Postscript to Schrödinger: So What Is Life?

Despite vast knowledge, our understanding is partial and, for all its familiarity and ubiquity, life remains fundamentally mysterious

Franklin M. Harold

Among the books that influenced our professional development, scientists of my generation are apt to list a small, slim volume by the physicist Erwin Schrödinger entitled *What is Life?* Schrödinger, one of the pioneers of quantum mechanics, took refuge from the Nazis at Trinity College, Dublin; his contract required him to give a series of public lectures, which were published in 1944 to great acclaim.

Schrödinger spoke of the chemical nature of genes, the energetics of life and the genesis of biological order; and he laid out the agenda for a new biology. The argument is abstract and does not make easy reading; one wonders what a general audience took from it. But the title remains irresistible: Schrödinger posed, in all innocence, one of those deep questions that children sometimes ask, to their parents' discomfiture. And his timing was perfect: with the war drawing to a close, numbers of young scientists were eager to put their talents to nobler uses; and they responded joyfully to Schrödinger's challenge to bring the science of life wholly under the umbrella of chemistry and physics.

Life is first and foremost a microbial phenomenon

A Durable Riddle

Sixty years later, the question still hangs in the air. Schrödinger wrote his book at the dawn of the most extraordinary era in biological science. Since his day, we have learned far more than any one of us can hold about biochemistry and physiology, ultrastructure and genetics, and evolutionary and molecular biology. And yet, should you be put on the spot by a bright teenager or an intelligent layman (a local minister, in my case), you may well find yourself at a loss to explain what life is. The easy way out will be to deflect the challenge with a nervous titter, a parable, or a joke; but here let me take the riddle seriously, and try to define how far we have come towards a scientific understanding of the phenomenon of life.

A noble goal, but what has it to do with microbiology? This question, at least, has a clear and simple answer: life is first and foremost a microbial phenomenon. Microbes are the most ancient organisms in the fossil record, and made up all of the biosphere for about three quarters of life's history on earth; they still account for the lion's share of the global metabolic economy and biomass, and for most of biological diversity, too. Higher organisms, far more recent twigs on the great tree of life, display traces of their microbial ancestry. Moreover, thanks to their small size and relative simplicity, microbes stand out as the most tractable exemplars of the living state. It is certainly no accident that so much of our understanding of heredity, metabolism, and energetics stems from studies with prokaryotes; they should prove just as valuable as we grapple with complexity, morphogenesis, and cell evolution. If not we microbiologists, who then should ponder the nature of life?

The object of the exercise is "understanding," which is not quite the same thing as "knowledge" and altogether different from "information." Scientists use the term in a particular sense that was neatly set out by the Oxford

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philosopher Mary Midgley in her book, *Science as Salvation*: "Understanding anything is finding order in it. It is simply putting [the object] 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." Midgley's prescription supplies the theme of this essay, which is that the hallmark of life is a special kind of organization (defined here as purposeful order). The living world is arranged into nested and interwoven layers (molecules, cells, colonies, ecosystems and so on), and no one layer holds all the secrets of life. Nevertheless, we shall focus here on the lower rungs of the ladder. When we have worked out how the molecular parts come together into a living cell, and how cells relate to the inanimate world, we will have gone far towards solving Schrödinger's riddle. But we are not there yet; I hope to persuade you that these are deep problems, with partial answers at most, and they lead into strange waters.

Defining the Fundamental Qualities of Life

We begin with the obvious. Objects in the world around us fall cleanly into one of two classes: living and nonliving. We have rabbits and carrots on the one hand, stones and running water and our own machines on the other. There are very few intermediate forms, and in practice we have little difficulty in assigning objects to one class or the other. Formal criteria for recognizing living things are listed in any biology textbook. Living things display complex organization, which we acknowledge whenever we speak of organisms. They carry out metabolism (energy generation in particular), reproduce their own kind, and have functional parts adapted to their environment. Inanimate objects do not do these things, at least not all of them. We can say, then, that life is a quality or attribute of entities that meet the criteria. They come in a vast range of shapes and sizes, from *Escherichia coli* to the blue whale, but the minimal units that meet all the criteria are microbial cells, both prokaryotic and eukaryotic.

Life is not hard to recognize, but the very devil to define; just what is it that marks organisms and sets them apart? Of the many published definitions, here are two that come straight to the point. According to Lynn Margulis of the University of Massachusetts at Amherst (upholding a position first developed by two Chilean colleagues, F. G. Varela and H. R. Maturana), "Living organisms are autopoietic systems." In other words, they make themselves. Meanwhile, according to John Maynard Smith of the University of Sussex, Brighton, United Kingdom, organisms are defined "by the possession of those properties which are needed to ensure evolution by natural selection."

The two definitions overlap but emphasize different aspects of life; and they differ with respect to viruses, which make up the only significant borderline category. If evolution is the litmus test, viruses are alive; if it is autopoiesis, they are not. I am inclined to combine the two statements: living organisms are autopoietic systems capable of evolution by natural selection.

A Web that Weaves Itself

Autopoiesis is not part of our professional vocabulary, but all of us practicing microbiologists have observed it. Take a few cells of *E. coli* from an established culture (in principle, a single cell will do), and place them in a flask of fresh, sterile growth medium. The medium consists of a mixture of inorganic salts and a pinch of glucose. Incubate overnight, preferably on a shaker. Next morning the glucose has been consumed and the medium swarms with cells, billions per milliliter, each one identical with the cells in the inoculum.

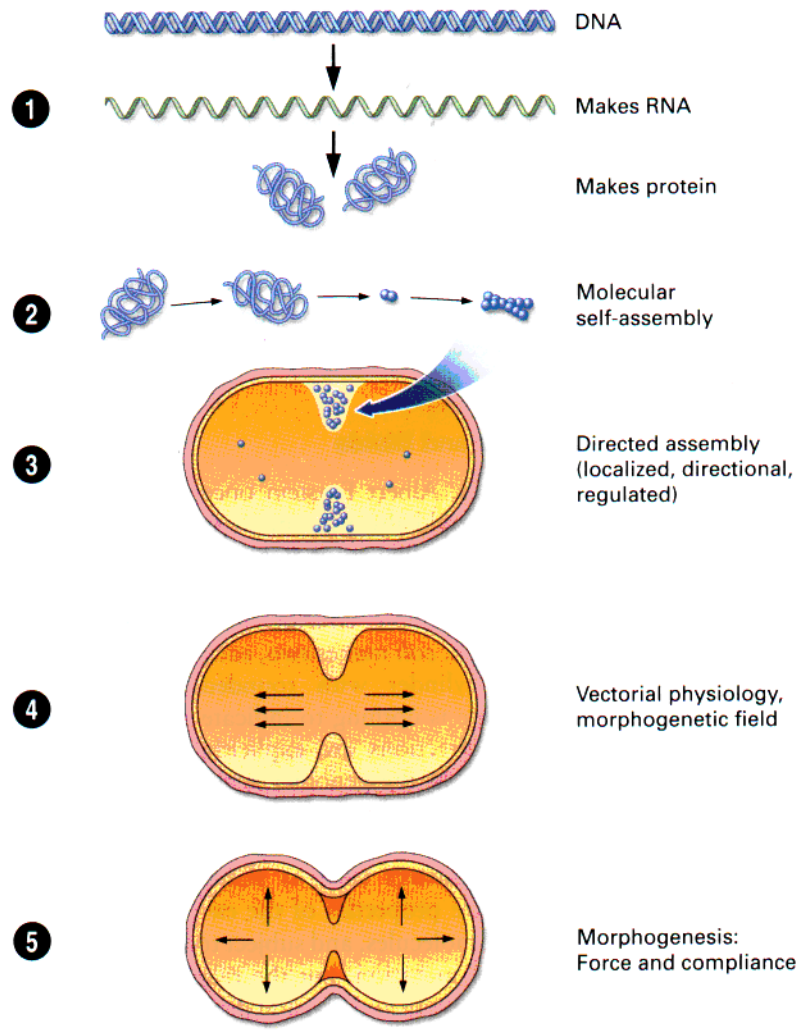
Here in microcosm is all the mystery of life. As each cell grows and divides, it synthesizes about 100 million new molecules large and small, and puts them in a particular spatial and functional order; the cells make themselves, converting energy into organization. As they multiply, the cells reproduce their own kind and no other; like begets like. And cells never arise spontaneously; as Rudolf Virchow proclaimed 150 years ago, *Omnis cellula e cellula*, every cell comes from a cell. Each cell is a dynamic system, a pattern of molecules in space and time that maintains its identity even though its constituents undergo continuous replacement. If we would read Schrödinger's riddle, we must look beyond the molecules themselves and discover how the molecular parts relate to the cell as a whole.

Well then, how do patterns, such as the living pattern which we call *E. coli*, produce and reproduce themselves? We know an enormous

amount about this process, and we also have a conceptual framework on which to hang the data collected to describe and analyze it. The "genetic paradigm," given classic expression by Francois Jacob in *The Logic of Life*, encapsulates the viewpoint that has dominated research on the organization and operation of bacterial cells for the past 30 years. It builds on the established relationship between genes and proteins, but greatly enlarges its scope. Broadly speaking, the thesis is that what a cell is and does is wholly determined by its molecular constituents, which are in turn encoded in its genes. Chemical composition, anatomical structure, form and functions and behavior are all written down in that genetic record. The genome serves as the cell's central directing agency: cells make themselves by executing the instructions contained in the genes. When we know what's spelled in the genes, we will have uncovered the secret of life.

Most microbiologists were raised on this genetic paradigm, and probably take it for granted. The idea underlies the fervid enthusiasm for genomics, and now for proteomics, and it resonates with ancient and deep-seated beliefs in the duality of matter and spirit, body and soul. I would say also that there is a lot of truth in this view of life, albeit partial truth. In a metaphoric sense, we can take the cell as the meaning implied by the sum total of its genetic instructions, and the genome as a recipe for making that cell. The devil, as usual, is in the details. One needs to inquire just how molecular structures and specifications, on the nanometer scale, give rise to cellular organization on a scale three to five orders of magnitude larger. And also, whether the information inscribed in the genes is sufficient to account for the generation and persistence of biological patterns.

FIGURE 1



The hierarchy of biological order. The spatial and functional organization of a bacterial cell is made up of successive nested layers. (1) DNA sequences are transcribed into RNA and then translated into amino acid chains; the latter fold spontaneously into functional proteins. (2) Ribosomes and some other supramolecular complexes are formed by self-assembly of their molecular constituents. (3) Other structures arise in a controlled manner at a particular time and place; an example is the Z-ring of dividing cells. (4) Certain physiological processes have a direction in cellular space; proton translocation is one example, DNA segregation another. (5) During morphogenesis, the cell wall is synthesized locally and expands in response to the global force of turgor pressure.

I hold the mildly heretical view, fully spelled out in my recent book *The Way of the Cell*, that the genetic paradigm as it stands is insufficient, incomplete, and fundamentally misleading. Briefly, biological organization is made up of multiple layers (Fig. 1), which span the range from molecules to cells. Genes do, of course, specify order at the level of molecules and of supramolecular complexes that arise by self-assembly, such as ribosomes. But molecular structures do not suffice to specify cellular structure, for cells do not arise by self-assembly of their molecular constituents.

Instead, cells grow. Over and above synthesis of the molecules, production and reproduction

of cells require integrative processes that confer spatial organization upon the molecular events. Timing, location, and direction are not spelled out in the genes but are supplied by the cell as a whole; and some of these are passed from one generation to the next by the continuity of cell structure, including plasma membrane and cell walls. This is why, at the end of the day, every cell comes from a prior cell. We know far less about cell heredity, self-organization, and the nature of complexity than we do about genes and proteins; but unless we come to grips with these matters, we cannot hope to understand how molecules make cells.

To Grow and Divide

Hypotheses, Albert Einstein once warned, should always be made as simple as possible—but not simpler. To see why the genetic paradigm is too simple, consider how one cell of *E. coli* makes two, each a short cylinder with rounded caps. There is nothing to indicate that the directions are explicitly spelled out in the genome: genes specify the sequences of proteins and nucleic acids, not cell dimensions. Parameters such as shape and size are properties of the ensemble of molecules, and subject to alteration as a result of mutation, but the relationships are indirect. Growth and division display the capacity of the system as a whole to enlarge and duplicate its particular pattern.

Slowly, and at times painfully, we are muddling towards an appreciation of how the molecular parts relate to the cell as a whole

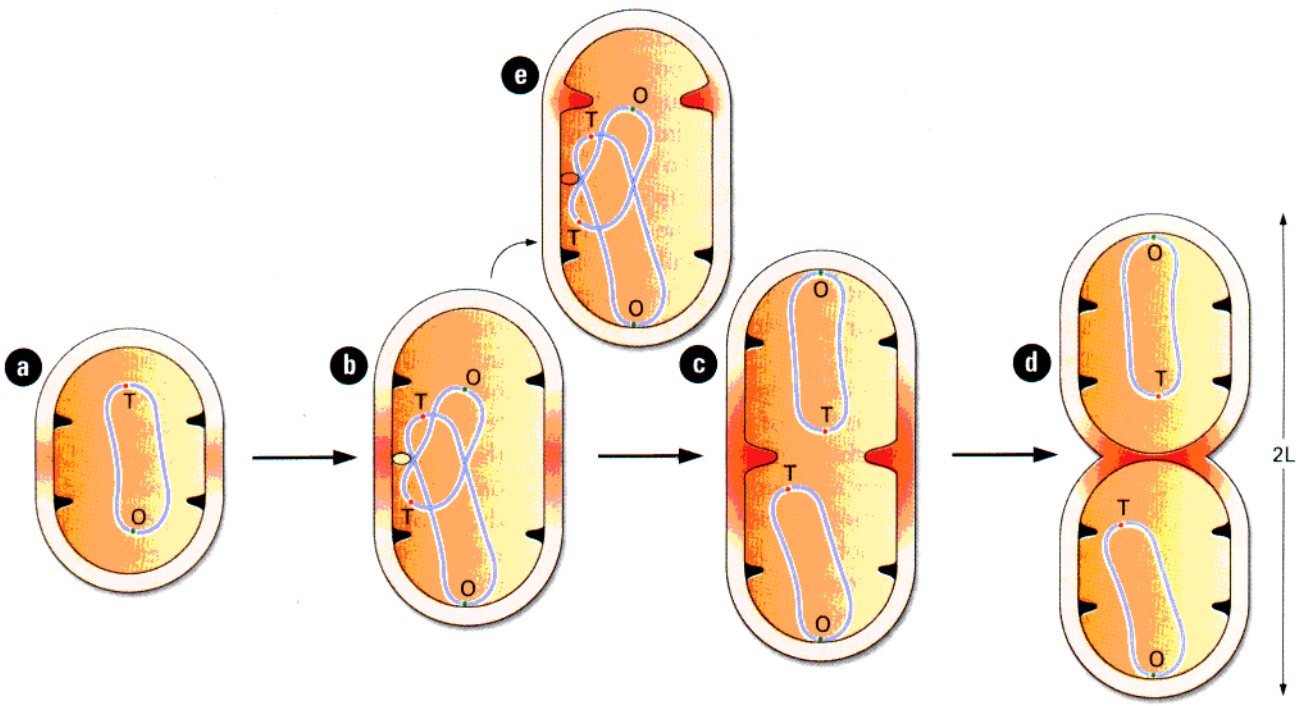
We do not know how the trick is done, but the outlines are beginning to emerge, and they include at least two key features (Fig. 2). One is duplication of the genome and segregation of its products, in part by linkage to the poles of the elongating cylinder in the case of *E. coli* and similar bacteria. The other is the periodic expansion of the cell wall. Sidewalls extend by the random insertion of new muropeptide units into the fabric, involving some 2 million new units per cell and 600,000 cleavage steps, according to James T. Park of Tufts University Medical School in Boston, Mass.

Cell poles are stable while the cell lengthens; they are ordinarily laid down in the form of a septum, normally at the midpoint of the cylinder. How do cells know where and when to do this? Apparently, they do so by measuring the concentration of an inhibitory protein that oscillates from one pole to the other; septum forms in the middle because the time-averaged inhibitor level is lowest there. And how do these localized, regulated events shape a cylinder? According to the surface-stress theory, developed by Arthur Koch of Indiana University in Bloomington, the forces that mold the cell are akin to those that govern the behavior of soap bubbles. At the instant when a new wall unit slips into place, the peptidoglycan fabric is plastic; the wall then expands in response to turgor pressure. This process can generate a cylindrical form, provided mechanical supports are in place (the poles), and certain physical parameters fall within the right range.

This orchestrated physiology cannot all be understood by the study of genes alone, for it reflects the collective activities of their products in an organized state. It takes a whole cell to supply the controlled environment, timing, spatial localization, and hydrostatic pressure. Morphogenesis commonly requires positional markers, and in some organisms (enterococci, for example), these are visibly transmitted from one generation to the next. Membranes, also, are inherited features: they are never synthesized de novo, but arise by extension of a pre-existing membrane. Phospholipid bilayers and even some biological membranes do, of course, self-assemble in vitro, but apparently never do so in vivo. The point has recently been reiterated by Thomas Cavalier-Smith of Oxford University, Oxford, United Kingdom.

Once your eyes have been opened to these higher levels of order, you see them everywhere. I take them to mean that the cell as a whole supplies a framework, or template, for the construction of its offspring. Genes are part, but only part, of what is passed from one generation to the next. It follows that the genetic paradigm leaves out something utterly essential to life—its spatial organization. Now that we know most of what is worth knowing about the contribution of the genes, it is the epigenetic levels that are most likely to hold novel insights into the nature

FIGURE 2



One *E. coli* making two. The diagram emphasizes two aspects, wall synthesis and DNA replication. Stippling indicates the intensity of peptidoglycan synthesis. Symbols O and T mark the origin and terminus of replication, respectively. (a) A resting cell of length L. The spikes mark potential division sites left over from the previous cell cycle. (b) Growing cell. Sidewalls elongate by the dispersed insertion of new wall units, while the poles are inert. There is evidence that the DNA replicase is linked to the cell envelope near its midpoint; the duplicated strands attach to the poles. (c) Nucleoids separate; the cell assembles the septum precisely at the midpoint. (d) Septum closes creating two cells, each with one old pole and one new. (e) Aberrant division initiated at a silent site, producing a minicell without DNA. After several sources, none of whom should be held responsible. (Reproduced from F. M. Harold, *The Way of the Cell,* with permission of Oxford University Press.)

of living systems. That this commonsense proposition should, in practice, remain so much of a minority view never ceases to astonish me.

The Mother of All Problems

Slowly, and at times painfully, we are muddling towards an appreciation of how the molecular parts relate to the cell as a whole. We are also making progress in understanding cell evolution, and the genesis of that great tree of all life. By contrast, what remains altogether mysterious is just how living systems relate to the nonliving world of chemistry and physics from which they presumably sprang. The black hole at the very foundation of biological science is the origin of cells, and of life.

Here again we have a conventional framework, parts of which go back to the 1930s, that structures our thinking. It calls for a broth of organic substances formed by chemical processes on the lifeless earth. Somehow, in a favorable locale, a selection of the "correct" precursors coalesced into a primordial cell; alternatively, a molecule capable of self-replication arose by chance, and somehow "learned" to make proteins and then cells. The notion that life began with free, self-replicating RNA molecules, which begat primordial cells based on ribozymes, holds particular fascination for molecular biol-

ogists. A voluminous literature records all sorts of variations on these themes, some of which claim support from laboratory experiments. Unfortunately, there is no pertinent evidence whatever from the geological record supporting this framework and, in its absence, gauging how seriously one should take all these imaginative tales proves practically impossible. To my mind, even the more persuasive tales come up woefully short on the central issue, which is the origin of cells. Whence came organized molecular assemblages that draw matter and energy into themselves, reproduce their own structure, and evolve over time?

I do not mean to disparage serious scholars who are doing their level best to crack the hardest nut of all. Quite the contrary: I would argue that, if our purpose is to understand life, the origin of life is the most consequential question in all of biology. It holds the key to understanding the relationship between the living and the inanimate, the quick and the dead. Each new bit of evidence strengthens our belief that organisms obey the laws of chemistry and physics; and scientific investigations have turned up no traces of a vital force to nurture the wellspring of life.

We assume, then, that cells are material systems that arose by some sort of evolutionary process four billion years ago here on earth (or conceivably, someplace else). I share this premise, but feel obliged to note that, in the absence of evidence as to how this came about (or even of a plausible hypothesis), this explanation is merely a belief—a leap of faith. Of all the gaps in our understanding of life, this one is the widest. Until we bridge it, we cannot lay to rest lingering doubts as to whether science has read nature's book of biology correctly.

Well, here she comes again, that pesky teenager—and this time she wants an answer, not a meditation. Quickly now, how do we reply to the recurrent question, "what is life?" Perhaps along the following lines.

Living things are so much part of everyday experience that we scarcely realize how strange they are, and how sharply they differ from inanimate objects. All organisms, from bacteria to humans, are exceedingly intricate molecular systems that have the unique capacity to make themselves. On the level of the individual, each one grows and reproduces its own kind. Collectively, on a timescale of millennia, they continuously make themselves over, adapting to changes in their external and internal environments. Nothing else in the known universe has such powers. Living things obey all the laws of chemistry and physics, and we have learned an enormous amount about the molecular mechanisms that underlie all biological operations. We know much less about how these components and processes are organized in space, and almost nothing about their origin when the world was young. Our knowledge is vast, but our understanding is partial and full of gaps; for all its familiarity and ubiquity, life remains fundamentally mysterious.

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