in helping defray part of the expense of the Symposium.

October 10, 1956

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CELLULAR UNITS OF HEREDITY

THE ROLE OF THE NUCLEUS IN HEREDITY

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SEVERAL FACTORS have interacted to accelerate the advance of genetics in recent years. The widespread use of microorganisms, including viruses, has been one of these (10). Such material makes feasible the study of phenomena that occur with a frequency several orders of magnitude smaller than those that are investigated in higher forms. An increasing tendency for geneticists and biochemists to think about biological problems in common terms and to make use of each other's methods has also been important. Perhaps even more significant has been the formulation of the Watson-Crick hypothesis of deoxyribonucleic acid structure (5, 50). This has made it increasingly profitable for biologists and chemists to think, talk, and write about genetic units in terms of clearly defined chemical concepts. Symposia such as this, in which investigators from a variety of disciplines come together to exchange information and views, likewise play an important part.

I believe it will be useful to attempt, at the beginning of the Symposium, to summarize present knowledge about genetic material. I propose to do this briefly and simply, making use of those interpretations and hypotheses of gene structure and gene function that seem more probable to me. This is not easy, for there is much that we do not yet know and many points on which presently available evidence appears to be conflicting. I fully realize that my presentation will be colored by my prejudices and will suffer from my incomplete knowledge of certain lines of evidence.

THE GENE AS A BIOLOGICAL UNIT

Beginning with Mendel and for some sixty years thereafter geneticists worked almost exclusively with higher plants and animals. The garden pea, maize, the jimson weed, the fruit fly, the mouse, and man

were some of the organisms that contributed importantly to the knowledge of classical genetics. The "factor" or "gene" of the genetics of this time was a unit of inheritance, detected only if it existed in two or more forms each with a characteristic developmental effect (37, 38).

In the second decade of this century it became clear that genes are carried in chromosomes and are arranged linearly. The many genes carried in a single one of the several kinds of chromosomes of a given species are "linked," i.e., transmitted from one generation to the next as a group. During chromosome pairing at meiosis, heterozygous linked genes may recombine through "crossing over" between homologous chromosomes. The frequency with which such recombination occurs for any two linked genes is a function of the distance between them and provides the basis on which linear genetic "maps" of gene loci are constructed.

Until recently it was widely believed that the process of crossing over does not alter individual genes—that it occurs between genes, not within them. The evidence on which this belief was founded is the basis for considering the gene to be an elementary biological unit, occupying a definite position in a chromosome (a locus), and transmitted intact from one generation to another.

In recent years evidence has accumulated that can be interpreted to mean that the gene is divisible by intragenic crossing over. The nature and significance of this evidence will make up an important part of this Symposium (2, 3, 4, 18).

The Chemical Nature of the Gene

Chromosomes are composed of deoxyribonucleic acid and protein combined in a way that is not yet completely understood (25, 32, 42). For many years it was assumed that genetic specificity was to be accounted for entirely in terms of the structures and configurations of proteins.

The demonstration that transformations in type specificities of pneumococcal bacteria can be brought about by highly purified preparations of deoxyribonucleic acid (DNA) first focussed attention on this substance as possible carrier of genetic information (1). Over the years it has become increasingly clear that DNA does indeed constitute the primary genetic material in this organism (11, 12, 23, 24).

In the phages (bacterial viruses), too, the evidence is strong that genetic continuity resides in DNA. In these relatively simple systems,

infection of host cells is accomplished through the injection of phage DNA. Experiments in which DNA and protein are labeled with P-32 and S-35 show that the injected material is 97 per cent DNA and only 3 per cent protein (19). The protein coats remain outside. Although it remains conceivable that the protein injected plays some direct genetic role, it seems more probable that continuity of phage genetic material depends solely on DNA at this stage of the life cycle.

Unlike phages, tobacco mosaic virus contains ribonucleic acid (RNA). In the virus rod RNA is carried inside a cylindrical protein jacket (13, 14, 17, 30). No DNA is present. Obviously in this system the primary genetic information must be carried in the form of RNA, for RNA alone can bring about infection under certain conditions (14, 15). This conclusion is confirmed by the behavior of artificially reconstituted virus particles consisting of protein and RNA from genetically different strains. The progeny of such "hybrid" viruses are like the strain that contributed the RNA (14).

The evidence in higher forms is less decisive. By analogy with viruses, it is assumed as a working hypothesis that the primary genetic material is DNA rather than protein.

The Watson-Crick Hypothesis

The Watson and Crick hypothesis (5, 50) that the polynucleotide chains of DNA normally assume the configuration of a double helix in which chains are hydrogen-bonded together through complementary base pairs is strongly supported by evidence from x-ray diffraction patterns and from analytical data on base ratios (52). In the double helix, adenine (A) and thymine (T) form one base pair. Guanine (G) and cytosine (C) constitute the second pair. Since there are two ways in which a given base pair can be turned at a given level in the helix, there are four base pairs possible.

The Watson-Crick structure is attractive from a biological point of view because it provides a plausible basis for gene specificity, for gene replication, and for gene mutation.

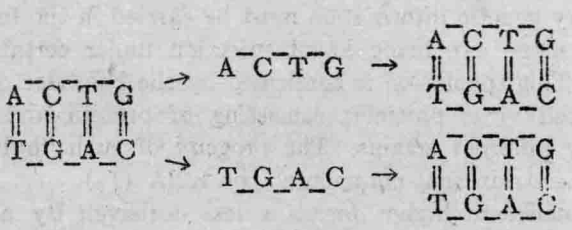
Gene Specificity.

It is assumed that gene specificity resides in sequence of base pairs in a DNA double helix. If there were no restrictions as to the proportion in which base pairs occur or in the sequence in which they occur, the number of different DNA molecules possible is 4^n, where n is the

number of base pairs. Thus it is clear that DNA provides an adequate basis for gene specificity.

Gene Replication.

The two complementary polynucleotide chains of the Watson-Crick structure provide a plausible basis for gene reproduction (50). It is postulated that the complementary chains separate and that each acts as a template for the synthesis of a new partner. Indicating the building blocks with the letters A, T, C, and G, the replication process can be schematically represented as follows:



It is not at all clear in detail how this process might occur, a situation that accounts for the fact that the subject is dealt with in this Symposium (5, 6).

Since replication of genetic material never occurs in the absence of a living cell in which RNA and protein are present in addition to DNA, the possibility must be kept in mind that replication could be less direct than is suggested by the above simplified scheme. It is an impressive fact that DNA is the only large molecule so far known to have a structure that so plausibly provides for multiplication through replica formation.

Gene Mutation.

If genetic specificity does indeed consist in base-pair sequences in DNA molecules, mutation almost certainly consists in alteration of these sequences. Four types of such alteration are obviously possible, viz.: (a) substitution at one or more base-pair levels, (b) rearrangement of base-pair sequences, (c) duplication of one or more base pairs, and (d) deletion of base-pairs. Watson and Crick (50) have suggested a mechanism by which the first of these might occur. In terms of chromosomes, which are structures many times larger than DNA helices but in which genetic information may well be carried in the form of DNA, both inversions and deletions are known to occur.