The Way of the Cell: Molecules, Organisms and the Order of Life

Franklin M. Harold

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ABOUT THE AUTHOR

Frank Harold was born in Germany, grew up in the Middle East and was educated at the City College of New York and the University of California at Berkeley. His professional career spans forty years of research and teaching, mostly in Colorado; he is presently Professor Emeritus of biochemistry at Colorado State University. Dr. Harold's scientific interests center on the physiology, energetics and morphogenesis of microorganisms, and he is a member of the American Academy of Microbiology. He is also a keen traveler and outdoorsman, and a lifelong student of Asian history and civilizations.

"A momentous change had come about when what scientists did came to be taken for granted, even by those who understand little or nothing of it. The crucial change in the making of the modern mind was the widespread acceptance of the idea that the world is essentially rational and explicable, though very wonderful and complicated."

John M. Roberts
The Triumph of the West, 1986

For Ruth: Microbiologist, artist, traveler, hill walker, friend, colleague, wife, mother; and the best thing that ever happened to me.

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PREFACE

This book is not about biology, biochemistry or any other finished and finite discipline, but about life. Life seems to me the supreme marvel of the universe—familiar, thoroughly material, probably ubiquitous yet elusive and ultimately mysterious. My purpose is to assess how far we have come toward a scientific understanding of the phenomenon of life.

With so broad, not to say nebulous a subject, it seems best to spell out the premises on which this inquiry rests. First, I am a scientist by profession, not a philosopher; we shall be concerned here with what natural science has to say about the nature of life, not how it appears to a psychologist, theologian, poet or epistemologist. Second, I take it that the term "life" designates a real phenomenon, recognizable by a set of properties characteristic of some natural objects and lacking in others; one of our goals must be to identify the essential features that distinguish living organisms from other things. Although we have been able to study but one kind of life, the terrestrial variety, it is likely that life exists elsewhere in the universe, and it is arguable that life everywhere will be based on this common set of general principles. Third, during the past century we have come a very long way by scrutinizing the workings, architecture and chemistry of cells and organisms; what we have learned makes a solid foundation for reflection on the nature of life in general. Finally, I hold that the quest for an answer to the riddle, "What is Life?" is one of the grand themes that resonate through the scientific conversation of this century—a period whose science is also its singular glory. That riddle embraces and transcends the subject matter of all the biological sciences, and much of physical science as well. A physics that has no place for life is as impoverished as would be a biology not informed by chemistry. The study of life as a natural phenomenon, a fundamental feature of the universe, must not be allowed to slip into the black hole of departmental tribalism.

Let me enlarge for a moment on the latter point, for herein lies much of the motivation for writing this book. What science knows of the nature of life, it owes to the labors of countless specialists—physicists and chemists, mathematicians and geologists, geneticists and biochemists and physiologists, biologists evolutionary and biologists molecular. The fruits of our labors are first inscribed in shelf upon shelf of professional journals, and subsequently reincarnated in textbooks that have grown too heavy to carry, let alone read. But the nature of life is not a practical topic for research. General insights, if there be any, must be distilled from numberless particular discoveries, and here time may no longer be on our side. The relentless accumulation of information on all subjects, however desirable in itself, frustrates understanding by pressing everyone into ever narrower borders. A second hindrance is the spirit of the times, the clamor that knowledge has value only insofar as it lends itself to practical ends. Scientists themselves increasingly subscribe to the thesis that science must serve the uses of power, not of philosophy: it is, after all, on our usefulness that we base our claim to scarce public resources. The most productive era of fundamental inquiry may thus be approaching an end, and that makes it timely to gather the threads of knowledge spun out by research and see what pattern they make.

That conversational word "understanding" has already cropped up several times, and since it stands for the object of this entire exercise some attempt at definition is in order. Scientists use the word in a somewhat special sense, that was nicely set forth by Mary Midgley in her critical study, *Science as Salvation*. "Understanding anything is finding order in it. . . . It is simply putting [the pattern] into the class of things meaningful—noting how its parts relate to it as a whole, and how it itself relates to the larger scene around it" (1). And "explanation?" To strive for a plausible, self-consistent view of the world, and to communicate it to others, is a less exalted quest. But I cannot agree with those who dismiss it as unworthy, as long as we remember the difference.

One response to the question, What is Life? is simply, Look Around! Note the birds and the butterflies, zebras and ammonites, the intricate web of life present and past, and join the unending struggle to ensure its continuance in the face of human arrogance and mindlessness. This has been eloquently said by others, far better than I could, and it is not what I have in mind here. For the past forty years, I have been immersed in research on the biochemistry and physiology of microorganisms, with emphasis on the fundamental aspects such as bioenergetics and morphogenesis. In consequence, the central problems of life present themselves to me at the interface of chemistry and biology. How do lifeless chemicals come together to produce those exquisitely ordered structures that we call organisms? How can molecular interactions account for their behavior, growth, reproduction? How did organisms and their constituents arise on an earth that had neither, and then diversify into the cornucopia of creatures that enliven each drop of pond water? My purpose is not to "reduce" biology to chemistry and physics, but to gain some insight into the nature of biological order. In an earlier book, I wrote that "Living things differ from non-living ones most pointedly in their capacity to maintain, reproduce and multiply states of matter characterized by an extreme degree of organization" (2). This still rings true; biological organization is the key to the nature of life, and the central theme of this book.

Most branches of science bear on the problem of life, but some are more pertinent than others. This book celebrates microorganisms, and that requires explanation because with most folks the word "life" does not conjure up the image of bacteria or protozoa. Microorganisms do not receive much attention in books about biology, and the public at large knows them chiefly as agents of disease. We who love microbes are apt to justify our peculiar passion by extolling their diversity, far greater than that of all higher forms of life. We point to their manifold interactions with humans, more commonly beneficial than harmful; and we insist that the operation of the biosphere is wholly dependent on microbial ministration. But the reason they star in this book is that reflection on the smallest and simplest forms of life has been singularly fruitful: whether it is molecules we seek to understand or organisms, communities or evolution, the proper study of mankind is often not man but microbes. Geological history reinforces the point. Microorganisms, the bacteria and protists, can make a biosphere all by themselves, and did so for billions of years when the earth was young. Higher organisms hold mysteries that are of special concern to us humans: the genetic basis of disease, the immune response, embryonic development and the nature of mind are now at the forefront of the research effort. But for the purposes of an inquiry into the nature of life, these are peripheral issues. They represent potentialities inherent in living matter, but are not required for its existence.

A company of potential readers looked over my shoulder throughout this writing. First my colleagues from academe, quick to find fault, demanding factual accuracy at all costs and restraining my penchant for generalization; I have heeded their admonitions as best I could. But there was also a party of students, surfeited with facts but curious still, wanting to be reminded of what it was that drew them into science in the first place. A couple of teachers came from a local college or high school, charged with making science intelligible to students whose interests all lie elsewhere; at the end of the day, such teachers may hold in their hands the future of science. I spotted a few members of that endangered species, the educated laity, pleading for simplicity and clarity in the face of unavoidable complexity. And every so often Lyndon Johnson's ghost would whisper in my ear the late president's favorite question: And therefore, what? The latter all persuaded me to step back from technicalities and detail, and to paint with a broad brush. In the end I tried to write the kind of synoptic and non-technical volume that I myself seek out when my reading draws me into strange waters.

Inevitably, then, this is a personal book—one scientist's attempt to wring understanding from the tide of knowledge. It grew out of the experience of a lifetime devoted to research, scholarship and instruction; but since my purpose is to make sense of the facts of life rather than to expound the facts themselves, this inquiry walks the edge of science proper. The arguments and conclusions presented here seem to me sound, but they are certainly not the last word on the subject. The most valuable lessons that the discipline of science teaches are to play the game of conjecture and refutation, to appreciate the provisional nature of our knowledge, and to prize the doubt! If what I have written here encourages a few readers to look up from their gels and genes to peer at the far horizon, I shall be well content. Of my shortcomings as an investigator, scholar, philosopher, and expositor I am keenly aware. But I can claim to share one merit with Erwin Schrödinger, who gave us our marching orders fifty years ago: I, also, am willing to make a fool of myself in a good cause.

ACKNOWLEDGMENTS

No man is an island, a scholar least of all. This book owes something to most everyone that I have ever engaged in serious conversation about life, the universe and the nature of science. They are too numerous to mention by name, even if I could call them to mind, but I must not fail to acknowledge those among my friends and critics that made me think again. Salomon Bartnicki-Garcia, Dennis Bray, David Deamer, Ford Doolittle, Marty Dworkin, Joseph Frankel, Brian Goodwin, Ruth Harold, Lionel Jaffe, Arthur Koch, Darryl Kropf, Nick Money, Harold Morowitz, Gary Olsen, Norman Pace, Martin Pato, Howard Rickenberg, Willie Schreurs, Mitchell Sogin, Bruce Weber and Carl Woese, thank you all for making the labor of science so great a pleasure. Colleagues in my present department tolerated my eccentricities and created an environment in which I could remain productive past formal retirement. James Bamburg, Norman Curthoys, Jenny Nyborg, Marvin Paule, Craig Schenk, Robert and A-Young Woody, thank you. Much of what I have written here was inspired by the teachings of the late Peter Mitchell and Roger Stanier; I believe that they would have approved of this final jog in my professional journey.

My debt extends to many scientists, writers and scholars whom I have never met, but whose books and articles shaped my thinking. I shall cite the most pertinent ones below, but such casual courtesy does not do justice to the influence exerted by John Tyler Bonner, Jacob Bronowski, Paul Davies, Stephen Jay Gould, François Jacob, Lynn Margulis, Ernst Mayr and Rupert Riedl. Special thanks are due to the late Loren Eiseley, from whom I learned during a crisis of doubt that the true use of science is to make the world intelligible. There are also institutions to thank, notably the National Science Foundation, which supported the work of my laboratory as well as the early stages of this writing. Colorado State University did its part, not only by providing

support and a library, but also by requiring me to face a class of non-science majors enrolled in Biochem 103 (Cells, Genes and Molecules).

Transformation of a manuscript into a book is again the work of many hands. Nancy Graham turned yellow pages thickly scribbled in longhand into neat, legible typescript, not once but time and again. Individual chapters were scrutinized by D. Bray, D. Deamer, M. Dworkin, R. Harold, D. Kropf, N. Money, G. Olsen, M. Pato, R. Woody and several anonymous reviewers, who spotted more errors and ambiguities than I care to admit. Kirk Jensen proved himself a shrewd and patient editor, whose sage advice let me avoid more than one pratfall. The illustrations were drawn by Gary Raham and Steve McMath at Visible Productions, Inc., Fort Collins, Colorado.

The ever-swelling technical literature presents special problems for one who writes for a general audience. Scholars are expected to acknowledge their sources, but readers find a drizzle of references distracting. By way of compromise, I have tried once more to steer between glibness and pedantry. Most of the citations identify review articles and books, supplemented where necessary by reference to the most recent experimental reports. They are intended to offer a foothold to readers who wish to pursue some aspect in greater depth, but they are far from exhaustive and do not necessarily indicate priority of discovery. Responses to the literature extend through 1999.

And so, having come to the end of a road that began nearly a decade ago, I wonder still what makes one persevere in such a laborious and painstaking effort, whose chief reward is likely to be the satisfaction of bringing it to completion. Is it merely the urge to relieve what the Romans called the writer's itch? The best explanation I have ever found comes from the preface to *Practicing History*, a collection of essays by the eminent historian Barbara Tuchman (1). Let me quote her here for the benefit of anyone who may be contemplating a major writing commitment with mingled dread and desire. "Research is endlessly seductive, writing is hard work. One has to sit down in that chair and think and transform thought into readable, conservative, interesting sentences that both make sense and make the reader turn the page. It is laborious, slow, often painful, sometimes agony. It means rearrangement, revision, adding, cutting, rewriting. But it brings a sense of excitement, almost of rapture, a moment on Olympus. In short, it is an act of creation."

1

SCHRÖDINGER'S RIDDLE

"It is better to know some of the questions than all of the answers."

James Thurber

In the spring of 1938, Adolf Hitler launched his conquest of Europe by annexing neighboring Austria. Nazism had struck deep roots in Austria and the populace cheered as the German troops marched into Vienna, but what was left of the country's cultural and intellectual elite scattered into flight. Among those who had left their escape to the last was Erwin Schrödinger, one of the pioneers of quantum mechanics and Austria's premier physicist. Schrödinger found a haven at the Institute for Advanced Studies of Trinity College, Dublin, where his contract required him to deliver a series of public lectures. He elected to discourse on a physicist's view of life and published the lectures in 1944 in the form of a small sprightly volume boldly entitled *What is Life?* (1). It proved to be an enormously influential work that drew students and young scientists into a new biology. I read it as an undergraduate, understood the easier parts and remember that first encounter nearly half a century later.

Rereading Schrödinger today, with the benefit of knowing what came after, leaves one wondering just where the book's appeal lay. Max Perutz, disappointed by the deficiencies of its scientific content, commented acidly that "what was true in his book was not original, and most of what was original was known not to be true even when it was written" (1). Quite so, but the book was directed to a general audience, and it succeeded admirably as a manifesto for a new era. It centered on two topics that were to dominate research for the next thirty years, the nature of the gene and the energetics of biological order; Schrödinger had drawn up an agenda for the new biology. Besides, the book's title posed the crucial question. To be sure, the nature of life is not a subject that experimental science can tackle head on, but it is one that has engaged and eluded natural philosophers for millennia. Schrödinger placed the nature of the gene at the very heart of the mystery and argued that heredity and biological reproduction, which seemed to defy the known laws of physics, could be accommodated within a broader framework. Unlike most physical principles, which were derived by averaging the behavior of large numbers of particles, heredity must reflect the unique properties of one or two individual large molecules. Schrödinger likened these to "aperiodic crystals," which can contain a "codescript" because each group of atoms plays an individual role that is not exactly equivalent to that of any other group. The idea, though not the language, had originally been put forward by a young physicist named Max Delbrück, and one of Schrödinger's objectives was to give Delbrück's insight a wider hearing. "Aperiodic crystal" and "codescript" foreshadowed the structure and function of DNA, the molecule that encodes hereditary information, whose central role had not yet been recognized. But the time was ripe. With the war over, numbers of young scientists (by no means all physicists) were eager to turn their talents to nobler uses, and they responded joyfully to Schrödinger's challenge to bring the study of living organisms fully within the compass of physics and chemistry. The premise that life, though complicated, is rational and explicable has taken root, justified by the tremendous success of Schrödinger's program.

Schrödinger wrote at the beginning of an extraordinary era in biological science, a great eruption of knowledge that cast a brilliant light into the chemical and physical foundations of life. Perhaps one must have lived through this revolution to appreciate how radically it transformed our perception of what biology is about. In the forties, biology was still primarily centered on living creatures, and quite separate from the physical sciences. Research on the molecular constituents was just gathering steam, and the nature of macromolecules in particular was a matter for doubt and debate. Thirty years later, biology seemed well on the way to becoming a province of chemistry. By 1975, it was becoming a tedious but routine task to determine the primary structure of macromolecules, and three-dimensional images were appearing regularly. The pathways by which the major biological molecules are produced and broken down had been worked out. Enzymes continued to challenge the chemical imagination, but how they ensure the high rate and precision of biochemical processes had in principle been clarified. In principle, though not yet in detail, biochemists had discovered how living organisms capture energy and harness it to the performance of work. But the single most spectacular accomplishment was the solution to the problem that Schrödinger had held up as central, the nature of the gene. It led quickly to the discovery of the principles that govern the replication, transmission and expression of genetic information. Those were heady days, splendidly recreated by H. F. Judson in *The Eighth Day of Creation* (2). Unsolved problems remain in all these areas, even today, but we see them as puzzles, not as mysteries. How matter, energy, and information flow through living organisms is nowadays quite thoroughly understood; the ponderous textbooks in which this knowledge is recorded stand as monuments to an achievement that has few parallels in the annals of science.

Can we say then, that the riddle of life has been read—or soon will be, pending only the clarification of a few outstanding details? Those who believe that the object of the quest is to discover the physical and chemical mechanisms that underlie universal biological processes may be inclined to nod assent. But anyone familiar with living creatures will protest that the compendium of molecules and mechanisms omits the very singularities that answer to one's intuitive sense of what "life" means. Surely, a satisfying reading of Schrödinger's riddle should have something to say about cells, those universal units in which the phenomenon of life is dispensed. And it should bear on the kind of observations with which biology has traditionally been concerned: morphology, structure serving function, goal-seeking behavior, reproduction, adaptation. It must, in short, take cognizance of *organisms* in all their complexity, uniqueness and diversity. Physicists and chemists have every reason to take pride in their achievement. But traditional biologists are equally justified in pointing out how much remains to be accounted for, and to wonder whether, in abandoning the organism for its molecules, we have forgotten what the question was.

The open questions about the workings, behavior and functions of organisms differ in degree, and possibly in kind, from the problems that were so satisfyingly solved in the salad days of molecular biology. Biochemical mechanisms, the structure of DNA, even the replication and translation of genetic information are simple—not in the sense of being easy to discover, but in that they involve a limited number of interactions. Moreover, the structures and interactions are literally linear: DNA makes RNA makes protein describes the transformation of one linear set of symbols into another. But when we inquire how an amoeba crawls, or how a yeast cell grows and buds off a daughter, the phenomena are inherently very much more complex. The functions of the living organism typically depend upon the coherent operations of molecules by the million, belonging to hundreds or even thousands of different kinds, and marshalled into order by a hierarchy of controls. Few of these molecules are free in solution. On the contrary, many are first assembled into elaborate constructs whose dimensions are measured in micrometers or even millimeters, orders of magnitude greater than those of individual molecules, and their collective actions characteristically display a direction in space. These features underscore what Warren Weaver, in another seminal essay of the forties (3), called the problems of organized complexity. A satisfying reading of life's riddle demands a rational account of biological organization, and that has yet to be achieved.

During the next fifty years, Weaver thought, science will have to address such questions as "What makes a primrose open when it does?" And we are doing that. We have ample reason to believe that every biological phenomenon, however complex, is ultimately based on chemical and physical interactions among molecules. With this principle as the point of departure, intense efforts are presently underway to understand how and when a flower blooms (and how the amoeba crawls and the yeast buds), by identifying all the relevant molecules and describing how they intermesh. Many of these projects have been successful, some dazzlingly so, and that enables us to supply a mechanistic explanation for a growing number of biological phenomena. Muscle contraction is a case in point: We can explain in a full and satisfying way how the machinery works, given that the molecular elements have been placed in the structural framework revealed by microscopy. But it is not at all clear that we can answer Weaver's question by extrapolating from the molecular parts to the functional whole. If we knew the chemical structure of every muscle molecule, and understood their chemical interactions, would that suffice to specify how these molecules are articulated in time and in space to generate a working muscle?

This is actually a genuine philosophical puzzle, one version of the question whether biology can ultimately be "reduced" to chemistry and physics or is an autonomous science with principles of its own. I shall return to this issue more than once in subsequent chapters, but for present purposes the answer is plainly that there is more to life than just molecular mechanics (4). From the chemistry of macromolecules and the reactions that they catalyze, little can be inferred regarding their articulation into physiological functions at the cellular level, and nothing whatever can be said regarding the form or development of those cells. It therefore seems to me self-evident that the quest for the nature of life cannot be conducted exclusively on the biochemist's horizon. We must also inquire how molecules are organized into larger structures, how direction and function and form arise, and how parts are integrated into wholes. Besides, we must never forget that molecules, cells and organisms are all creatures of history, brought forth by the interplay of chance and necessity. There can be no simple answer to the question, What is Life? It is an invitation to explore the successive levels of biological reality, and a lecture on molecular biology is intrinsically no more (and no less) illuminating than a walk through the woods in the springtime.

Erwin Chargaff made the same point years ago, in one of the most perceptive (and disturbing) autobiographies composed by a scientist (5). "Our understanding of the world is built up of innumerable layers. Each layer is worth exploring, as long as we do not forget that it is one of many. Knowing all there is to know about one layer—a most unlikely event—would not teach us much about the rest." Next time you fly, reflect upon the airplane's wing. It is designed to provide lift, and its component parts serve that function; a skilled mechanic, supplied with aluminum sheeting, a box of rivets and the blueprints, might well be able to produce a serviceable wing, but would he or she deduce the principles of aerodynamic flight from copying the wing? By the same token, Mendel's laws could not have been predicted from the structure of DNA, or even that of chromosomes; in fact, they have meaning only in the context of cells and meiosis. It is common experience that to understand the whole we must know its parts, but the properties of the whole can seldom be predicted from the properties of its parts alone. That is what is meant by the chestnut that the whole is greater than the sum of its parts. And so, I find it unbelievable that the forms and functions of cells (let alone those of Weaver's primrose) will ever be predictable from a knowledge of their molecular constitution alone, however comprehensive. It would be a gross mistake to brush off the higher levels of biological order as if they were secondary or derivative;

on the contrary, how the parts come together must be key to any inquiry into the nature of life.

Schrödinger sensed this, and devoted the final pages of his slender book to the problem of biological order. The exquisite organization of every cell and organism appears to contravene the second law of thermodynamics, which insists that the universal tendency of physical processes is the dissipation of order and the production of entropy, a measure of disorder. Schrödinger credited the extraordinary ability of living things to generate, maintain and reproduce their orderly state to the extraction of "negentropy" (negative entropy) from the environment. Today, following Harold Morowitz (6), we would put this rather differently by saying that living organisms extract energy from the environment, use it to perform all manner of chemical and physical work, and thus convert energy into organization. Life does not contravene the second law; it evades it. But the problem remains that entities capable of converting energy into organization are not predictable from the laws established by classical physics. This suggested to Schrödinger that organisms stand outside physics in some essential respect; or else, that physics contains additional principles that pertain to organized systems, which remain to be discovered.

Can we discern any higher-order principles that are required for a fundamental understanding of life? One, at least, leaps to mind: Darwin's principle of evolution by random variation and natural selection. It has shaped molecules as much as organisms, and there is no explaining life without it. To be sure, the mechanisms that underlie evolution, like those of heredity or energetics, operate at the level of molecules, and some molecular processes that involve random variation and selection among macromolecules mimic biological evolution. But I doubt that evolution by natural selection would have been inferred from molecular science, had Darwin never lived; here is another generalization that finds full meaning only in the context of organisms. There may be others, such as the speculative proposition that the origins of biological form should be sought in the spontaneous self-organization of physical systems subjected to a flux of energy. Schrödinger, for one, considered that "living matter, while not eluding the 'laws of physics' as established up to date, is likely to involve 'other laws of physics' hitherto unknown, which, however, once they have been revealed, will form just as integral a part of this science as the former" (1). Here we touch one of the grand themes of a future biology, to which we shall return more than once.

Order, complexity, organization, function: these deceptively familiar words point the way toward the high intellectual frontier of biological science. Explorers who would travel that wilderness must put their trust, not in molecular biology alone, but in physiology—the science of complex systems. We all know in our hearts that a cell is far more than an aggregate of individual molecules; it is an organized, structured, purposeful and evolved whole. Unfortunately, analytical practice dictates that we begin our inquiries by grinding the exquisite architecture of the living cell into a pulp. No wonder, then, that the integrative perspective is woefully absent from the molecular view of life as it has developed over the past half-century.

So, what is life? The question is as good as ever. Despite decades of spectacular advances, the essential nature of life continues to elude us. We know much and explain more, but one sometimes suspects that our capacity to explain has outstripped our understanding. And when we have reinvented physiology, mastered self-organization and ransacked the rocks for fossil vestiges of genesis—will we then have read Schrödinger's riddle? Probably not. But we should have a much better grasp on the essential principles of the science of life, that grammar of biology for which Erwin Chargaff once wrote a memorable preface (5). At the very least, we should see more clearly what the riddle means, and how best to ponder it.

2

THE QUALITY OF LIFE

“The man behind the microscope
Has this advice for you:
Never ask what something Is
Just ask, what does it Do?”

Hilaire Belloc

We picked our way gingerly down the boulder-strewn canyon, keeping an eye out for cactus spines and rattlesnakes. One walks warily in the Big Bend, and so it was some time before we spotted our first “living rock.” The nickname is apt: flat, grey and crusty, half-covered with sand, they blend into their stony environment. But once noticed, their nature is not in doubt; they are unmistakably living plants masquerading as rocks. It is almost always so: though the definition of life is elusive, we seldom have difficulty distinguishing living creatures from lifeless objects by their special qualities.

As a subject for serious inquiry, the category “life” has all but vanished from the scientific literature; it is the particulars of life, not its nature, that fill the numberless pages of scientific journals. But any attempt to extract general principles from that tide of information must begin, if not with a definition of life, then at least with the criteria by which we recognize the phenomenon. With the advent of space travel, the question has ceased to be purely an academic one. When explorers from

Starship Enterprise boldly land upon some planet orbiting Betelgeuze, will they recognize life if they encounter it in an unfamiliar guise? Probably yes, for wherever the restless search for novelty takes us, we expect life to be a quality of the peculiar class of objects called "organisms." They are the devil to define, but it is not difficult to set forth general criteria that map out the process of living as we see it all about us, and that should apply as well to life as we can imagine it elsewhere in the universe. Here are the main ones.

(i) *The Flux of Matter and Energy*. Living organisms are the seat of incessant chemical activity. They absorb nutrients, produce biomass and eliminate waste products plus heat; most constituents undergo breakdown and resynthesis during the lifetime of an individual organism. Metabolism, a term derived from the Greek word for change, designates the totality of all the chemical transformations carried out by an organism. It is so practical a hallmark of life that evidence of metabolism is what the space probe sent to Mars in 1976 searched for, without success.

Much of this chemical business revolves around energy. The characteristic activities of living things—their growth, movements, the very maintenance of their structure and integrity—depend upon input of energy from the environment. That is one of the chief functions of the metabolic web, for chemical substances serve as carriers of energy as well as matter. Like a flame or an eddy, an organism is not an object so much as a process, sustained by the continuous passage through it of both matter and energy.

(ii) *Self-Reproduction*. Living things are generated autonomously, not by external forces, and what they generate is their own kind. Like begets like. Biological heredity is quite unlike the point-by-point transfer carried out by a copying machine. Instead, characteristics are transmitted from parent to offspring by a program or recipe that embodies instructions for producing the next generation. The process is extremely accurate, yet subject to occasional errors that account for the variation observed in every natural population.

(iii) *Organization*. Whenever we speak of organisms we acknowledge the fundamental connection between the living state and a special kind of order. Even the simplest unicellular creatures display levels of regularity and complexity that exceed by orders of magnitude anything found in the mineral realm. A bacterial cell consists of more than three hundred million molecules (not counting water), several thousand different kinds of molecules, and requires some 2,000 genes for its specification. There is nothing random about this assemblage, which reproduces itself with constant composition and form generation after generation. A cell constitutes a unitary whole, a unit of life, in another and deeper sense: like the legs and leaves of higher organisms, its molecular constituents have functions. Whether they function individually, as most enzymes do, or as components of a larger subassembly such as a ribosome, molecules are parts of an integrated system, and in that capacity can be said to serve the activities of the cell as a whole. As with any hierarchical system, each constituent is at once an entity in itself and a part of the larger design; to appreciate its nature, one must examine it from both perspectives. Organization, John von Neumann once said, has purpose; order does not (1). Living things clearly have at least one purpose, to perpetuate their own kind. Therefore, organization is the word that sums up the essence of biological order.

(iv) *Adaptation.* Any organism that is made up of distinct parts, and that reproduces by heredity with variation, must evolve parts that promote the organism's survival and multiplication. Their structure and function will alter over time, tracking changes in both the internal and the external environment. The reason is that an individual's reproductive success must be affected by environmental factors, and natural selection will favor the better adapted over the less well adapted. Adaptive evolution is seen throughout the living world, not only at the level of legs and leaves but also at that of enzyme proteins and cellular organelles. That adaptation stems from the interplay of random variation and natural selection was, of course, Darwin's central contention. By recognizing adaptation as a criterion of life we do justice to life's intrinsic diversity. And we assert that the chemical and physical features of organisms find their meaning, first in the context of organization and then of history. Physiology and evolution are both central to the grammar of life.

With the help of these criteria we can quickly dispose of some doubtful cases. Is a flame alive? No. True, one candle lights another, but the size and shape of the flame are wholly determined by the supply of fuel and air, not by whether it was started with another candle or with a match. Fire propagates, but not by heredity. Viruses make a more interesting issue. They do propagate their kind by means of heredity, and they evolve and adapt all too quickly to changing circumstances; those who regard reproduction and adaptation as the crucial features of life will consider viruses to be alive. But viruses are structurally far simpler than cells, even than many organelles, they lack metabolism of any kind and are obligatory intracellular parasites. Their capacities are so much more limited than those of any cell that I, for one, would disqualify viruses. Much the same argument applies to mitochondria, and intracellular organelles in general: since the genes required for their production are located chiefly in the cell nucleus, organelles do not reproduce autonomously and must therefore be excluded from the ranks of the living. And what about freeze-dried bacteria? They were alive once, and provided they are "viable," may be alive again, but they are not alive at present. Such borderline cases are instructive rather than alarming. If life originated from the mineral realm via natural processes, we should expect the line that divides the quick from the dead to be a little fuzzy. Sharp categories are generally something that we put into nature, not something we find there.

It was the ambiguous status of viruses, whose crystallization had just been accomplished, that led N. W. Pirie to conclude that the terms "life" and "living" are inherently meaningless. That has not deterred his successors from proposing definitions, the best of which slip a kernel of truth into the nutshell of epigram (2). To J. Perret, "Life is a [property of] potentially self-replicating open systems of interlinked organic reactions, catalyzed stepwise and almost isothermally by complex and specific organic catalysts which are themselves produced by the system." Gail Fleischaker and Lynn Margulis, following the original proposal of Francisco Varela, make the point more succinctly and with sharper emphasis on the deep organizational features, when they define living organisms as "autopoietic systems," i.e., self-generating. Freeman Dyson puts himself in the same camp with the assertion that "life resides in organization, not in substance." Others are content with contemporary fashion; for Dulbecco, "Life is the actuation of the instructions encoded in the genes." Maynard Smith, however, points in quite another direction when he suggests that life might simply be defined "by the possession of those properties which are needed to ensure evolution by natural selection. That is, entities with the properties of multiplication, variation and heredity are alive, and entities lacking one or more of these properties are not" (2).

I have come to suspect that the definition of life is a mirror in which the various biological specialties chiefly see themselves. Functional biologists—biochemists, molecular biologists and physiologists—tend to look upon organisms as complex, integrated, and self-reproducing systems maintained by the stream of matter and energy. They ask how these systems work, and search for the proximal causes of the phenomena they observe in terms of physical and chemical mechanisms. Evolutionary biologists, by contrast, take a longer view. They ask how these systems came about and how their parts became mutually adapted.

Their hope is to discover ultimate causes, such as selective advantage or historical contingency, that shaped the patterns of form and function which we observe in all organisms. The secret of life is that these are two aspects of a single reality which we must strive to see in the round. No biological phenomenon can be said to be understood until we have found both its functional and its evolutionary explanation—and each of these is sure to be multilayered. To thread the maze of arguments woven about the relationship between living and non-living states of matter we must walk on two legs, one functional and the other evolutionary.

Of all the inanimate objects in the universe, few have so captivated the imagination of biologists as our own machines and automata. Nowadays it is the computer that is held up as the most instructive analog of living organisms, with cellular architecture as hardware and the DNA tape as software. Automata have complexity, functional parts and purposeful behavior just as living organisms do, but since they are man-made they carry no metaphysical baggage. Ever since Descartes there have been mechanistic biologists who see it as their task to "reduce" biology to chemistry and physics, for instance, to demonstrate that all biological phenomena can be completely explained in terms of the motions of their constituent parts and the forces between them. Biochemists and molecular biologists, in particular, commonly believe that such reduction is their objective, though they will not all agree on the meaning of the term. Some are satisfied that reduction has effectively been accomplished, thanks to the near-universal consensus that all that living things do is based on their physical substance, and that no metaphysical agencies or vital forces need be invoked. Many more would agree with Francis Crick (3) that "the ultimate aim of the modern movement in biology is in fact to explain all of biology in terms of physics and chemistry." And a few reductionists go still farther, maintaining that the laws and theories formulated in biology should be rephrased as special cases of those propounded in the physical sciences. That the two latter goals are illusory has been amply documented by George Gaylord Simpson, Michael Polanyi, Ernst Mayr and Alexander Rosenberg (4). Indeed, even a machine is not explained by mechanical principles alone, for its construction is guided by the designer's purposes which constrain the blind operation of physical laws. In the case of living organisms, it is their hierarchical organization and their origin in the interplay of random variation and natural selection that should give pause to any radical reductionist. And it is noteworthy that our unquestioned success in unraveling the molecular mechanics of life have thus far yielded little insight into the genesis of coherent forms and functions on the scale of cells and organisms.

For that reason, a majority of organismic biologists would probably be found aligned with an alternative general position, commonly known as holism (some prefer the more precise but awkward term "organicism"). Adherents hold that living organisms make up a set of unique, hierarchically organized systems each of which functions as a whole. Whenever a system is assembled from its constituent parts, novel properties emerge that could not have been predicted from a knowledge of those parts alone. The airplane wing that we contemplated in Chapter 1 is a case in point, and the argument applies *a fortiori* to any organism. Morphology, behavior and development are examples of such emergent properties that would never be inferred from molecular mechanisms, even if these were known in every particular. It follows that biology is an autonomous science (5), governed by laws and theories that emerge successively at the level of a cell, a frog, a flock of birds and a prairie pond. We can set aside, for the present at least, the question whether biology is autonomous in principle or only in practice, but we must note that holists feel the pinch of a shrinking domain. Time was when heredity and energy conversion were thought to be strictly the prerogative of living systems. Is it not likely that, given a few more decades, development and morphogenesis too will have been successfully reduced to the play of mindless molecules obeying only local rules?

I do not think so, and am often reminded of the arid quarrels over the nature of the Trinity that kept Byzantium in turmoil for centuries. Why should we be compelled to swear fealty to either reductionism or holism? Like John Tyler Bonner (6), "What is utterly baffling to me is why one cannot be a reductionist and a holist at the same time." Reductionism is commonly the best strategy in research, and when successful, supplies satisfying (albeit partial) explanations. Holists remember the inherent complexity of living things, and keep the reductionists honest. I was pleased to see that Hunter (6), re-examining the question whether biology can be reduced to chemistry, likewise takes a conciliatory position. The two extremes are complementary, not antagonistic: those who seek to understand living organisms require both the holist's perspective from the top down and the reductionist's scrutiny from the bottom up. Neither is sufficient by itself.

Many years ago, in a delightful essay celebrating the origins of molecular biology, Gunther Stent (6) spoke of the paradoxical quality of living things, which obey all the laws of physics and chemistry yet are not fully explained in terms of those sciences. Niels Bohr, Max Delbrück and Stent himself hoped to discover new laws of physics, hitherto unknown, that would supply physical and chemical explanations for the functions peculiar to life. No such laws have turned up, but one wonders whether we have been looking in the wrong direction. Biological phenomena of any interest are almost always properties of a system, more or less hierarchically organized into multiple layers. Simplification ("reduction") is commonly useful, even essential, to make a problem tractable, but it carries the risk of changing the question rather than answering it. To my mind, the beginning of wisdom is to recognize that living things are wholly composed of molecules, and everything they do finds a mechanistic explanation in terms of the actions and interactions of their constituent molecules. But their organization into systems of mounting complexity guarantees the emergence of supramolecular structures and activities. The more advanced the level of organization, the less informative is it to seek understanding solely in terms of their molecular constituents. It makes little sense to seek the molecular basis of hibernation because that is inherently the function of an organism (though one may hope to find genes and proteins specifically involved in hibernation). By the same token, the chemistry of leather is of little use in describing a shoe. Common sense suggests that we steer cautiously between molecular machismo and a veiled vitalism, some insights can be usefully expressed in molecular terms, others call for physiological explanations or for ideas appropriate to still higher levels of organization. We should be especially on the lookout for organizational principles that link molecules into cells and organisms, and for the historical forces that shaped the outcome. Common sense concurs with Paul Weiss that, "There is no phenomenon in a living system that is not molecular; but there is none that is wholly molecular either." For all their ubiquity and familiarity, living organisms are truly strange objects.

3

CELLS IN NATURE AND IN THEORY

> "The cell is the microcosm of life for in its origin, nature and continuity resides the entire problem of biology."
>
> W. S. Beck (1)

THE CELL THEORY
FROM FIVE KINGDOMS TO THREE DOMAINS
THREE PROFILES
REDISCOVERING THE ORGANISM

All through the eighteenth century microscopes improved in magnification, resolving power and optical clarity. In the middle of the nineteenth century, a large volume of observations on the tissues of higher plants and animals coalesced into a grand unifying conception, the "cell theory," rightly acclaimed in every textbook as a cornerstone of biological science. It states that all living things, notwithstanding their exuberant diversity, share a common architectural plan: every organism is composed of cells, either many or a single one, that constitute the fundamental units of life. It is a statement, not about the molecules of life and their chemical interactions, but about the spatial patterns into which these molecules are organized. In the hierarchy of biological order cells hold a special place, for they alone have the capacity to make themselves autonomously, and to multiply by division. Consequently, the cell represents the simplest level of organization that manifests all the features of the phenomenon of life. In the present chapter we shall examine how this conception arose, and how its meaning has evolved over the past century. For this purpose, our proper study is the world of microorganisms, whose manifold forms and lifestyles display the full range of options available to life in its most elementary mode.