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Molecules to Living Cells

With Introductions by Philip C. Hanawalt

Readings from

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MOLECULES TO LIVING CELLS

With Introductions by
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PREFACE

One of our most fascinating intellectual endeavors has been to study the molecular workings of the very cells of which we ourselves are composed. This selection of readings from *Scientific American* unfolds the miracle of life by developing the structural hierarchy of living cells and showing how they are assembled from relatively simple small molecules. Beginning with a successful origin-of-life "event" in the prebiotic milieu 3 billion years ago, the course of evolution on earth has led to the existence of self-reproducing multicellular beings that include a unique species called Human. That highly developed species has now learned enough about the molecular architecture of life that some of its members have begun to manipulate it at very basic levels. The implications of this recently acquired and developing technology are awesome, perhaps terrifying to some. Furthermore, we humans are constantly "enriching" our environment with new chemical combinations that are incompatible with most living forms. Biology no longer should be the specialized domain of a few professional biologists, since we are all called upon to register opinions and make decisions that may affect the future of life on earth. It is incumbent upon all of us to be "biologists" to the extent that we try to understand the possible consequences of our actions on the future of the biosphere. We need to learn how the exercise of our intelligence may enable us to survive even though many other life forms have become extinct. As a start we should all gain some appreciation of the way in which living systems are put together and how they proliferate.

The articles in this collection span the broad field of molecular biology between two other recent *Scientific American* readers on specialized topics—*Life: Origin and Evolution* and *Recombinant DNA*. The emphasis here is upon molecular structures, their interactions in forming supramolecular structures, and the genetic control of their synthesis in the growing cells that constitute life. The story develops from George Wald's thoughtful speculations on the probability of life's origin as a chance occurrence and it leads to Stanley Cohen's discussion of the new technology of gene manipulation in which the element of chance has been minimized if not eliminated.

This is not a text, yet it is definitely intended for use in the classroom. It does not include an essay on each important topic in the field of molecular biology, even though most of those topics have in fact been documented through the years in *Scientific American* articles. To include most of them would have resulted in an unwieldy and costly volume. The articles that are included were selected to highlight material that I consider to be important but which is not normally emphasized in textbooks. I have selected many articles that are much more current and detailed than any textbook in print. Others have been selected for their historical value and because they enable the student to appreciate the perceptiveness of some of the early researchers in the field of molecular biology. Students will learn how the classic experiments were done from the scientists who performed them. My choice of articles has been guided by the experience that my colleagues and I have had in the teaching of molecular and cellular biology at Stanford University and by our use of *Scientific American* readers for many years. Many of my colleagues have been of help, and I particularly wish to acknowledge the counsel of Robert Simoni and Charles Yanofsky in assembling this collection. The collection includes ten articles usually assigned to our students from an earlier reader, *The Chemical Basis of Life,* which I assembled in collaboration with Robert Haynes six years ago. The present volume includes the classic article on the gene by George Beadle, written five years before the proposal of the DNA structure by Watson and Crick. The other selections are all more recent, and they include 12 articles from the past six-year period, of which seven are from the past three years. The earlier articles have been updated and placed in current perspective through my commentary in the Introductions. Some of the authors contributed to the updating task, and I particularly want to thank Harold Morowitz, Daniel Mazia, David C. Phillips, William B. Wood, Masayasu Nomura, Charles Yanofsky, and Arthur Kornberg for their help. A list of references cited and suggested sources for additional reading (including *Scientific American* Offprints) has been provided at the end of each Introduction.

The 26 articles in this volume have been assembled in five sections. Section I considers the origin of life on the barren earth and the present-day range in complexity of cellular types from the simplest free-living cells to the component cells of mammals. Section II describes the structure and function of proteins—the principal building blocks of living organisms and the catalysts that regulate most biological activity. The assembly of subcellular organelles and those ultimate parasites, the viruses, from proteins and nucleic acids is also described. Section III deals with the boundary of the cell—that is, the membrane—and its role in compartmentalization as well as in the organization of certain essential cellular functions, such as the energy transducing systems. In Section IV, an historical flavor is intended through descriptions of classic experiments that elucidate the way in which information is transferred from the primary genetic blueprint to the synthesis of proteins and its expression in the visible properties of organisms. Finally, Section V deals with the nature of the primary genetic material, the DNA, and its transactions. The DNA is replicated, repaired, and manipulated by living cells. These same processes are now carried out in sterile glassware in the laboratories of scientists.

If the five Introductions are read first, that will be helpful in providing an overview as well as an understanding of the rationale for the arrangement of the articles selected for this volume. In the Introductions, I have tried to strike a balance between simplifying background information for the articles and commenting on current developments not discussed otherwise. I suggest that each Introduction be read as though it were the menu in a fine international restaurant, for the articles that follow are indeed delicacies from some of the great scientific "chefs" of the world.

I wish to thank my secretary, Maria Kent, for typing endless revisions and for her enlightened proofreading skill, which included worthwhile editorial suggestions. I thank Dr. Evelyn Parker for preparing the index. My father, J. Donald Hanawalt, has been a continuing source of encouragement, and my wife, Graciela, a source of inspiration.

I wish to dedicate this volume in loving memory of my mother, Lenore Smith Hanawalt, 1902–1978. She taught me to look for the beauty beyond the facts.

February 1980 *Philip C. Hanawalt*

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Note on cross-references to Scientific American *articles:* Articles included in this book are referred to by title and page number; articles not included in this book but available as Offprints are referred to by title and offprint number; articles not included in this book and not available as Offprints are referred to by title and date of publication.

I

SIMPLE INORGANIC MOLECULES TO COMPLEX FREE-LIVING CELLS

SIMPLE INORGANIC MOLECULES TO COMPLEX FREE-LIVING CELLS

I

INTRODUCTION

The phenomenon of "life" may be traced to the coordinated behavior of molecules within cells. The cell is the self-contained and self-reproducing fundamental unit of life. Cells may exist independently as free-living organisms like bacteria or as constituent functional units in a multicellular organism. (The human body, for example, consists of 100 trillion cells!) In the construction of cells, a molecular hierarchy exists in which a few types of small molecules are utilized as building blocks for a large variety of macromolecules of several major classes. These macromolecules in turn are assembled into complexes and organelles, which are still further organized into the self-perpetuating units that we call living cells. The molecules in cells are guided by the same basic laws of chemistry and physics that apply throughout the universe. They attract each other, repel each other, and form aggregates with each other. They combine to form stable new compounds that differ in size, shape, and chemical properties. There is nothing mysterious about any of the individual chemical reactions that occur in living systems. The mystery lies rather in the programmed coordination of the myriad of chemical reactions necessary for the metabolic activities of cells. In growing and carrying out its unique mission, each cell regulates its own internal environment and draws selectively from the external environment whatever raw materials it needs. The programmed accomplishments of these tiny chemical factories go far beyond the capabilities of the scientist in his laboratory. Although we now understand many of the molecular interactions and essential chemical processes required for the creation of a living cell, we simply cannot generate "life" in the test tube.

A given cell—indeed, any given organism—has but a fleeting existence in the cosmos. It comes into being and formulates its own identity as it develops from some pre-existing life entity; it carries out specialized functions and prepares for its procreation; then it disappears forever to be replaced by nearly identical descendants, repeating the cycle. Our wonderment and fascination with cellular growth are further stimulated by the realization that the living cell adapts its biochemical habits to a wide range of environments without losing its unique species identity for generation after generation. The progeny from a single bacterial cell are still identifiable with the characteristics of that parent cell after many millions of generations. Likewise, the cells from a carrot or from the liver of a mouse consistently retain their respective tissue and organism identities after countless cycles of reproduction. In the following discussion, we will explore the molecular components and the internal workings of cells. We will most certainly develop an increased appreciation for the complexity of the living cell, but we will also obtain some feeling for how our present understanding of the molecular basis of life may be utilized to benefit mankind and, it is hoped, the entire biosphere.

Even before dissecting a living cell, we can list some essential features that we are certain to find among its components. First, there must be a very detailed master blueprint, or "memory tape," that is transmitted intact from generation to generation. Second, there must be an intricate "read-out" system for translating the instructions from the blueprint into the synthesis of cellular structures. This system must include many contingency plans and the possibility of making use of alternative building materials as available in a particular environment. Third, there must be an energy-generating system and some means for storing chemical energy for allocation as needed in metabolic activity. Fourth, there must be a semipermeable boundary to separate inside from outside and to control which molecules enter and leave the cell. It sounds very simple in principle, doesn't it?

Consider, though, that the normal growth of even the simplest living cell requires that tens of thousands of chemical reactions occur in coordinated fashion. Each of these reactions could be carried out individually in a test tube if the appropriate reactants were present. In the test tube we can control the rates of reactions by altering the concentrations of reactants, changing the temperature, varying the pH (acidity-alkalinity), or in general by adjusting the "environment." But how, within one tiny cell, can 20,000 reactions all be controlled at once? At least part of the answer lies in the different types of environment that exist in different parts of the cell. Although most of the cell contents diffuse freely in an aqueous medium, many reactions occur at designated sites on the surfaces of membranes rather than in the spaces enveloped by them. In fact, many reactions are localized at the sites where highly specific catalysts, called enzymes, are fixed. Enzymes are largely responsible for the control of the molecular processing required for growth of living cells. Most of the biochemical reactions in the cell would take place at immeasurably slow rates were it not for these remarkable biological catalysts.

The essential activities in living cells are generally mediated by large macromolecules of four major classes: proteins, polysaccharides, lipids, and nucleic acids. Their general chemical structures are given in George Wald's article. The detailed structures and functions of these essential molecules are discussed in Sections II, III, and IV. Proteins serve catalytic functions as enzymes, and they are found in structural association with lipids in membranes. The lipids are responsible for cellular compartmentalization; they also serve as a form of stored energy. The polysaccharides are polymers composed of simple sugars like glucose; they form structural materials like cellulose and chitin and function as energy stores in starch or glycogen. The nucleic acids are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA); their primary roles are in the storage and translation of genetic information, respectively. A typical bacterium, *Escherichia coli* (which thrives as a symbiote in the intestine of mammals), contains about a million protein molecules, which make up about 15 percent of the mass of the cell. However, the most abundant molecule in the cell, if not the simplest, is water, which constitutes over 70 percent of the total mass. The lipids and polysaccharides account for only 5 percent, and the nucleic acids make up another 7 percent of the cell mass. Finally, low-molecular-weight precursors, inorganic ions, and other small molecules account for another 1 percent of the total cell mass. This gross tabulation tells us almost nothing about how a cell works. Yet it is the kind of information one obtains from a straightforward chemical analysis of cell composition, and it is an essential early step in learning how molecules organize in cells. A more detailed analysis tells us that those million proteins are of about 3,000 different kinds, that there are several different classes of RNA, but that the DNA exists as one long thread, a chainlike molecule nearly one thousand times the length of the cell in which it is packed. At this point we can stop wondering about how to unravel life's mysteries and worry instead about how to unravel this one long molecule of DNA! It is the master blueprint for the cell; there is only one precious copy, and it is packed into the cell like a convoluted mass of spaghetti rather than carefully wound on a reel! Nevertheless, this apparent organizational disorder poses no evident problem for the growing cell. The information is carefully preserved, used as needed, and the entire thread of DNA is duplicated in time for the parent bacterium to divide into two daughter cells. Furthermore, the rest of the cell substance is also duplicated in that same period of time. We still have much to learn about how the organization of molecules in cells promotes efficient growth.

We have briefly introduced the internal chemical composition of the bacterial cell; how about the external environment? *Escherichia coli* thrives in an aqueous soup containing surprisingly few essential ingredients. Dissolved in the water required for the growth of this bacterium are certain salts and ions; those available in greatest concentration are sodium chloride, potassium chloride, magnesium sulfate, ammonium, and phosphate. In such a salt solution at 37°C and at pH 7 (neutral), an *Escherichia coli* cell will duplicate its substance and divide into two essentially identical cells in a mere 40 minutes—if we additionally provide oxygen, a source of carbon, and a source of energy. The simple sugar glucose is adequate both as a source of carbon and as a source of the chemical energy needed to metabolize it. Most of the cellular energy obtained from the systematic degradation of glucose will go into the synthesis of small building blocks and the assembly of these "monomer" precursors into the large polymers called macromolecules. Incidentally, what we have listed above is not the bare minimum of ingredients required in the growth medium. For example, had we left out the oxygen, the bacteria would have adjusted to that condition, but they would have been able to utilize much less of the available chemical energy in each glucose molecule and consequently would have grown more slowly. Alternatively, we might have supplemented the growth medium with many of the known precursors for cellular structures. The bacteria would then have adapted to growth in this rich broth, turning off some of their now superfluous synthetic machinery, and would consequently have been able to reproduce more efficiently, with a generation time as short as 20 minutes. The weight of one bacterial cell is only 0.00000000000001 gram (customarily written as 10^{-14} gram). Within 14 hours in the enriched growth medium, the mass of progeny from one cell would be greater than 1 gram, and within 36 hours the entire earth could be layered with a frosting of *E. coli* 6 centimeters deep! This exemplifies the fact that optimal growth is an exponential process, following the simple relationship $N = 2^n$, where N is the number of cells present after n generations, or division periods, starting with one cell. Fortunately, exponential growth for any living system cannot continue indefinitely. A theoretical end point would be that time when essentially all the carbon in the universe is tied up in molecules that constitute living cells. No such end point is ever approached, however, as the elements are continually reshuffled and recycled in endless rounds of chemical synthesis and degradation in the present-day biosphere.

How did it all begin? This is an unanswered question that continues to intrigue us and to challenge the ingenuity of organic chemists who would attempt the recreation of that incredible happening. In all likelihood, life arose as a series of spontaneous chemical events in which simple molecules combined to form more complex molecules, which in turn formed supramolecular complexes that eventually appeared in aggregates that were ultimately compartmentalized into cells. From that point on and continuing today, the process of biological evolution has directed the course of life on earth.

Evidence to date singles out the earth as the only planet in our solar system that supports life. Although other solar systems in our galaxy and in the 100 million other galaxies undoubtedly include planets that closely resemble our earth in composition and environment, such planets are generally at distances more than human lifetimes away at present rates of space travel. Thus, although the universe contains 10 million million earthlike planets, our speculations and our experiments are necessarily confined to exploration of the life forms on our own planet. On the geological time scale, life began "shortly" (about a billion years) after the earth was formed, and it has been continuously evolving for 3 billion years since then. What raw materials were available and what conditions prevailed 4 billion years ago? Although the physical laws that govern behavior of molecules were the same then as they are today, the chemical environment as well as the physical conditions (e.g., temperature, radiation levels) were quite different. The prebiotic earth contained water, carbon dioxide, carbon monoxide, nitrogen, and hydrogen, but no free oxygen. The absence of oxygen was essential for the accumulation of cellular precursors, since that highly reactive element, if present, would have readily combined with any organic material to destroy it almost as soon as it was formed. In fact it should be appreciated that the development of photosynthesis in primitive cells was responsible for the eventual appearance of free oxygen in our atmosphere.

We come now to the problem of the initial production on the barren earth of the essential low-molecular-weight precursors for biological macromolecules. In the classic "spark gap experiment" of S. L. Miller and Harold Urey (described in George Wald's article), the simple substances methane, ammonia, hydrogen, and water vapor were placed in a sterile vessel and subjected to a maintained electrical discharge. This simulation of one possible primitive earth environment generated a number of organic substances, including amino acids, the monomer units of which proteins are composed. More recently it has been shown that dilute solutions of hydrogen cyanide (HCN) under another simulated prebiotic environment will form purines and pyrimidines, the precursor building blocks of nucleic acids. The conditions on the primitive earth included energy sources other than electrical discharges—heat pockets from volcanic discharge, a broad spectrum of solar radiations (with no ozone layer in the upper atmosphere to attenuate the ultraviolet rays), and probably some unique combinations of ionizing radiations from the radioactive decay of unstable elements. Each of these energy sources may have been important for particular events in the scenario for prebiotic synthesis of essential organic compounds. The first step in the assembly of a cell—the synthesis of low-molecular-weight precursors—was achieved in the prebiotic milieu, and that part of the puzzle at least may eventually be solved as we experiment with various possible mixtures of simple compounds and different energy sources.

The synthesis of the small-molecule building blocks is complex in itself, but it is child's play in comparison to what must have followed in order to generate the first living cell, George Wald (see p. 13) points out the improbability of the chance occurrence of all of the appropriate precursor molecules being in the right place at the right time to form the first cell, but he argues that such random events might in fact generate a living combination given enough time. (This rationale has been elaborated by Jacques Monod (1971).) One can wonder whether a mere billion years is really enough time for such an improbable series of events! However, as we learn more about the construction of cells, we find that many of the essential assembly events are not improbable at all. Spontaneous assembly of biological structures is quite common in present-day biology—for example, the self-assembly of the protein and nucleic acid components of virus particles and ribosomes, as described in Section II. Even the assembly of lipids to form a micelle, a simple sort of membrane-bounded enclosure, is a natural occurrence. This is not to say that the formation of the first living cell could have been an inevitable event—just that it was aided by some basic chemical principles to be elaborated upon below.

Molecules tend to associate with each other on the basis of different levels of interaction or "recognition." Molecules that carry a net charge and molecules that have electrically charged regions seek interaction with each other and with small polar molecules like water. These are appropriately called hydrophilic (water-loving) interactions. In contrast, nonpolar regions of molecules tend to associate with each other and to exclude water. These are called hydrophobic (water-abhorring) interactions. The aggregation of the hydrophobic lipids into clusters is thus not random at all, but rather an event driven thermodynamically to achieve the lowest potential energy in the system. Yet it is an essential process for the assembly of a cell—even the very first one! In addition to the generalized interactions between molecules due to the distribution of electric charge, there are highly specific recognition features that characterize certain types of macromolecules. These will be discussed in more detail in subsequent sections. Suffice it to say at this point that it is possible to design a protein molecule that will recognize (i.e., bind specifically to) essentially any other molecule, including another protein. Furthermore, it is possible to construct a nucleic acid strand that will bind specifically to any other designated nucleic acid strand to form a highly stable, two-stranded structure.

Since it is appropriate to begin a story at the beginning, we have initiated this selection of readings with Nobel Laureate George Wald's article, "The Origin of Life," which treats that problem with excellent perspective and at a fairly elementary level. Wald elaborates upon the fact that biochemical reactions are reversible and that spontaneous dissolution normally proceeds more readily than spontaneous synthesis of most large biological molecules. He also stresses the formation of complexes in stabilizing macromolecules and the eventual need for a continuous expenditure of energy to maintain biological order. Lastly, he discusses the important role that evolving life forms played in bringing free oxygen to the earth. Even today the concentrations of oxygen and carbon dioxide in our atmosphere are dependent upon the totality of life forms that inhabit our planet.

In "The Evolution of the Earliest Cells," J. William Schopf elaborates further on the indispensible role that oxygen played in the rise of the eukaryotic cell. This article includes an outline showing how a glucose molecule is metabolized in the absence of oxygen (anaerobic fermentation) and in its presence (aerobic respiration). *Escherichia coli* can operate by either the anaerobic or the aerobic mode, as we have discussed. Schopf distinguishes clearly between prokaryotic cells, such as bacteria, and eukaryotic cells in which the DNA is organized in chromosomes in a defined nucleus and in which organelles such as chloroplasts and mitochondria are parts of the more highly developed subcellular organization. It is likely that both cellular types evolved from a much simpler life form, a progenote, in which the relationship between the primary genetic message and the expression of that message in the cell had not yet been fully worked out (Woese and Fox, 1977). The first photosynthesis probably evolved in a group of prokaryotes called the cyanobacteria, and the eukaryotes may have begun to develop only after oxygen was abundantly present. It may seem peculiar that the earliest life forms evolved in the presence of poisonous gases, such as carbon monoxide (CO), hydrogen cyanide (HCN), and hydrogen sulfide (H_2S), but those gases are in fact poisons only for aerobic forms of life. Schopf describes the analysis of single-celled fossils in fascinating detail, placing the first eukaryotic cells at about 1.5 billion years ago. Finally, he emphasizes that "in the Precambrian the influence of life on the environment was at least as important as the influence of the environment on life." Is that not also true today?

What is the lower limit of complexity required for a free-living cell? Harold Morowitz originally suggested that fundamental biological processes may be more accessible to study in very small cells in which the total number of molecules might limit the degree of complexity. In "The Smallest Living Cells," Harold J. Morowitz and Mark E. Tourtellotte describe the mycoplasma. An example of this group, *M. gallisepticum,* is roughly one-tenth the size of an *E. coli*, and it contains fewer than 10 percent as many molecules. Its tiny 0.2 micron sphere is at the very limit of resolution of the optical microscope. Further research since the article was written has revealed no smaller free-living life forms. However, more recent determinations yield a value of about 5×10^8 (500 million) daltons for the molecular weight of the DNA in the "unit genome" of the mycoplasma, which is still only one quarter the size of the *E. coli* genome. (The genome is that amount of DNA required to specify the organism.) Wallace and Morowitz (1973) have suggested an evolutionary scheme in which the mycoplasma are descendants of the "protokaryotes" (or progenotes), which arose before the divergence of prokaryotes and eukaryotes. These simplest of cells require a very complex growth medium supplemented with all of the amino acids and many other low-molecular-weight precursors for cellular structures. They lack the cell wall structure that gives rod-shape form to an *E. coli;* their interiors are separated from the environment by only one delicate membrane. The reader should refer to Section III for our current view of membrane structure. Maniloff and Morowitz (1972) point out that if living cells appreciably smaller than the mycoplasma are ever discovered, "the finding will challenge our ideas of what constitute the necessary biochemical processes for life."

Let us turn now to the more highly structured eukaryotic cells, which are at least 100-fold larger than the mycoplasma. Daniel Mazia, in "The Cell Cycle," explores the period of frenzied biochemical preparation between one cellular fission and the next. Historically, the phases of the cell cycle were identified through microscopic analysis of chromosome configuration in cells at different growth stages. An outline of these stages is given by Mazia, and actual drawings from observations made in the 1880s are reproduced in Mirsky's article in Section V. An abundance of these fascinating sketches from the early microscopic examination of living cells is provided by E. B. Wilson (1896) in a classic text that places our "pre-modern-biology" understanding of life in excellent perspective. The "nucleinic acids," as the nucleic acids were then called, were already identified and localized in chromosomes. It was suspected that they were involved in the "control" of life processes and, in particular, that they were intimately associated with the process of cell division. Mazia stresses the essential role of DNA replication in the cellular commitment to ultimate division. However, many other specific processes must occur in addition to molecular syntheses to prepare for this event. The experimental technique of fusing two cells to form a hybrid cell is described as a powerful approach to an understanding of cell-cycle regulation and of other processes as well.

Up to this point we have given the impression that a living cell controls its own destiny as regards growth and division. That may sometimes be the case for a free-living cell, but it is never true for the component cells of a multicellular organism. The problem of the coordination of cell growth and the differentiation of cells during development to form the specialized organs and structures in multicellular organisms is beyond the scope of this volume and nearly beyond comprehension. Mazia does cite, however, the important role of the cell surface in sensing the presence of other structures and in regulating growth. When normal human cells are cultured *in vitro,* their growth is restricted by "contact inhibition" as a monolayer of cells develops on the surface of the growth vessel. In contrast, cancer cells are not responsive to such external control on proliferation, and they tend to grow into multilayered piles of cells. The cancerous cell thus behaves more like an independent, free-living organism—to the detriment of the "host" organism. It is a cruel irony that the malignant cell contains essentially the same genome and most of the same regulatory machinery as do the normal cells of the victimized host.

The essential concepts of life are very simple and logical. In detail the processes of life are incredibly complex. It is not surprising that we should experience difficulty in comprehending them. As Nobel Laureate Max Delbrück pointed out thirty years ago, " . . . any living cell carries with it the experiences of a billion years of experimentation by its ancestors. You cannot expect to explain so wise an old bird in a few simple words."

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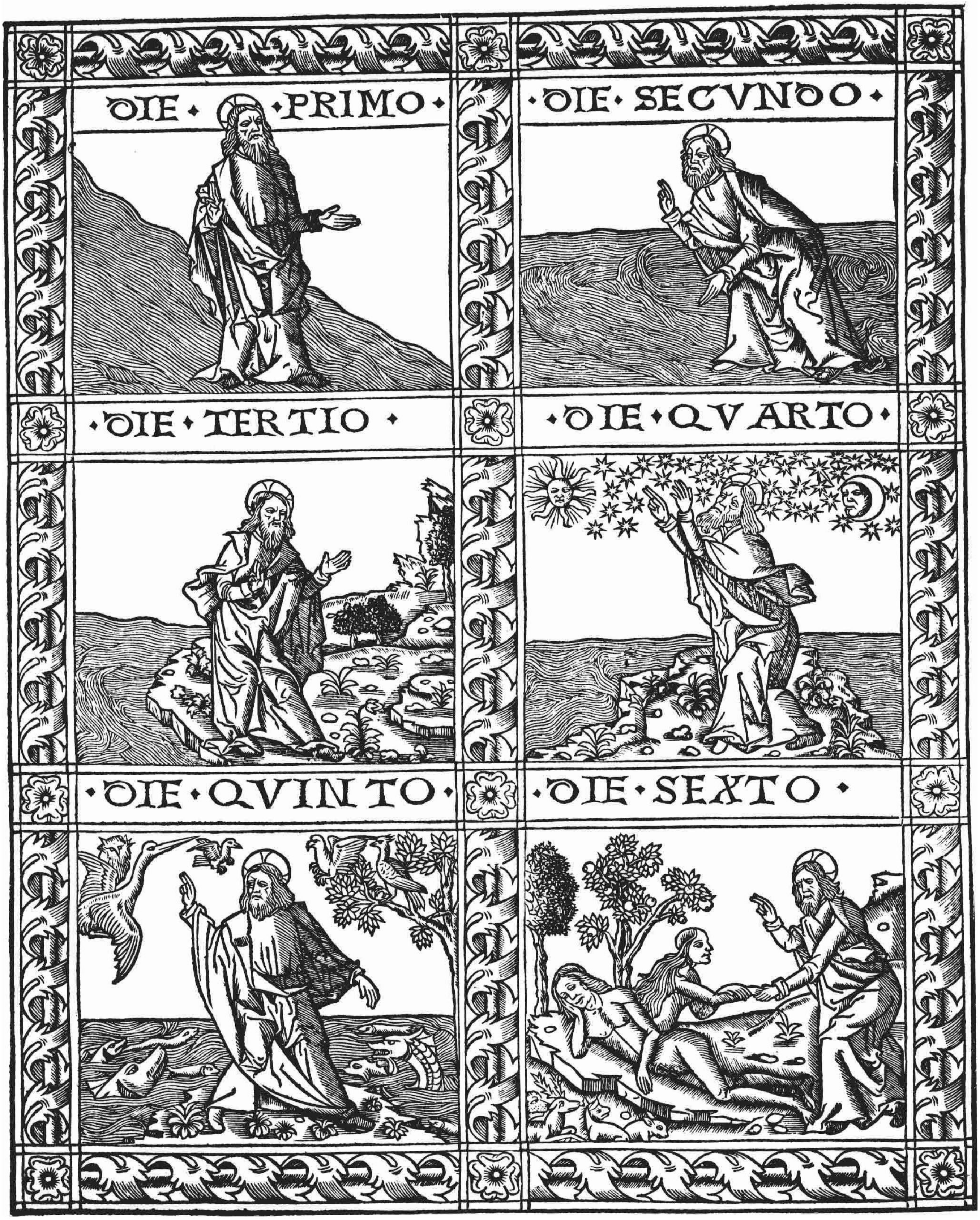

BIBLICAL ACCOUNT of the origin of life is part of the Creation, here illustrated in a 16th-century Bible printed in Lyons. On the first day (*die primo*) God created heaven and the earth. On the second day (*die secundo*) He separated the firmament and the waters. On the third day (*die tertio*) He made the dry land and plants. On the fourth day (*die quarto*) He made the sun, the moon and the stars. On the fifth day (*die quinto*) He made the birds and the fishes. On the sixth day (*die sexto*) He made the land animals and man. In this account there is no theological conflict with spontaneous generation. According to *Genesis* God, rather than creating the animals and plants directly, bade the earth and waters bring them forth. One theological view is that they retain this capacity.