Life Evolving: Molecules, Mind, and Meaning

Christian de Duve

OXFORD UNIVERSITY PRESS

Life Evolving

OXFORD
UNIVERSITY PRESS

Oxford New York
Auckland Bangkok Buenos Aires Cape Town Chennai
Dar es Salaam Delhi Hong Kong Istanbul Karachi Kolkata
Kuala Lumpur Madrid Melbourne Mexico City Mumbai Nairobi
São Paulo Shanghai Singapore Taipei Tokyo Toronto

and an associated company in Berlin

Published by Oxford University Press, Inc.
198 Madison Avenue, New York, New York 10016

www.oup.com

Library of Congress Cataloging-in-Publication Data

De Duve, Christian.
Life evolving : molecules, mind, and meaning / Christian de Duve.
p. cm.
Includes bibliographical references.
ISBN 0-19-515605-6
1. Life—Origin.
2. Evolution (Biology)
3. Life (Biology)
I. Title.

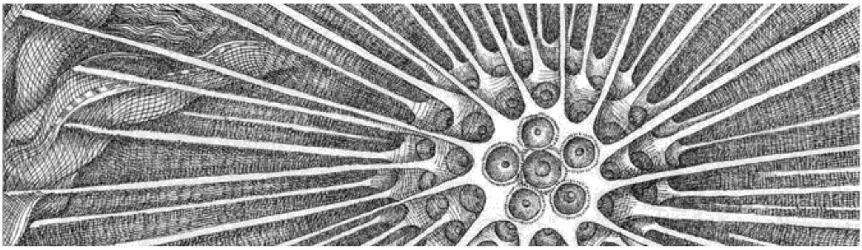
QH325 .D415 20002
576. 8'8—dc21 2002075407

9 8 7 6 5 4 3 2 1
Printed in the United States of America
on acid-free paper

Contents

This page intentionally left blank

Preface



This preface is dedicated to all my colleagues,
past and present, at the Catholic University of Louvain

A WHIFF OF WOOD SMOKE

On a clear summer night almost 75 years ago, I was sitting, wrapped in a blanket, a scarf on my head, with a group of similarly clad youngsters circling a campfire. There was not a breath of wind. The flames rose straight toward an inky sky studded with stars. So did our voices joined in song, the only sound, with occasional crackling of burning wood, to break the silence of the night. All of a sudden, for a brief instant, light fused with darkness, song and silence became one, and I felt carried to another world, seized by intense emotion, suffused with a sense of unfathomable mystery, feeling, beyond the infinite depths of space, the awesome majesty of God.

Today, the boy scout of my reminiscence is an old man. What was then his future is now my past, a past that happened to coincide with the most dramatic burst of knowledge in the whole history of humankind. The night sky of my youth has been explored to the outermost distance and earliest beginnings of the universe. The innumerable appearances of matter have been reduced to a small set of elementary particles and forces. Life itself has yielded its secrets. Its central mechanisms have been unravelled in intimate detail, and its history, which, as we now know, includes that of humankind, has been probed back to an origin lost in the mists of time.

As chance would have it, I did not live through those momentous events merely as a passive spectator. I was a privileged inside witness to them and even, to a modest extent, an active participant. This dizzying adventure was also a revealing discovery of reality, which totally upset the naïve set of beliefs from which had sprung the romantic mysticism of my childhood. Yet memory of that summer night never entirely faded away. It needs only a whiff of wood smoke to bring back the feeling of fervor and wonder that filled me at the time. The magic has gone, but not the sense of mystery.

EARLY INFLUENCES

I have recalled this childhood experience because it helps explain the tenor of this book, greatly influenced by my family background and early upbringing, especially in the religious domain. My family was Catholic, more by tradition and social conformism than by deep-felt conviction. We believed, without asking why, as a matter of course. Observance was faithful but largely perfunctory. We scrupulously refrained from eating meat on Fridays, attended mass every Sunday, confessed our sins regularly—or, in the case of the more tepid, at least once a year at Easter time, as prelude to the obligatory yearly Communion known as one's "Easter duty"—and we took care not to eat any solid food a minimum of twelve hours before receiving the sacred host at Communion. Religious holidays, such as Christmas or Easter, were duly celebrated. Church ceremonies underlined all major family events. We were baptized soon after birth and, later, when we had grown old enough to understand what was going on, confirmed by the local bishop, who took the trouble to come personally on that occasion. We married in church, which was also our last stop on the way to our final resting place.

Religion itself, however, hardly entered our home, except for the presence of a crucifix or other sacred image in every room. We never prayed together, read devout literature, or talked about religious topics. Politically, my father was mildly anticlerical and always voted liberal, not Catholic (the name of a political party at the time). I myself learned early, from spending holidays with German relatives who were Lutherans and with English friends of my parents who were nominally Anglicans but hardly bothered with religious practice, that one could reject the authority of the pope and skip mass on Sundays and still escape eternal damnation—that, at least, is what I believed—if one led a decent life. Rumor had it that some family members were actually unbelievers, perhaps even—perish the thought—Freemasons!

This broad-minded and tolerant family atmosphere did not prevent me from taking religion very seriously. In the Jesuit school I attended, Catholic doctrine was strictly imposed by highly intelligent and cultured Fathers, who described it as an unassailable, rational construction, firmly based on the teachings of Aristotle, as revised by Thomas Aquinas. Science, on the other hand, was poorly taught by teachers who distrusted it and took care not to present it as an opening to understanding the world. Only mathematics, thanks to its abstract character, escaped this neglect and was well expounded. Not knowing any better and not being inclined to question the wisdom of my teachers, I found this combination of reason and faith intellectually satisfactory and even appealing.

At the end of my "humanities," as classical high-school studies were called, there was never a moment of doubt in my mind or anyone else's that I should enter the Catholic University of Louvain, steering clear of its nearby rival the godless Free University of Brussels, founded in 1834 by a group of wealthy Freemasons with the aim of promoting, in direct opposition to dogmatic Louvain, a pernicious doctrine of "free thinking." In spite of my love for the classics, I opted for medical studies, mainly because I was attracted by the popular "man in white" image of the physician in the service of suffering humanity.

Through a combination of circumstances that have no place in this account, I discovered scientific research as a medical student and became so enamored with it that I abandoned clinical practice and specialized in biochemistry. At that same time, thanks to my first mentor, professor Joseph Bouckaert, to whom I remain deeply indebted, I discovered the scientific method of seeking truth, not by rational deduction from an a priori statement presented as incontrovertible, but by observation and experiment, continually questioned and subjected to the rigorous criterion of objective verification. It was an illumination that swept away, as by a tidal wave, the scholastic approach of the Jesuits and severely shook its doctrinal foundation. Claude Bernard[1] replaced Aristotle and Thomas Aquinas as my intellectual guide.

Notwithstanding this personal upheaval, at the end of my training I accepted an academic position at my alma mater. Given the almost complete inbreeding rampant in Belgian universities, there was no alternative if I was to stay in the country. I could have gone abroad—I had an attractive offer from the United States—but decided on Louvain in spite of my doctrinal qualms. There were several reasons for that decision, the main one being a sense of patriotic obligation, not yet seen as corny at the time, and the desire to help in the reconstruction of my war-ravaged country. I was no “rat leaving the sinking ship,” was the way I put it to myself.

THE CATHOLIC UNIVERSITY

My qualms were not without justification. Probably not many of today’s readers, even in Louvain, can readily imagine the kind of intellectual climate that existed at the Catholic University of Louvain in the time of my youth. In that venerable institution, founded in 1425 by Pope Martinus V, and within the conservative bourgeoisie from which much of its professorial staff was recruited, religious belief and practice were not so much an obligation as a deeply embedded way of life essentially taken for granted. The Belgian bishops made up the University’s directing body, with as main prerogative the right to appoint professors (sons of professors and nephews of bishops were said to enjoy an undeniable advantage). The rector was a cleric, often of bishop rank. Students were carefully surrounded and watched, to the point that their lodging had to be approved by the vice-rector—a redoubtable individual, also a cleric—and a number of the town’s more frivolous establishments were out-of-bounds for them. Female students enjoyed special protection, required to reside in colleges kept by nuns. All major events of academic life were celebrated in the main church, to which the professors marched in procession through the streets of the old city, garbed in elaborate gowns designed in the Middle Ages. Professors generally prefaced each course with a brief prayer. Much of the University’s meager budget was fed from donations collected twice a year in churches throughout the country (with the reluctant collaboration of the local pastors, who did not gladly see a portion of their parishes’ resources diverted for the benefit of an institution many of them viewed as subversive). Many professors returned their salaries to the University, relying for their living on private means or on revenues from lucrative practices as lawyers, physicians, or industry consultants made possible by their positions at the University.

Surprisingly, this almost-medieval framework hardly stifled academic freedom. Barring open opposition to the Church, it left open a wide field within which theologians could gleefully disagree with Rome and philosophers could defend widely dissenting views. Scientists were totally untrammeled in their teaching, supported by the theologians, who silenced censorship with the assertion that there could be no contradiction between truth and the Truth. Physicists taught the latest theories, including the Big Bang, actually discovered as the "primitive atom" by a clerical colleague, Monsignor Georges Lemaître. Biologists were free to explain living processes in terms of chemical reactions and bioenergetics in the framework of modern thermodynamics. They were not prevented from accepting biological evolution—not yet recognized by the Church at that time—and even its Darwinian explanation. Not all took advantage of this freedom, but it existed. In the medical faculty, neurologists did not hesitate to attribute to collective hysteria the allegedly miraculous apparitions of the Virgin Mary in the village of Beauraing (which did not prevent religious authorities from encouraging what they considered a commendable manifestation of popular devotion), whereas gynecologists, while obeying Catholic morality on abortion, for example, felt no scruple prescribing the "pill." Religious faith, however, was not a topic for open discussion, whatever doubts a person might privately entertain. I kept to this rule, except with a few intimate friends.

For the better part of my academic life, I had little difficulty avoiding controversial issues. There was no such thing as Catholic biochemistry; I had no party line to toe in my teaching, even less so in my research. After 1962, when I received a second appointment at the Rockefeller University in New York, my duties in Louvain became more episodic, largely restricted to research. Only in 1974 did I have to avoid a crisis when I was to be hailed as a Nobelist in science who was also a faithful son of the Church. On the whole, science kept me fully occupied, leaving little time for wider issues, even though these always remained at the back of my mind, kept in reserve for some later day, which, however, appeared too far in the offing to be of immediate concern.

THE MOMENT OF TRUTH

Time has caught up with me. Unlike many of my aging colleagues, I have given up laboratory research, ceased to advise investigators, and even stopped following the details of my discipline, devoting increasing amounts of my time and effort to more general problems, especially the origin and evolution of life. From these new preoccupations to "philosophical" considerations only one more step was needed, encouraged by the “whiff of wood smoke” whose memory has remained with me all my life. Slowly and cautiously, in the course of my reflections and writings, I moved closer to the ultimate question, managing, however, to skirt the final issue—the G word—in double-edged sentences that could be interpreted according to the reader’s fancy. Between Teilhard and Monod, I ended up siding with Monod, but opting in favor of a meaningful world.[2] Between Pascal and Voltaire, I left the choice to the reader.[3]

No longer am I allowed to sit on the fence, even for the laudable intention of not hurting or shocking. This book is likely the last one I shall write. With apologies for such grandiloquent phrasing, it is to be my testament. I owe it to myself to express my true thoughts in it, with as much clarity and honesty as I can muster, whatever distressful surprise or disappointment such declarations may cause to a number of people. To all of those, I offer my apologies for what they may view as betrayal of my university, my colleagues, my friends, and my social milieu. At the same time, I beg them to read my testimony with attention and empathy. In actual fact, those who reproach me may perhaps not be as numerous as I fear. Today’s Louvain is not the Louvain of fifty years ago. To give just one example, a Louvain physicist has recently, without encurring rebuke, as far as I know, made a public defense of atheism that goes much further than my vision of what, in the book, I call “ultimate reality.”[4] This would have been unthinkable fifty years ago.

I suspect that many intellectuals who call themselves Catholics share my uneasiness but feel that religion is so necessary and beneficial that it is preferable not to rock the boat. As I mention at the end of this book, I have long felt the same and refrained from speaking out. But, as I approach the end of my journey, I have reached the conclusion that such an attitude is not defensible. Respect for truth takes precedence over the regard one may have for the opinions of others.

But most of my readers presumably will have no connection with Louvain University, Belgium, or the Catholic Church. I owe them an apology for this autobiographical account filled with details of interest only to myself. I hope they will understand, when reading the book, why I chose to bother them with seemingly trivial reminiscences and anecdotes. Perhaps my tale may strike a responsive chord in American readers. Whereas the world I depict has virtually disappeared from the European scene, the United States still harbors many fundamentalist institutions of so-called higher learning, in comparison with which even the Louvain of my youth would appear munificently liberal.

ABOUT THIS BOOK

The topic of this book is the history of life, from its earliest beginnings to the panoply of microbes, fungi, plants, and animals, including human beings, that envelops Earth today in a colorful web of throbbing life. As such, the book covers basically the same ground as my earlier *Vital Dust.*[5] But there are significant differences. First, there are additional chapters, devoted, for example, to biotechnologies and to extraterrestrial life and intelligence. Also, the language of the present book is less technical, more accessible than that of its predecessor. Most importantly, this book is unambiguously focused on explanation and on meaning. Rather than trying to describe even-handedly the present state of knowledge and to expose existing uncertainties or conflicts with the impartiality of an uncommitted onlooker, I do not hesitate to argue matters and take sides. Especially, I tackle for the first time—or, at least, more explicitly than before—a number of sensitive questions, such as the role of chance in evolution, "intelligent design," religious beliefs, and the nature and intervention of God.

In writing this book, I have stretched myself far beyond the boundaries of my own competence. Even the greatest polymath, which I definitely am not, could not knowledgeably cover such vast ground. But the attempt deserves to be made and can't be just left to philosophers, historians, science writers, or other "generalists," who have no personal experience in science. Nor can the attempt be left, among those who have such experience, solely to physicists and cosmologists, who most frequently tend to venture into more general considerations but are often poorly acquainted with the life sciences. For better or for worse, I have taken the risk, apologizing to the experts for the many instances in which I presumed to trespass on their preserves and even had the temerity to offer my own opinion or interpretation on controversial questions.

This book is not a scholarly work in which every sentence is bolstered by appropriate references. Citations are mostly restricted to findings or statements of special interest, as reported in recent books or in nonspecialized journals, such as *Science, Nature*, or *Scientific American*, my main sources of information in the last few years. More complete coverage of the literature may be found in my earlier *Vital Dust* (1995) and *Blueprint for a Cell* (1991).[6] In addition, many details of more specialized nature have been left out of the main text for easier readability and are given in separate notes grouped together at the back of the book. Readers with an appetite for more solid fare are referred to these notes, which can to some extent be read as appendices.

Before closing this preface, I owe the readers one more explanation. I have written this book more or less in parallel in my two mother languages: French, in which I was educated and most often converse; and English, in which, being born in England, I was immersed from my earliest childhood and which has become, for all practical purposes, my main scientific means of expression and even thinking. A book written in this manner is a strange chimera, not only stylistically—which can be corrected with appropriate assistance—but also conceptually. One thinks differently in French and in English. Readers belonging to one culture or the other may find this somewhat disconcerting. Unfortunately, that's the way the author's brain was wired.

ACKNOWLEDGMENTS

I owe a special debt of gratitude to my old friend Neil Patterson, who has not only applied all his editorial skills to pulling together the text into a reasonably readable whole, trimming it of most of its Gallicisms—I have insisted on keeping some to preserve my identity—and of many flowery, pompous, incautious, obscure, or misleading phrases. He has also addressed the book's actual substance and helped me greatly in keeping the science on a rigorous course and in clarifying my own thoughts and ideas. In addition, Neil has shared my writings with his wife, Ippy, a wonderful artist who already contributed the trees to my *Vital Dust*[7] and has now given the present book a unique flavor with her beautifully delicate drawings. I am deeply grateful to her.

A number of colleagues have kindly read parts of the book lying in their own area of expertise and given me the valuable benefit of their comments and criticisms—which I confess I have chosen to follow as I saw fit. I am particularly grateful, in this connection, to Jacques Berthet, Susan Blackmore, Ivar Giaever, Henri-Géry Hers, Miklos Müller, Sue Savage-Rumbaugh, Jill Tarter, and Marc van Montagu.

I also acknowledge with grateful thanks the valuable assistance of my New York secretary, Anna Polowetzky (Karrie), and her son Michael, who have helped me with many phases of the book, including biographical searches. In Brussels, Monique Van de Maele has also provided much useful aid. I have been particularly fortunate to have this book published, under their customary high standards, by Oxford University Press. I am pleased to express my appreciation to Kirk Jensen and his colleagues for their competent and dedicated professionalism. The editorial assistance of Catherine Humphries has been especially valuable.

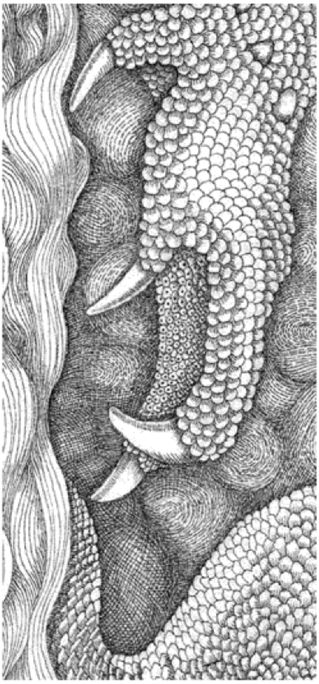
As in all my past endeavors, this one could not have been brought to successful conclusion without the devoted support and forbearance of my dear wife Janine. All I can do in return is to use this preface to acknowledge publicly and with loving gratitude her invaluable contribution.

Néthen and New York, Spring 2002

This page intentionally left blank

Life Evolving

This page intentionally left blank



Introduction

Look at the five "words" below, knowing that they were written with an alphabet of 20 letters:

ILDIGDASAQELAEILKNAKTILWNGP
GLDIGPDSVKTFNDALDTTQTIIWNGP
GLDVGPKTRELFAAPIARAKLIVWNGP
GLDCGTESSKKYAEAVARAKQIVWNGP
GLDCGPESSKKYAEAVTRAKQIVWNGP

If I were to tell you the words were typed separately by five different monkeys, would you believe me? Not if you have taken more than a passing glance at them. "All five words end with WNGP," you would point out to me, "and for monkeys hitting keyboards independently, this cannot be." Actually it can. But the probability of such a coincidence is one in 655 billion billions. You would need a pretty large number of monkeys for five of them to have a reasonable chance of coming up with the same word ending. Surely, a more likely possibility is that the monkeys cheated. They *copied*!

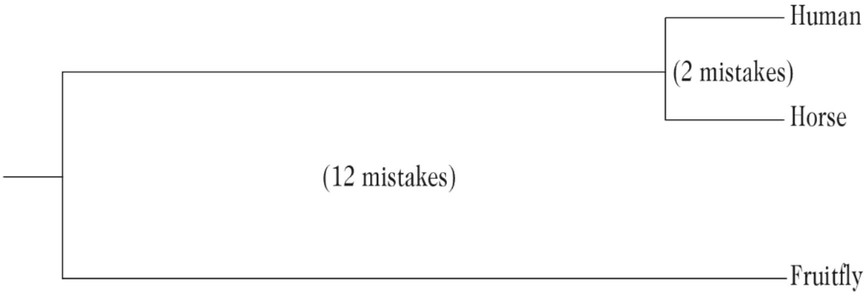
Actually, the fraud is even more flagrant than appears at first sight. If you look more closely, you will see that four other letters, in addition to the terminal four, are the same in all five words (LD in position 2 and 3, G in position 5, and I in position 22). This lowers the odds of a fortuitous coincidence to one in 429,500 billion billion billion billions. Trillions of planets like ours could not possibly provide enough monkeys. And this is not all. Five other letters are the same in four out of the five words (G in position 1, S in position 8, A in position 13, and AK in positions 19–20). Even more striking, the two last words have 25 out of 27 letters in common; they differ only in positions 6 and 17. There can be no doubt. If monkeys there were, they most certainly did not hit their typewriters' keys at random.

The words shown are not inventions. They represent real things, fragments of molecules called proteins, which are very long chains of up to several hundred units called amino acids, of which 20 different kinds are used in the assembly of the chains. Each word represents the sequence of a 27-amino acid piece (each letter standing for a given kind of amino acid) present somewhere in the heart of a large protein molecule containing more than 400 amino acids. This protein is an enzyme, or biological catalyst, known as phosphoglycerate kinase, PGK for short. PGK is a key participant in one of the most fundamental processes that take place in living organisms, the conversion of sugar to alcohol (or lactic acid), which occurs in virtually all forms of life, whether microbes of various sorts, plants, molds, or animals (including humans).

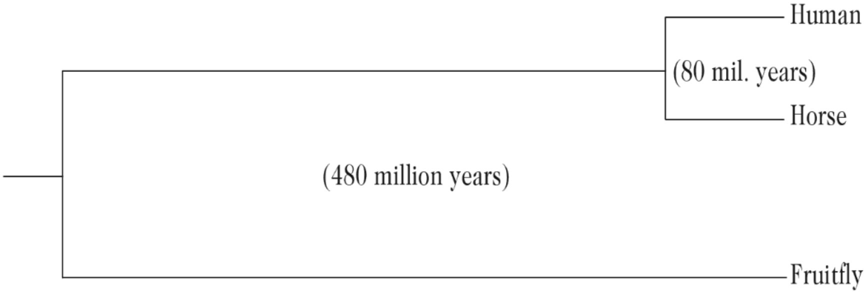
Now comes the central piece of information, which explains why the words serve as an introduction to this book. The five structures shown belong to the PGKs of five widely different organisms. The first one belongs to *Escherichia coli*, or colibacillus, a common microbe that we all harbor in our gut. The others are from the wheat, fruitfly, horse, and human PGKs, respectively:

Colibacillus:	ILDIGDASAQELAEILKNAKTILWNGP
Wheat:	GLDIGPDSVKTFNDALDTTQTIIWNGP
Fruitfly:	GLDVGPKTRELFAAPIARAKLIVWNGP
Horse:	GLDCGTESSKKYAEAVARAKQIVWNGP
Human:	GLDCGPESSKKYAEAVTRAKQIVWNGP

What our monkey parable has brought to light is that the similarities among the PGKs of our sample organisms could not possibly be due to chance. A possibility could be—this, no doubt, would be the "creationist" view—that the similarities betray the intervention of a "hidden hand." But, in that case, why the differences? Why, for example, does the human sequence differ from the fruitfly sequence in twelve amino acids and from the horse sequence in only two? No, the explanation given above for the monkeys is the correct one. The sequences show similarities because they were *copied*. And, they show differences because occasional copying mistakes were made. Thus, two mistakes would have been made in the horse and human lineages, twelve in the human (or horse) and fruitfly lineages, since their respective PGKs started being copied separately. Or, as shown graphically:



Make the additional assumption that it took some 40 million years, on an average, for one mistake to be made, and you get the following:

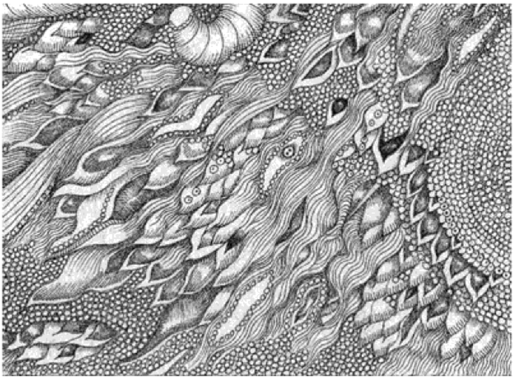


This, very roughly, is what paleontologists have long been telling us on the strength of fossil evidence. Humans and horses are derived from a common mammalian ancestor from which they diverged some 80 million years ago. The mammals themselves and the insects (the parent group of fruitflies) separated from a common ancestral form roughly 500 million years ago. What is new is that we can now estimate evolutionary times in terms of copying accidents (mutations) and that we can extend such estimates to lineages that have left no fossil remains. Also, we know how the copying takes place. It does not involve the protein molecules themselves, as suggested for simplicity's sake; it involves the DNA genes that encode the amino acid sequences of the protein molecules. For the purpose of our argument, it amounts to the same thing.

More will be said about this fascinating topic in Chapter 7. The main point, for the time being, and the reason for this Introduction, is that there is now overwhelming evidence that *all known living beings are descendants through evolution from a single ancestral form of life*. Many cogent reasons support this affirmation. Its most convincing proof is provided by the molecular sequencing results.[1] Even the very limited data presented in this Introduction should suffice to demonstrate the kinship among the five organisms mentioned (which, it should be noted, include us and the colibacilli of our intestinal tract). All the other available data—and their number is ever increasing—have confirmed this kinship and extended it to every other organism so far investigated. This fact is now so well established that researchers would be overjoyed if even one exception could be found—whether on Earth or elsewhere—because it would point to a second, independent origin for life.

1. What Is Life?

Chemistry



Until recently, the answer to the question "What is life?" posed no problem. Life, it was said, is "animated matter," from the Latin *anima*, soul. This, of course, was no explanation at all. It simply attributed to the soul, or vital spirit, all that was not understood about life. Nevertheless, vitalism, as this doctrine is called, maintained a foothold until well into the twentieth century, often—quite misguidedly—in connection with religious beliefs. This was especially true in France and other French-speaking countries.

The great Louis Pasteur was a confirmed vitalist. So was the philosopher Henri Bergson, winner of the 1927 Nobel prize in literature and author of *L'évolution créatrice*, in which evolution is depicted as propelled by an "*élan vital*," a vital surge. It was the case also for the physicist Pierre Lecomte du Nouy, who coined the term "*téléfinalisme*" to designate what he perceived as the innate ability of living organisms to act purposefully, in opposition to the second law of thermodynamics. When I was a student at the Catholic University of Louvain, in Belgium, all my biology teachers were vitalists, with the exception of the physiology professor, Joseph Bouckaert, in whose laboratory I had the good fortune of taking my first steps in science and who was a staunch mechanist. Which did not prevent him from attending church every Sunday and behaving like a perfectly good Christian. In his view, science and religion belonged to different domains, which, exhibiting no overlap, could not contradict each other.

Today, vitalism has few adherents,[1] as more and more of the remarkable properties of living organisms are being explained in terms of physics and chemistry. In turn, attempts at defining life call increasingly on these disciplines. In 1944, the Austrian physicist Erwin Schrödinger, world-renowned for the development of wave mechanics, addressed the question in a booklet titled *What Is Life?*, which was highly influential at the time. He perceptively singled out two properties as particularly characteristic of living beings: 1) their ability to create order out of disorder by exploiting external energy sources, feeding on what he called "negative entropy"; and 2) their capacity to transmit their specific blueprint from generation to generation, which property Schrödinger, who knew nothing of DNA, attributed to an "aperiodic crystal."

More recently, evolutionists, such as Britain's Richard Dawkins, have highlighted the paradigm of the "selfish gene," a powerful image intended to illustrate the notion that the genes are the ultimate targets of natural selection. Theorists, like Stuart Kauffman, long associated with the famous Santa Fe Institute, where so-called artificial life is being created by computers, insist on "self-organization" as a central property of life. My Belgian colleague Ilya Prigogine sees life as an example of those "dissipative structures" of which he has made a detailed theoretical study. Thus each, depending on personal interests, biases, and training, has his or her answer to the question "What is life?" Mine is simple.

Life Is What Is Common to All Living Beings

This answer is not a tautology, as it allows many attributes to be excluded from the definition of life. There is no need for green leaves, or wings, or arms and legs, or a brain, to be alive. It is not even necessary to be made of many cells. Hosts of living organisms consist of single cells. The simplest among them, namely the bacteria, lack a central nucleus and most of the other structures that can be seen inside the cells of more evolved organisms; so those cell features are also not requisites of life. What remains is what we humans have in common with the colibacilli in our gut. It is still a lot.

We and colibacilli, together with all other living beings, are made of cells, which are constructed with the same substances. We build our constituents by the same mechanisms. We depend on the same processes to extract energy from the environment and convert it into useful work. Most telling of all, we use the same genetic language, obey the same code. There are differences, of course. Otherwise, we would all be identical. But the basic blueprint is the same. There is only one life. In fact, all known living beings descend from a single ancestral form. We and colibacilli are distant cousins; very distant, but indubitably related.

A mere 50 years ago, these notions were still very dim and backed by little evidence. Today, it is no exaggeration to state that we know the secret of life. In just half a century, humankind has made the biggest leap in knowledge in its whole history. This revelation has come to us from the advances of cell biology, biochemistry, and molecular biology.

Living Beings Are Made of Cells

A literary person knowing nothing of biology might find this affirmation puzzling. Indeed, the word "cell" stands for a small room, a cubicle. One speaks of the cell of a monk or a prisoner. But what has life to do with such chambers? The explanation is to be found in a richly illustrated book, *Micrographia*, published in 1665 by the English physicist Robert Hooke, who built one of the first microscopes. Among the images reproduced in this work, there is a drawing of a thin slice of cork, in which Hooke distinguishes a fine, honeycomb structure, consisting, he says, of "microscopic pores," or "cells." The term has remained, to designate, not the cavities of cork, but the small bodies that occupy them in the living bark; it was adopted in 1837 by two German scientists, the physiologist Theodor Schwann and the botanist Matthias Schleiden, who proposed what is known as the generalized cell theory, according to which all living beings consist of cells.

Another German biologist, Rudolf Virchow, drove the generalization one step further in his classic opus *Die Cellularpathologie* (1855), in which he writes: "*Omnis cellula e cellula*" (all cells arise from cells). This was a paraphrase of the aphorism by the celebrated seventeenth-century English physician William Harvey, discoverer of blood circulation and explorer of animal generation: "*Ex ovo omnia*" (all [living beings] come from an egg).

Virchow's rule, as it is now known, suffers no exception. Everything that lives is made of one or more cells. And all cells come from other cells, by growth followed by division. This applies to our cells. The cells of our skin, our liver, our brain, and all our other organs originate, by successive divisions, from a single cell, the fertilized egg. The outcome, however, is not a simple collection of identical cells, a clone of the egg cell; it is a true organism. During embryological development, the cells, as they undergo successive divisions, become progressively differentiated and organized into tissues and organs. The egg cell itself arose from the fusion of two cells, the maternal and paternal germ cells, which were themselves decendants of egg cells. One can thus go back, by uninterrupted continuity, from any of our cells to the very first cells that existed on Earth. What is true for us is true also for any other living being. From cell to cell, all forms of life are descendants of those first cells.

How did the first cells originate from materials that were not organized as cells? How, in turn, did they give rise to the whole panoply of living beings that populate Earth today? Those are the two central questions raised by the history of life. To them must be added one more problem, of truly mind-boggling complexity: how does a fertilized egg cell produce, by multiplying, a harmoniously developed organism that closely resembles the donors of the germ cells from which that egg cell arose? In the chapters that follow, I shall try to sketch out the still-fragmentary answers science has, largely in the last 50 years, provided to these fundamental questions, which raise the existential problem of our presence here on Earth.

Cells are microscopic globules, of dimensions measured in thousandths of a millimeter. The human body contains trillions (thousands of billions) of cells. Of gelatinous consistency, cells have shapes that vary according to the internal and external constraints to which they are subjected. In the absence of such constraints, they tend to adopt a spherical shape.

To make a cell, there is first needed an envelope that serves as a border and, like all borders, isolates what it surrounds, while providing controlled entry and exit ports for the indispensable exchanges of matter that cells maintain with the outside. These functions are carried out by the *cell membrane*, a tenuous pellicle hardly ten-millionths of a millimeter thick. As fragile as a soap bubble, which it resembles in some of its physical properties, the cell membrane is most often, but not invariably, protected and bolstered by an external, rigid *wall*. In pluricellular organisms, this wall is replaced by scaffoldings, sometimes very elaborate, that shore up the tissues and delineate their architecture. Hooke's original cells were nothing but the putrefaction-resistant remnants of such scaffoldings.

The inside of the cell is occupied by a kind of semiliquid gel, called *cytoplasm*, showing little structure in certain cells and filled, in others, with a variety of granules, vesicles, and other entities, which constitute distinct organelles (small organs) and functional systems. The chemical processes that support the maintenance and growth of the cell take place largely in the cytoplasm.

Finally, the third indispensable component of any cell is what might be called its information center, the site in which are stored the instructions that command all that goes on in the cell and from which these instructions are issued. This information is written, in a coded chemical language, in one or more circular or rod-shaped structures, called chromosomes. These are naked and in direct contact with the cytoplasm in the simplest cells, those of bacteria. In the cells of more complex living beings, the chromosomes are confined within a central enclosure separate from the cytoplasm, the *nucleus*. On the basis of this distinction, the cells of bacteria are designated *prokaryotic* (from the Greek *karyon*, kernel), and the others *eukaryotic* (from the Greek *eu*, good).

First known by the diseases caused by some of them, bacteria are ubiquitous. Their sizes are small, on the order of one-thousandth of a millimeter, and their internal organization is rudimentary. They are found in a wide variety of environments. Most have no pathogenic effect; many are useful. It is estimated that bacteria represent, collectively, a mass equivalent to that of all trees and other plants combined.

Other unicellular microbes exist, but of eukaryotic nature, much larger and more complex than bacteria. Formerly subdivided into protozoa (primitive animals) and protophytes (primitive plants), these organisms are now grouped under the name of protists. They include the largest—up to the point of being sometimes visible with the naked eye—and most elaborate known eukaryotic cells. Certain severe illnesses, such as malaria and sleeping sickness, are due to protists. Many other protists are harmless and proliferate in many sites. They teem in the waters of puddles and ponds, to the delight of all those who have contemplated through a magnifying glass these "animalcules," thus named by Antonie van Leeuwenhoek, a Dutch contemporary of Robert Hooke and inventor, like him, of one of the first microscopes.

All pluricellular organisms (that is, plants, fungi, and animals, including humans) are made of eukaryotic cells. Mostly some 20 to 30 thousandths of a millimeter in size, these cells are all constructed according to the same general blueprint, the biggest differences being those existing between plant cells and the others. Within a given organism, the basic blueprint is subject to a number of variations linked to functional specializations. The number of different cell types in an organism increases with rising complexity. It reaches some 220 in the higher mammals, whose developmental programs are particularly complicated.

Living Beings Are Chemical Factories

Making life is what life is all about. What is thus made bears a remarkable similarity to what exists, leading many of those who have reflected on the phenomenon to insist that the central characteristic of life is the ability to follow a blueprint. This is, no doubt, an all-important feature of living organisms, and it will be considered in the next chapter. But blueprints are useless without builders. And life is built by *chemical* mechanisms. There can be no attempt at understanding life without the language of chemistry. This is all the more true because even biological information depends on chemistry. Unfortunately, few of us are familiar with even the basic elements of chemistry, in spite of the leading role of chemical industries in our technological civilization. Every effort has been made in this book to avoid technical details. But for life to be made understandable in modern terms, a minimum of chemistry has to be included.

THE FACTORIES NEVER STOP

Growth and multiplication are the most evident manifestations of life's self-building property. This activity is exercised also in a steady state, where nothing seems to change; but, in reality, construction work of all sorts continually takes place, offsetting an equivalent degree of decay. Indeed, breaking down life is as much a central characteristic of life as is making it. The two activities are inseparable and, together, account for the turnover, or renewal, of biological constituents. A bare few weeks after their birth, cells that have not multiplied and seem entirely unchanged start resembling those old houses that have maintained the same shape in the course of centuries but have had many boards, bricks, tiles, and window panes replaced.

This remarkable phenomenon and its astonishing magnitude have been revealed by the use of radioactively labelled substances, that is, substances in which certain atoms have been replaced by their radioactive counterparts (isotopes), carbon of atomic mass 12 by the radioactive carbon of atomic mass 14, for example, or hydrogen of atomic mass 1 by the radioactive hydrogen of atomic mass 3 (tritium).[2] When an organism is briefly provided—pulsed is the technical term—with some foodstuff containing radioactive atoms, these are found (detected by their radioactivity) to be rapidly incorporated into some biological constituents, from which they subsequently disappear just as swiftly, replaced by non-radioactive atoms as soon as the labelled foodstuff ceases to be supplied. Thus, even though the total amount of the constituents present has remained constant during the time of the experiment, their dynamic state, continually subject to breakdown and synthesis, has been brought to light by the use of labelled foodstuffs.

What, now, about the mechanisms whereby living organisms exercise their remarkable self-building ability? As for all chemical syntheses, three conditions must be fulfilled: raw materials, energy, and, in almost all cases, catalysis. In addition, a chemical factory that constructs itself must be able to combine the products of its industry according to a definite plan.

RAW MATERIALS

Let us first consider the case most familiar to us, our own. We derive our raw materials from our food. This is made easy because the animals and plants on which we feed are constructed with the same building blocks as our own tissues. The building blocks themselves are typically molecules of small size, made of carbon, hydrogen, and, most frequently, oxygen. They often contain nitrogen, sometimes sulfur. The number of atoms per molecule rarely exceeds 30, which gives molecular masses generally lower than two hundred times the mass of the hydrogen atom. For a chemist, these are simple substances, easy to make in the laboratory. On the whole, little more than 50 different kinds of such simple substances—mostly sugars, amino acids, nitrogenous bases, fatty acids, and a few other more specialized compounds—account together for more than 99 percent of the organic matter of any living being. To this must be added water, always the principal component, and a certain number of mineral elements, including sodium, potassium, chlorine, calcium, magnesium, iron, copper, and a few others.

What makes the difference, say, between our foodstuffs and ourselves is the way building blocks are assembled—somewhat like pieces of a

Lego game—into large molecules (macromolecules), mostly consisting of long chains in which as many as several hundred pieces, if not thousands, are joined together end to end. These chains are often folded and twisted into three-dimensional assemblages whose characteristic shapes are critically important for the biological properties of the substances. Both the organisms from which we derive our food and our own tissues—as well as all other living beings—are made of substances built according to the same general models but differing in the sequences of the chains—that is, in the order in which various building blocks follow each other along the chains. For this reason, and also because large molecules do not readily enter the organism, we cannot use food macromolecules directly. We must first dismantle them into their constituent building blocks. This process, called *digestion*, takes place in the alimentary tract. Intestinal absorption then transfers the products of digestion into the bloodstream, which, in turn, conveys them to all the cells of the body.

There, in the cells, the small molecules derived by digestion from food macromolecules enter a kind of chemical whirlpool called *metabolism*, in which thousands of reactions allow the substances present to be modified in various ways. It is from this metabolic pool that our cellular factories draw the materials with which they manufacture the characteristic constituents of our cells and tissues. The Lego pieces are thus reassembled into new structures proper to our organism. If, as is usually the case, certain necessary pieces are inadequately provided, they are made from others by metabolism, which also furnishes the energy required for the assembly reactions and other forms of work.

Feeding, digestion, absorption, metabolism, assembly: those are the obligatory steps in the transmutations whereby, for example, a baby makes human tissues from cow's milk. The same five steps allow the cow to make milk from grass. But here the food chain reaches the end. Grass does not eat in the usual sense of the word. It makes grass from simple inorganic substances: water from the soil, carbon dioxide from the atmosphere, a source of nitrogen, most often nitrate, and a few mineral salts, with, in addition, the indispensable source of energy, which is sunlight.

The examples just described can be generalized. There are two classes of living beings: those, like babies and cows, that feed on other living beings, and those, like grass, that utilize nonliving sources. The former, known as *heterotrophs* (from the Greek *hêteros*, other, and *trophê*, nourishment), include all animals and fungi and many microbes, both protists and bacteria. All use their foodstuffs by the same mechanisms. Even unicellular heterotrophs do so. Protists depend on special feeding processes whereby food is internalized and digested in intracellular pockets known as lysosomes. Bacteria digest their food extracellularly and then absorb the digestion products.

The organisms that make their constituents from nonliving sources are designated *autotrophs* (from the Greek *autos*, self, and *trophê*, nourishment). Most are *photosynthetic*, that is, derive the energy they need from light (*phôs* in Greek). They comprise the pluricellular plants and unicellular algae, which are eukaryotes, and photosynthetic bacteria. The last two are the main constituents of phytoplankton, the vast, life-generating solar screen that floats on the surface of oceans and initiates the marine food chain. Some autotrophic bacteria, called *chemosynthetic*, do not need light; they obtain their energy from mineral chemical reactions, such as the conversion of sulfur to sulfate or the production of methane (CH_4) from carbon dioxide and hydrogen. This property allows chemosynthetic organisms to develop in unlikely ecological niches, such as abyssal hydrothermal vents or deeply buried rocks.

Autotrophs, as well as heterotrophs, when cut off from their energy supply (plants in the dark, fasting animals) are able to cover their needs for a certain amount of time by subsisting on their stores (of starch or fat, for example) and even part of their active substance. All are now familiar with those shocking images of fleshless bodies, veritable living skeletons, who managed to survive in the Nazi horror camps or, closer to us today, try to subsist in regions ravaged by famine or war, awaiting the arrival of life-saving food supplies.

ENERGY

Biological self-constructions require energy. So do the other kinds of work—mechanical, electrical, osmotic, etc.—carried out by living beings. In the last analysis, the main source of this energy is sunlight, which directly supports all green plants and other photosynthetic organisms and, by way of the alimentary chain, all the other organisms that ultimately depend on food supplied by the photosynthetic ones. The baby fed cow's milk, for example, derives its energy from sunlight by way of the grass eaten by the milk-providing cow. Only chemosynthetic bacteria (those autotrophs that derive their energy from mineral chemical reactions) and the organisms that feed on them do not depend on sunlight. At present, only a small part of the living world belongs to this category, which, however, may be of great significance for the origin of life.

The biological utilization of light will be more readily understood if we first look at how we and all other *aerobic* (living in air) heterotrophic organisms—that is, animals, fungi, and many protists and bacteria—meet our energy needs. The operative word is combustion; more technically, oxidation,[3] the energy-producing interaction of certain substances with oxygen. In this respect, we resemble motor cars, which run on the combustion of gasoline; or heat power plants, which manufacture electricity by burning coal, oil, or natural gas. The fuel, in our case, consists of components of the metabolic pool (derived themselves from foodstuffs). Here, however, the analogy ends. Vital combustions are cold; and the energy they release is not utilized in the form of heat, a phenomenon that would be impossible in living cells, where temperature differences are negligible. Instead, this energy serves to drive a central chemical generator that, in turn, powers most forms of biological work. The nature of this generator will be considered below.

In cellular combustions, as in those we are familiar with, oxygen is used to convert the carbon of organic substances into carbon dioxide (CO_2) and their hydrogen into water (H_2O). Exactly the opposite takes place in photosynthesis.[4] What green plants do with the help of light energy is simply to reverse oxidations. Starting from carbon dioxide and water, the plants manufacture a sugar of formula $(CH_2O)_6$, throwing off the excess oxygen (one molecule of O_2 for each molecule of CO_2 used) into the atmosphere. The fuel is thus regenerated at the expense of the products of its oxidation, the required energy being supplied by light. Everything else, or almost, takes place as in aerobic heterotrophy—which is the state plants change to in the dark, subsisting on their reserves. Many photosynthetic bacteria act like plants, but a few rely on more primitive reactions that lead to sugar synthesis without the release of oxygen. As to nonphotosynthetic (chemosynthetic) autotrophic bacteria, they accomplish the same kind of syntheses with energy provided by the oxidation or other transformations of mineral substances.

The two processes—the dominant form of photosynthesis, which consumes carbon dioxide and produces oxygen, and biological oxidations, which consume oxygen and produce carbon dioxide—tend to balance each other worldwide, so that the levels of the two gases in the oceans and atmosphere remain constant. In recent years, however, this balance is being threatened by the ever-increasing consumption of fossil fuels combined with the progressive shrinking of forested areas. For oxygen, which represents 21 percent of the atmosphere, the disturbance is negligible. But for carbon dioxide, which makes up little more than 0.03 percent of the atmosphere, the rise caused by increased human-caused production and lower photosynthetic consumption has already become significant. There is increasing evidence that this phenomenon is beginning to cause a warming of Earth, due to the greenhouse effect.[5] If the present trend is allowed to continue, it could lead to the flooding of large coastal areas through melting of polar ice and to other catastrophic consequences for the environment. Awareness of these risks has reached higher levels of government. But the required measures will be very difficult to take, especially in view of the growing opposition to nuclear energy, at present the cheapest and most readily available substitute for fossil fuel consumption.

Oxidations, though playing a preponderant role, are not the only energy-supplying reactions of heterotrophic organisms. Some organisms, called *anaerobic* (living without air), can power the central generator by means of chemical processes that do not involve oxygen, for example, the fermentation of sugar to alcohol or lactic acid.[6] Some of these organisms are facultatively anaerobic; they can develop in the presence or absence of oxygen. Such is the case with yeasts, which (under oxygen-free conditions) make most of the alcohol we consume. Even our own muscles can be transiently anaerobic. The cramps that sometimes affect athletes are due to the lactic acid produced anaerobically in their muscles when these are inadequately supplied with oxygen during strenuous effort. Some organisms, such as the bacillus of gaseous gangrene, are obligatorily anaerobic. They can develop only in the absence of oxygen and are killed by this substance. We shall see later that this fact is of crucial importance for the origin and evolution of life. (It also explains why gaseous gangrene can readily be prevented simply by incising wounds and exposing them amply to the oxygen in air.)

What about the central generator powered by energy-yielding oxidations and fermentations? It is a chemical machinery that produces a compound called adenosine triphosphate (ATP), the fruit of the union of adenosine diphosphate (ADP) and inorganic phosphate (P_i). Never mind the exact chemical nature of these substances.[7] What counts is that energy is required to combine ADP with phosphate; this energy is quantitatively returned when ATP is split back into ADP and phosphate. These two reactions serve universally in the transfer of energy from metabolism to biological work.

Let us consider work first. Most forms of biological work are powered by the splitting of ATP,[8] with the help of specialized machineries, or *transducers*. Our muscles, for example, and other biological motor systems are driven by ATP. So, most often, are the cell systems involved in the specific import or export of substances; the generators that produce electricity in torpedo fish, electric eels, and the nervous system of animals; the light organs of fireflies and glowworms; and, of course, all the many chemical processes involved in biosynthetic constructions.[9] For those reasons, ATP is sometimes referred to as the "fuel" of life. This expression could be misleading, however. ATP is not burned, but split, to provide energy.

As to the reactions whereby ATP is assembled with the help of metabolic energy, they depend on special *couplings* between certain metabolic reactions[10] that produce energy and the energy-consuming creation of a chemical bond between ADP and phosphate. The two processes are linked in such a way that the energy-producing process cannot take place without driving the other. A similar thing happens in our engines. There is coupling between the combustion of gasoline and the propulsion of a motor car or between the energy-yielding process in a power plant—be it fuel combustion, falling water, or nuclear fission—and the rotation of an electric generator. But those are mechanical couplings. Biological couplings are chemical.

ATP is the universal vehicle of energy in the living world. Its role is analogous to that of electricity in the economy. Electricity, produced in central power plants and transported by conductors, drives all sorts of machines and appliances that convert it, with the help of appropriate transducers, into mechanical work, heat, light, and, sometimes, physical or chemical work. With ATP, the vehicle is different—a substance circulating by diffusion instead of electric current—and the couplings and transducers are of a different nature. But the principle is similar.

CATALYSIS

Biosynthetic assemblies, metabolic transformations, and bioenergetic couplings involve a very large number of chemical reactions, of which virtually none would take place if the participating substances were merely mixed together. Living beings carry out these reactions thanks to the mediation of specific catalysts. This term, coined by the great Swedish chemist Jakob Berzelius, designates a substance that helps a chemical reaction to take place, without itself being consumed in the reaction. Biological catalysts are called *enzymes* (recalling the fact that they were first discovered as agents of fermentation in yeast, which is called *zymê* in Greek).

Enzymes do truly stupendous things! They selectively fish out, by means of what are known as *binding sites*, the substances on which they act—the technical term is substrates—from the metabolic pool, a highly complex mixture containing up to several thousand different substances, most of them at very low concentration. Each kind of enzyme selects its own particular substrate or substrates from the metabolic pool. Substances thus caught end up accurately positioned with regard to another special part of the enzyme molecule, called the *active center*, that brings about their modification. This may be the splitting of a substance into two pieces, or the joining of two pieces into a single entity, or, more frequently, an exchange of electrons or chemical groups between two substances. As soon as the reaction is completed, its product or products detach from the enzyme surface, leaving the sites open for a new round. Thousands of such cycles—the record exceeds half a million—may take place every second on the surface of a single enzyme molecule!

Hundreds, if not more, of such reactions, each involving a different kind of enzyme and different participating substances, take place side by side in even the most primitive of living cells. In most cases, the products of certain reactions serve as substrates for others, thus linking consecutive reactions into a variety of chains, which may be linear, branched, or cyclic. Called *metabolic pathways*, these chains of reactions mediate all the chemical modifications that take place in cells. The metabolic pool consists essentially of all the substrates and products of the enzymes present. A few substances feed into this pool from the outside; a few end products are discharged from it as waste.

Any living being is a reflection of its enzyme arsenal. We are and do what our enzymes permit. This is so true that the absence of a single enzyme—as a consequence of a genetic deficiency, for example—often suffices to completely disorganize metabolism, to the point of severely endangering survival. This is the explanation for many hereditary diseases, to which, in the early twentieth century, the British pediatrician Sir Archibald Garrod gave the imaginative name of metabolic errors. Similarly, poisons and drugs frequently owe their biological effects to their ability to block certain enzymatic reactions.

Faced with these facts, you begin to get an idea of the power of enzymes and their significance for life. You also wonder at the nature of chemical structures that can create such a wide spectrum of finely tuned configurations as make up all the various binding sites and active centers present in enzymes and that can, in addition, have these binding sites and active centers arranged with pinpoint accuracy in the relative positions needed for the chemical reactions to take place. Clearly, substances capable of that kind of jugglery must belong to a class of substances with exceptionally rich and versatile properties.

These substances are the *proteins*, which are, indeed, the most complex substances found in living beings. Like other natural macromolecules, proteins are long, very thin strings made by the linking end-to-end of a large number—most often several hundreds—of pieces. Remember, we saw a small fragment of an enzyme protein in the Introduction. What makes proteins particularly complex is that 20 different kinds of pieces serve in the making of the strings and that these pieces, which belong to the group called *amino acids*, show an extraordinary variety of physical-chemical properties. Some amino acids carry a positive electric charge, others a negative charge, and yet others no charge at all; some attract water molecules, others have oily affinities; some depend for their particular properties on a strategically located oxygen atom, others on a nitrogen or sulfur atom. In contrast, rarely more than four different kinds of building blocks, usually with similar properties, enter in the formation of other macromolecules.

A given protein molecule owes its particular properties to the order, or *sequence*, in which amino acids follow each other along the string. Because of the many attractions and repulsions between the characteristic chemical groups carried by the amino acids, the string most often folds into a complex ball, in which certain groups distant from each other in the string join on the surface of the ball into highly specific three-dimensional configurations. This is how the binding sites and catalytic centers of enzymes are formed. Some protein molecules retain their linear conformation and assemble into fibers, trellises, plates, and other structures. These proteins, many of which have no catalytic activity, play a structural role.

An important aspect of proteins is that the existing molecules represent a vanishingly small fraction of those that are possible. In technical terms, they occupy a vanishingly small part of the *sequence space*, which, in fact, exceeds by far anything that can materially exist, or even be imagined.[11] This fact is often brandished by creationists and other adversaries of a naturalistic explanation of the origin of life, as proof that some intelligent choice presided over the selection of the proteins present in living organisms. I shall come back to this point in a subsequent chapter.

Many enzymes act with the collaboration of specific small organic molecules, called *coenzymes*, which often contain a vitamin as their active component. In addition, enzymes frequently bear one or more metallic elements, such as iron, copper, calcium, magnesium, manganese, molybdenum, or zinc, which play an essential role in the catalytic mechanism. These facts explain the nutritional importance of vitamins and trace elements. Note that we require vitamins because, contrary to the organisms from which we obtain these substances, we lack one or more enzymes needed for their synthesis. These are special cases of metabolic errors, which we correct by an appropriate diet and partly, also, with the help of bacteria present in our digestive tract, where these microorganisms manufacture some of the vitamins we need.

A few biological catalysts do not belong to the group of proteins, but to that of ribonucleic acids (RNA). Although few, these catalytic RNAs, which are called *ribozymes*, carry out important functions, some of which probably played a crucial role in the development of life. We shall come back to them.

SELF-ASSEMBLY

Until now, we have only examined the basic conditions that allow living beings to function as chemical factories. But a collection of molecules is a far cry from a living cell, just as a heap of bricks, boards, and tiles hardly makes a house. It remains for these pieces to be combined into walls, doors, windows, a roof, and other parts, according to a definite plan. Similarly, in biological constructions, the products of syntheses have to be assembled into structural elements, such as membranes, fibers, or granules, which must themselves be combined into more elaborate structures, up to the formation of that highly complex organism, a living cell (not counting the association of the cells themselves into pluricellular organisms). In the building of a house, the construction is done by workers, following a blueprint drawn by an architect. In the building of a cell, where are the workers, where is the architect?

There are none. It all happens automatically, according to instructions written into the structures of the molecules involved. At a first level, the information is provided by the enzymes. These define, by the configurations of their binding sites and catalytic centers, what may be termed the manufacturing program of the living chemical factories, their catalogue of products, so to speak.

At the next level, assembly is guided by the structures of the molecules thus made. Enzymatic proteins often participate in this combinatorial game, by means of sites that are different from those involved in their catalytic properties. They thus form complex multi-enzyme systems, organized so as to carry out reaction sequences or cycles in a coordinated fashion. Many structural proteins devoid of enzymatic activity and other macromolecules also take part in the self-assembly of biological structures.

What is remarkable about these phenomena is their spontaneity. Even though several hundred parts may be involved in the assembly of a structure, it all happens without outside instruction. The location of each piece is inscribed in its shape, as with a piece of a puzzle, with, in addition, sufficient attractive forces to stabilize the combinations created by chance encounters. Just mix the pieces and allow them enough time to get together—which, at the rate of molecular collisions, rarely demands more than a few hours—add a pinch of ATP as a source of energy and, possibly, a catalyst or two, and an object as complex as a chromosome, for example, will form spontaneously, even in a test tube. It is as though a puzzle could be put together simply by shaking the pieces.

The key notion here is *complementarity* between molecular configurations that fit and interlock with each other. This phenomenon, whose importance could hardly be overestimated, governs the combination of pieces in self-assemblies. It also explains the selection of substrates by the binding sites of enzymes. It is likewise involved in the interactions between active agents, such as hormones or drugs, with their cellular receptors, and in the recognition of antigens by antibodies in immune defense phenomena. We shall meet it as forming the basis of all genetic information transfers. Complementarity is often illustrated by the relationship between lock and key, or between mortise and tenon. The image is suggestive but only partly appropriate. Biological mortises and tenons have over those of cabinet makers the advantage of being more flexible and adaptable, so that they can to some extent mold themselves on each other. In addition, they bear with them, in the form of mutual affinities, the "glue" that helps them stick together.

The chemistry involved in these phenomena is different from that catalyzed by enzymes. Instead of true molecules, consolidated by strong linkages between atoms, as arise by the action of enzymes, the products of assembly are looser associations between molecules that remain distinct and are kept together by relatively weak forces. These are often electrostatic attractions, such as exist between entities bearing opposite electric charges. Repulsions between charges of the same sign may also be involved, keeping certain molecules or molecular parts at a distance from each other. Often also, the kind of physical phenomenon responsible for the fact that water and oil don't mix plays a role in biological assemblies. The same kinds of forces serve to stabilize the three-dimensional conformations adopted by proteins and other large, complex molecules.

THE CENTRAL ROLE OF PROTEINS

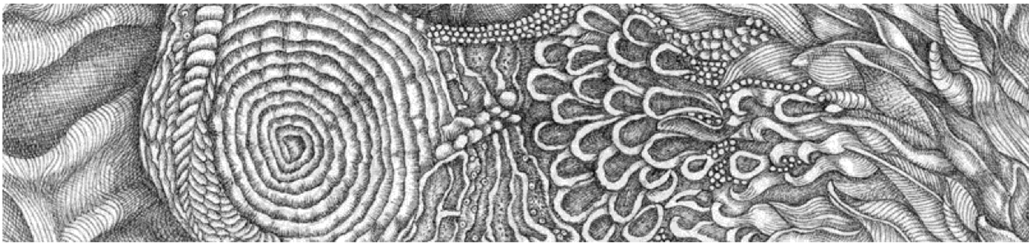
A conclusion emerges clearly from all that we have considered thus far: proteins occupy a truly central position in the organization of life. As enzymes, proteins are responsible for the vast majority of chemical reactions that take place in living cells, including such vital processes as the construction of biological constituents, the interconversion of materials by metabolism, and the production and utilization of biological energy. In addition, proteins play a leading role in the self-assembly of biological structures of a higher order. We shall see later that most of the substances involved in regulation and in signalling are also of protein nature.

Protein molecules owe their properties to their three-dimensional shapes, which are themselves determined by the amino acid sequences of their constituent chains. This leaves a key question: how are amino acids linked to each other into protein chains according to specific sequences?

Chemically, the assembly of amino acids into proteins is carried out, like other biosynthetic mechanisms, by specific catalysts acting with the help of energy provided by ATP. But, contrary to what happens in the construction of other substances, the specificity of the catalysts does not, by itself, suffice to ensure the correct reproduction of molecular structures. There is the additional need of a model, or *template*, that indicates to the catalytic systems which of the 20 available amino acids is to be attached to the chain at each step of its elongation. Chemistry no longer suffices; *information* must be added. This deserves a separate chapter.

2. What Is Life?

Information



So far, we have seen how life produces life. It remains for us to see how life *reproduces* life, that is, produces life similar to itself. The answer to this question is already contained in the preceding chapter. Inasmuch as the information needed to make a cell is largely written into the amino acid sequences of its proteins, all, or nearly all, that is required to reproduce the cell is to reproduce its proteins.

The Language of Life

In principle, the simplest way to reproduce proteins would have been to use them as models for their own synthesis. This is not what happens in reality. For reasons that, as we shall see in a later chapter, tell us a great deal about the manner in which life originated, the information that guides the assembly of proteins is not provided by proteins but by nucleic acids. And these are the molecules that are actually copied. Those functions are carried out by the genetic apparatus, which, therefore, stands at the top of the hierarchy in the organization of cells.

nucleic acids

Thus named because they were first discovered in the cell nucleus, nucleic acids consist, like proteins, of very long chains of interconnected units. Known as *nucleotides*, these units share a common "handle" made of a five-carbon sugar, or *pentose*, and *phosphate*. To this handle is attached a nitrogenous substance, called a *base*, of which four different kinds are coding for a given amino acid. Such coding base triplets are termed *codons*, and the table of correspondences between codons and amino acids is called the *genetic code*.[3] The need for codons of at least three bases is evident, since there are 20 different amino acids in proteins, and only four distinct bases in DNA. Were codons made of two bases, only 16 distinct combinations would be possible, which is still insufficient. With codons of three bases, the number of combinations is 64, which is excessive. In practice, 61 of the 64 triplets are used as codons, which means that several different codons (up to six) may code for the same amino acid. The three other triplets serve as chain termination signals.

DNA does not itself direct the assembly of proteins. It does so by way of RNA molecules, appropriately termed *messenger* RNAs (mRNAs), whose base sequences are dictated by those of the corresponding DNAs. The DNA-encoded synthesis of RNA is named *transcription*, as the two alphabets are very similar (A, T, G, and C for DNA; as opposed to A, U, G, and C for RNA). The step from RNA to protein, which involves two entirely different alphabets—20 amino acids for only four bases—is understandably termed *translation*. The copying of DNA is called *replication*.

Three processes, therefore, participate in the circulation of genetic information: replication, in which the information is transferred from DNA to DNA; transcription, in which it goes from DNA to RNA; and, finally, translation, in which it moves from RNA to proteins. Note that *only information* is transferred in this way. The actual *chemical* processes involved in the making of the information-bearing DNA, RNA, and protein molecules are, like all biosynthetic mechanisms, catalyzed by specific enzymes and energetically supported by ATP. The function of the nucleic acids is to tell the synthetic machineries which of the four nucleotides or which of the 20 amino acids is to be inserted at each step in the assembly process.

The relationships just outlined are of universal significance. In all known living beings, the genetic information is stored in the base sequences of DNA molecules, reproduced by replication of this DNA, and expressed by way of the RNA and protein molecules synthesized according to the information held by the DNA. The sum total of the DNA of an organism is called its *genome*; it is subdivided into units called *genes*, each of which may be said, in rough approximation, to code for a distinct protein chain (except the few genes coding for functional RNAs, see