Reproduction: Molecular, Subcellular, and Cellular

The Twenty-Fourth Symposium The Society for Developmental Biology

(Formerly The Society for the Study of Development and Growth)

Carleton, Minnesota, June 1965

Reproduction: Molecular, Subcellular, and Cellular

Edited by

Michael Locke

Developmental Biology Center
Western Reserve University
Cleveland, Ohio

1965

ACADEMIC PRESS, New York and London

ACADEMIC PRESS INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS INC. (LONDON) LTD.
Berkeley Square House, London W.1

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 55-10678

PRINTED IN THE UNITED STATES OF AMERICA

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Reproduction: Molecular, Subcellular, and Cellular

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Introduction

The purpose of this symposium is partly to clarify and define specific aspects of reproduction at different levels of biological organization, and partly, in common with other symposia held by the Society, to stimulate interaction between various intellectual approaches to a broad phenomenon of common interest. Whether or not a cell reproduces true to parental type, or whether a cell reproduces at all, are issues of fundamental interest in developmental biology. Reproduction of a cell is impossible without reproduction of molecules, but the kinds of molecules reproduced and the conditions effecting reproduction are dependent upon the intracellular pattern of molecular organization and the influence of the environment on the metabolic poise of the cell. The production of a chlorophyll molecule, for example, may be fully stated in terms of the enzymes in its biosynthetic chain. The reproduction of a chlorophyll molecule is, however, quite a different matter. A necessary condition for reproduction is the *transmission* of proplastids or plastids from parent cell to offspring. Even if such transmission occurs, the production of chlorophyll remains dependent upon the location of the cell within an appropriate region of the plant. Thus, excluding environmental and mutational factors, a clarification of the phenomenon of chlorophyll reproduction requires the elaboration of certain rules governing the behavior of subcellular organelles with respect to transmission, as well as rules governing the development of organelles with respect to cell differentiation. A counterpart of this example may be found in the reproduction of many other cell components. The involvement of a cytoplasmic particle is incidental to the general question of reproduction. Applicable to all situations, however, is the fact that just as the reproduction of cells does not assure the reproduction of all molecules, so the reproduction of molecules does not assure the reproduction of cells. We cannot avoid the

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challenge of defining rules for the formation of molecules within the biosynthetic framework of cells, for the assembly of molecules within the architectural framework of cells, and for the reproduction of molecules or their complexes within the genetic framework of cells as governed by the interaction between cells and their environment.

We may justifiably make the dogmatic assertion that a complete understanding of cell reproduction requires a complete understanding of the molecular events underlying such reproduction. We cannot, however, extrapolate from molecular behavior to cell behavior without guidance from the cells themselves. A molecular mechanism, to the extent that it is perfectly understood, imposes clear restrictions and suggests fruitful possibilities with respect to the elaboration of rules concerning reproduction at more complex levels of organization. But unless we make the extremely doubtful assumption that the present organization of living systems is a necessary and inevitable consequence of molecular properties, we cannot hope to achieve a knowledge of reproduction by a unidirectional acquisition of information from molecule to man. Even if we allowed for this theoretical possibility, we would have to atribute to biologists a flawless prescience never witnessed previously in the history of science. Were it not for the discovery of mitosis, meiosis, and Mendelian inheritance, the Watson-Crick helix would not have come into existence; and, if it were somehow envisaged, it would have remained a conversation piece. If the molecular biologist must be defined as one who chooses problems which can be solved, then the biologist must be defined as one who chooses problems which need to be solved. These appositions and oppositions are, however, trivial. The point of view that clarity of formulation is essential in approaching the phenomenon of reproduction at all levels of organization represents the spirit in which this symposium was fashioned.

We are generally concerned with two aspects of reproduction, the mechanisms themselves and the regulation of these mechanisms. Although a distinction between these two aspects is often difficult to make, we may nevertheless attempt to outline the structure of the symposium with this distinction in mind. We should be able to define reproductive mechanisms at the molecular, subcellular, and cellular levels with some degree of rigor. Similarly, we should be able to define molecular, subcellular, and cellular regulatory mechanisms.

Molecular Mechanisms of Reproduction

Our present concepts of molecular reproduction are based entirely on two fundamental principles, enzyme catalysis and complementary nucleo-

tide pairing. The first is an oldtimer in biology; the second is a newcomer. The enthusiasm which greeted the discovery and studies of enzymes in the late nineteenth century is now focused on investigations of the function of nucleic acids. Whether molecular biology begins with base pairing, or dates back to the studies of Claude Bernard, is a matter of pride and prejudice with no relevance to the symposium. Our interest lies in the fact that enzymes select from the thermodynamically possible world and construct the real world of living matter. Bond formation without enzyme mediation is an event which can at best be of only marginal interest in biological reproduction. All molecules are synthesized by virtue of specific enzymes. But the very specificity of an enzyme, the relatively small intramolecular distances which its active site can recognize, precludes its operation in specifying the order of extended intramolecular sequences. To this particular aspect of ordering nucleic acids furnish an essential contribution.

Three categories of molecular synthesis have been considered in this symposium—autosynthesis, heterosynthesis, and antibody synthesis. Whether the categories are variants in the operation of enzyme catalysis and nucleic acid pairing, or whether other mechanisms are yet to be disclosed, remains to be seen. At present, we feel confident that the two basic mechanisms described are sufficient to account for all forms of molecular biosynthesis. In autosynthesis, an enzyme transcribes a complementary base sequence out of subunits identical with those of the template. This type of synthesis is considered universal in DNA and operative in RNA only in the case of RNA viruses. In heterosynthesis, an enzyme also transcribes a nucleic acid template, but in the case of protein synthesis, the transcribed product must be translated into a sequence of amino acids by a different set of processes. Antibody synthesis may be *formally* described as the formation of proteins complementary to antigen molecules. The discussion of this topic by Nisonoff should make it amply clear, however, that formal identities between nucleic acid complementarity and antigen-antibody complementarity have no counterpart in molecular terms. Present evidence virtually rules out the possibility that an antibody molecule may be synthesized by a transcription of antigen. Doubt even exists as to whether the total sequence of molecular events, from antigen challenge to antibody production, is encompassed by a single cell. It would appear that rules must first be formulated at the cellular level before molecular mechanisms can be properly resolved.

The two basic molecular mechanisms, if rigorously examined, reveal certain limitations and some possibilities with respect to molecular reproduction. On the assumption that the mechanisms are properly under-

stood and that no other mechanisms exist, direct copies of molecules are ruled out. Since sequences are transcribed by base pairing, the primary product of transcription must always be complementary to the template. The molecular distinction between autosynthesis and heterosynthesis is blurred, inasmuch as the primary determinant of the subunits used in transcription (whether ribo- or deoxyribonucleotide) is the enzyme. Nothing in our present concept of nucleic acid reproduction excludes the possibility of RNA being transcribed into DNA. Our failure thus far to discover instances in which DNA is replicated from an RNA template, or in which native cellular RNA is transcribed from RNA templates, cannot be sanctioned by molecular rules of reproduction. Moreover, since the agent of transcription is the enzyme, we must also allow for the possibility that direct rather than complementary copying may occur if the appropriate enzyme is found. Either the rules must be tightened, or our knowledge of cell behavior must be broadened. We may, on the other hand, dogmatically assert that the amino acid sequences within a polypeptide chain can only be derived from nucleotide sequences and that the reciprocal derivation is impossible. We are thus compelled to account for the reproduction of protein molecules in terms of nucleic acid templates.

Subcellular Mechanisms of Reproduction

At the subcellular level, the existence of a supply of molecules is taken for granted and the question to which we must address ourselves is how the various structures in a cell are reproduced from the molecular pool. The presence of DNA templates in the cytoplasm mainly influences the phenomenon of intracellular regulation. The geography of transcribing systems is largely, though not entirely, incidental to the mechanisms involved in the generation of subcellular structures. Our knowledge of these mechanisms has none of the crispness characteristic of our present understanding of molecular events. Currently, we envisage three possible mechanisms in the formation of structures from molecular pools: self-assembly, accretion by intussusception or end addition, and assembly on preformed templates. The first of these has evoked considerable conceptual interest because of the implication that individual macromolecules contain sufficient information to arrange themselves in recognized biological patterns. Bacterial flagella and collagen fibers are among the structures thus studied for which the evidence pertaining to self-assembly is impressive. The biological consequences of such a process are clear. If the information contained in a coded amino acid sequence is sufficient to determine the tertiary structure of a macromolecule, and also to assemble