Life: The Defining Enigma of Biology

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It all started, we are told, with a big bang, the ultimate (or, more correctly, primal) display of randomization and disorder. The Universe is still reeling and expanding from the blast. And yet here, 15 to 20 billion years later, the most exquisite example of order, namely life, and particularly human life, has arisen and flourishes. We human beings have the privilege of not only being alive, but also of being aware of it. In contrast, the cabbage, itself a universal marvel, lives and dies oblivious of its own existence.

But we still do not really know what life is. Perhaps no definition is possible. Or perhaps we do not know where to start, or if we are asking the right questions. The new student of biology, who has a reasonable expectation of learning what defines life, is confused. The old student, who has wrestled with the problem for years, also remains confused. Contemporary biology's view of life, under the influence of the concepts of chaos (Gleick 1988) and of complexity (see Lewin 1992), is poised on the intellectual knife-edge separating the reductionism of molecular biology from more holistic approaches (see Rosen 1991), culminating in a total biospheric view of life expounded in the Gaia hypothesis (Lovelock 1979). This essay identifies some ways by which the student might approach the question of the nature of life, and perhaps develop a personal framework within which his/her fascination with biology can flourish.

In 1938, N.W. Pirie's influential essay, "The Meaninglessness of the Terms 'Life' and 'Living,'" expressed his concern that lay words are often appropriated to scientific issues, and that components (growth, irritability, reproduction, etc.) of the meanings of "life" and "living" also apply to other, clearly nonliving situations. But he also realized that, until we understand the philosophical and scientific dimensions of life more clearly, a more appropriate terminology will not evolve. We, too, will have to make do with the existing imperfect terminology.

With our students, we must explore the concepts embodying our understanding of the nature of life—their strengths, susceptibilities and potential. This is not simply to provide a philosophical basis for study, important though that is, but for the pragmatic reason that the material and aesthetic benefits of the variety of life in the biosphere are vital to our continued existence. During evolution, humankind has acquired some ability to determine the future direction of the biosphere and its inhabitants. Even the very future of life itself on Earth is increasingly becoming our responsibility. We must attempt to understand it, because we compromise it at our peril.

The question "What is life?" leads quickly to profound and intensely personal issues. These include (1) the intrinsic nature of human life, and (2) the differences between human life and that of other living forms. Attempting to understand the human condition is a truly interdisciplinary undertaking, which helps to develop important elements of the students' intellectual, moral, ethical, philosophical, artistic and scientific fabric. The immediacy, and enormity, of the associated issues is intimidating: abortion, capital punishment, organ transplants, the definition of human death, the nature of death, the soul, the very justification for religion, cloning, the ethics of genetic engineering, patenting of life forms, race relations, vegetarianism, and more, all against the pervasive questions: "Who and what am I?" These debates require an intimacy with the questions about the nature of life, even if the answers elude us.

Introductory biology texts usually describe living things in terms of what they can do as whole organisms (feed, grow, reproduce, respond to stimuli, move, etc.). Attempts to engage the student in the possibility of there being, for example, some generic molecular organizational basis from which the phenomenon of life ensues are, perhaps understandably, absent. However, even in an introductory text, I think that this is a significant error of omission. Examination of the issue and its ramifications is an intellectual pilgrimage that every student biologist must make. Even if the neophyte is not yet fully equipped to wrestle with this most challenging and current of biological problems, he/she must, at least, be introduced to its defining centrality in biology, and in our human nature. The following discussion identifies some possible departure points.

The Cell

Two features of living beings are organization and containment. The former is a prerequisite to orderly and progressive molecular interactions. Containment

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permits the maintenance of structural and functional integrity, and requires the development of selective systems that enable the cell to use, or protect itself from, external chemical, physical and biological influences. Basic cell structure variously provides these features. For example, the inner hydrophobic region of the cell membrane provides the cell substantial independence. Each cell (with a few exceptions), even among the metazoa, contains a copy of the total genetic information for the organism of which the cell is a part. Cell differentiation reflects the pattern of activities brought into play by the particular cell type concerned. Sophisticated chemical communication systems, internal and external, regulate the activities of the cell itself, and determine the manner and degree of the cooperation and collaboration with other cells, tissues and organs. (Examples of such systems range from the ability of many microorganisms to respond, chemotactically, to the presence of chemical substances in the environment, to the many complex hormonal systems that regulate the functioning of higher life forms.) Organization and containment are also features of tissues, of whole organs, and of the entire body of complex organisms.

The cell is often called the "unit of life," because it is the smallest structure exhibiting the form and properties typically associated with life, including organization and containment (see, for example, de Duve 1991). However, the expression "unit of life" begs the question of the nature of life, and suggests that identification of a unit of life stems from a knowledge of what life is. Is life a cell, or the organization of a cell, or the properties of that organization? Is the nature of the cell important here? Are somatic cells different in this regard from germ cells? If the cell is the sole unit of life, then is there no intellectual space to consider whether or not subcellular, or noncellular, entities such as viruses, are alive?

Life & Death

Most of us have empirical knowledge of death. Death is usually described as either the loss of life (the removal of an entity?) or the termination of life (switching off an organized system?). Also, the word "death" has different implications in different contexts. For single-celled organisms, death is unequivocal. The cell's organization disintegrates, and it ceases to function. However, for metazoans, death is recognizable at various levels. Individual cells can die, and do so continually (*cf.* the phenomenon of apoptosis, or programmed cell death (Duke et al. 1996). Tissues can die from disease or injury, or by natural design, as in the shedding of antlers by deer. At higher levels of organization, whole organs can die. Or the whole body can die.

Deaths at these various levels are not necessarily mutually inclusive or exclusive. While our integrated body can die, still-living components (organs, tissues and cells) can be salvaged, maintained and used as replacements in other bodies. When tissues die they can, if the trauma is not too extensive, be repaired or replaced by the body's defense mechanisms. Sometimes surgical intervention (e.g. skin grafting) is effective. Even individual cell types (e.g. suspensions of bone marrow cells) can be harvested and used to combat certain blood cell problems. What does all of this tell us?

The word "life" has different meanings, depending on whether we are considering (a) different organisms of various complexities, or (b) the various organizational levels within a complex individual being. As a first approximation, life is a quality or phenomenon reflecting a continuum of organizational complexities. Should a definition of life be sought in terms of the simplest life-form, whatever that is? If so, how would such a definition relate to the life (or death) of the most complex living beings? Or should we seek a concept involving a nonspecific organizational threshold separating the animate from the inanimate?

Human Life & Nonhuman Life

Consideration of the taxonomy and hierarchy of biological forms raises the question as to whether or not there is a corresponding hierarchy of forms of life itself. At the pinnacle is *Homo sapiens*, "wise man." This position reflects (1) complexity (brain, intelligence, self-awareness, creativity) and (2) behavior and the impact of the human population on the biosphere. The clear difference between the human being and all other life forms has prompted the troubling assumption (in many cultures and religions) that the intrinsic essence of human life is of a higher quality than that of others. (To our shame, this approach is still sometimes applied to differentiate the races of *H. sapiens* itself.) We have certainly assumed the right to dominate, and to exploit, other life forms. The Book of Genesis (*i*,28) speaks of our having dominion over *"the fish of the sea, and over the fowl of the air, and over every living thing that moveth upon the earth."* For many, this assumption of total subservience to humankind seems appropriate, for reasons stemming either from religion or from capitalism. For others, including many adherents to the animal rights movement, environmental protection groups, and vegetarians, this attitude is unacceptable.

Distinctions between human and other forms of life are usually attempted in terms of either (1) the politics of consumerism, (2) the attribute of sentience, or (3) religion. I will leave politics aside, and consider sentience and religion, very briefly.

Sentience

Sentience, often equated with consciousness, can be described as the state of being aware of the messages of the senses. Our perception of sentience in other organisms is complicated by the extent (which varies widely) to which they are capable of response to the messages of the senses (including communication messages). Of particular significance are those responses that are nonautomatic and benefit the organism. However, responsiveness is not a defining element of sentience; there are enough examples of human beings who, through disease or trauma, are unable to respond to stimuli, but whose sentience is clearly unimpaired.

In general, our attitude towards nonhuman life forms, particularly animals, depends largely on (at least) two factors: (1) whether we consider them to be sentient and (2) the extent to which they are responsive. Beings at different levels of complexity elicit very different attitudes. Chimpanzees, the near-human, intelligent tool-users, intrigue us, and we (usually) value them; cattle we consume, provided that someone renders them amorphous, thereby (irrationally) relieving some of our reservations about their fate; dogs and cats we keep specifically as companion animals, but are widely ambivalent about snakes and spiders; earthworms we will prong onto a fish-hook without a thought; and, in the interests of hygiene and sterility, we deliberately consign micro-organisms by the billions to a dreadful end in our autoclaves. The more certain we are that sentience is absent, the more cavalier we are in our attitude to that life form, and its expendability. Is it therefore really sentience that we value, rather than life, *per se*? Should we think of life in the same terms as those used for sentience, and will, therefore, an examination of sentience provide us with a model for the consideration of life itself ? If such a model proves appropriate, it could obviate the initial (e.g. religious) constraints that some students have in contemplating the nature of life in any other than strictly divine terms.

There are some dangers here. If our attitude to living beings is determined, at least in part, by our perception of their degrees of sentience, a sort of biological snobbery and arrogance can, and does, ensue. These attitudes have the potential to distort and be distorted, and to spill over into relationships with different human groups, and the value that we assign to those groups. The negative social consequences of this perspective remain shamefully evident.

We may perhaps conclude that, while sentience would not be a factor in any "lowest common denominator" definition of life, it certainly colors our attitude to life in its various higher manifestations. And while both sentience and life are highly variable reflections of extremely complex molecular organizations, they invoke common philosophical considerations. A partial understanding of one could provide important insights into the other.

The Religious Element

My reasons for interpolating religion here are strictly pragmatic, and not ideological or confrontational. (I subscribe to no religion.) Many students have religious backgrounds and beliefs. Concepts of creation, of mortality, perhaps of the soul and aspirations for everlasting life, will be familiar to them. These concepts may represent, therefore, possible familiar starting points for the more generic discussion of the nature of life.

Human beings, besides being sentient, also display two other properties significant in this context: (1) self-awareness and (2) a sense of time, of history, the present, and the ability to project into the future. This latter includes a sense of individual mortality. The question of the fate of our sentience, our self-awareness, our identity, our life when we die, exercises many people mightily. The Judeo-Christian traditions include concepts of the soul and of everlasting life to provide a resolution to this intellectual problem. Other traditions take different approaches. The Christian believes that human life is a reality, of divine origin, sacred, and immortal. It is embodied in the soul, which leaves the body on death, and becomes the focus for the prophecies of resurrection and everlasting life. Human life, therefore, is seen as being more than a quality, or a reflection of a particular form of organization. It ultimately has an existence beyond, and separate from, the body, in heaven or elsewhere, depending on the performance of its owner during the earthly life-span. And in this, for the Christian, the human body and life, being in the image of God, is clearly distinct from the life of other forms. Many Christians believe that animals do not have souls, although Thomas Aquinas distinguished between rational souls in humans, nutritive and sensory souls in animals, and nutritive souls in plants (Kretzmann 1993). All this can, for the Christian, provide satisfying answers to the intense difficulties surrounding our personal mortality and other untoward life events.

While none of this provides insights into the real nature of life, it does give an intellectual focus, or a model, of human life as an entity, or a quasi-entity, and can make it easier for some students to embark on further exploration. However, some, with religious commitment to the concept of the human soul, may not wish to participate further, but rather to maintain their own viewpoint unchallenged. Or they may wish to proceed only if the human condition is excluded from the discussion.

The Rise of Molecular Biology

In 1953, Watson and Crick reported the configuration of the DNA molecule and stood biology on its head. Since then, knowledge of the living cell has expanded to the point that biotechnology can now directly manipulate the very molecular fabric of life to our own ends. Recombinant DNA technology resulted from an understanding of the nature, roles, and regulation patterns of macromolecules, which complements our knowledge of networks of intermediary metabolism. Two points emerge from this.

First, we have extensive knowledge of the molecular biology of many cell types. We can therefore develop views of the minimal physical and chemical circumstances that led to the origin of life and the assembly of the first cell. The origin of life, and the nature of that life, with its apparent ability to defy the second law of thermodynamics, are clearly very closely related. In two recent books, S. A. Kauffman (1993, 1995) has suggested that life originated from a random collection of catalytic reactions which crossed an organizational threshold, and "flipped" from randomness to order, forming closed, interactive and autocatalytic loops of reactions. These loops would have permitted the collective and continuous use of external energy sources and chemical elements, and the production of the components of the loops themselves, i.e. they were replicative. He suggests that the first life was not simple, but was necessarily complex. Not only do such systems constitute a model for the minimal form of life, but Kauffman asserts that their emergence from the catalytic prebiotic environment was not fortuitous; it was inevitable.

Second, knowledge of these molecular cycles could eventually lead to the design of experimental systems to verify Kauffman's hypothesis. Such a development would be particularly exciting, as it would simultaneously represent the initial steps towards the possible construction of primitive life forms in the laboratory.

The Margins of Life

The nature of life is complex even in the simplest independent organism. It becomes much more so in the interactive relationships in which many cells participate, including, for example, those with obligate parasites, mitochondria, viruses, viroids or prions, none of which exhibits the usually recognized life characteristics independently of the respective host cell. Are these structures living beings or not?

Viruses are obligately parasitic particles that invade appropriate cells, replicate intracellularly, and are only visible using the electron microscope. Outside the host cell, they have no activity; the particle cannot confidently be said to be alive. They are, however, packages of genetic information, with all the potentiality that implies. And they can be stimulated, by contact with the host cell, to enter that cell, recruit its metabolic processes, control them by means of the viral genetic information, and use the cell's metabolism to replicate themselves. Ultimately, new, but initially completely inactive, particles are released into the environment, and the cycle continues.

Are Viruses Alive or Not?

Outside the cell, they are probably not alive, at least in terms of the traditional definitions of life. Within the cell, they disassemble, change the character and activity of the cell, and may kill it. Some infected cells, such as those harboring herpes viruses, can remain alive and shed new virus particles for long periods. Is the infected cell still alive in its own right? Or is it now the living stage, or form, of the virus that has now acquired all the equipment to qualify as a living being? Or do the cell and the virus collaborate in a new form, or expression, of life?

In the retroviruses, which include the human immuno-deficiency virus (HIV), the viral genome integrates into that of the host cell, which thus acquires new characteristics; it is said to have been "transformed." At this stage, life has become a joint venture. The distinction between the participants is that, prior to the association, the cell was undeniably alive; the virus arguably was not. Not only that, but the natural assumption would be that the isolated virus would remain devoid of life signs indefinitely.

Is "Are viruses alive?" the appropriate question? Should it be asked of the intact isolated virion? Or of the functional association in which the disassembled virus is participating in the cell? A virus-infected, and still functioning, cell is alive. The new virus particles, formed and liberated at the end of the infection process, probably are not. However, a dilemma remains. On the one hand, it is difficult to argue that an isolated virion is alive; on the other hand, if it was once alive (in the host cell), but is no longer, then are we observing some form of microresurrection when the particle infects a new host cell? Or is our dualistic view (life *versus* nonlife) too restrictive?

Many organisms suspend, or slow down, their life activities to cope with adverse circumstances. Some hibernate; some freeze; others aestivate, desiccate, sporulate, or simply wait. The life equipment remains intact, essentially complete, and usually functioning, albeit at a very low level. Is the virion a bare-bones survival form, that has discarded all metabolic baggage? Are viruses, rather than being primitive forms, in fact extremely sophisticated evolutionary entities, reduced to an elegant, but often deadly, efficiency? If all this applies, can we then deny that the virion is alive? (Strauss, Strauss & Levine 1990).

Living Molecules?

Consideration of the nature of viruses helps clarify some perceptual problems. But there is one more step.

The tobacco mosaic virus (TMV) consists of just two types of molecule: the single RNA genome molecule and 2130 copies of a single protein molecule that encase the genome. Simplification appears to be essentially complete. But not quite. Two other categories of infectious molecules are significant here. Viroids are single naked RNA molecules that invade and cause diseases of certain plants. Prions are single protein molecules that invade certain animal tissues, causing neurological diseases, including Creutzfeldt-Jakob disease in human beings, and bovine spongiform encephalopathy (BSE or "mad cow disease") in cattle. Viroids and prions are proliferated within their respective host cells and the situations have some parallels with those of the viruses. Are such molecules alive? The famous geneticist, philosopher of biology, and essayist J. B. S. Haldane (1932), in his essay, "The Origin of Life," refers to cells consisting of "... *numerous half-living chemical molecules* ..." generating the possibility that "living" molecules could include not only those that infect living cells, but also catalytic molecules, such as enzymes. These, when assembled and coordinated appropriately, are the very scaffolding of life, however we may perceive the phenomenon.

Two intriguing implications arise from our ability to replicate the DNA molecule in the test-tube by means of the polymerase chain reaction (Mullis et al. 1994). First, in this reaction system the DNA molecule directs its own replication, a property normally associated with living forms. Second, this reaction, notwithstanding its relative simplicity, provokes thoughts about the eventual possibility of artificially assembling a simple living form.

Some Concluding Comments

My reduction of the issue down to the level of viruses and individual molecules makes it difficult to argue that "life" at this level is in any sense a material entity or component of a living being. From consideration of such cases, life, at least for me, is a function of what the molecule or particle or cell or organism can actually do, rather than what it is. It is also clear that, while life forms share substantial similarities (e.g. the carbon molecular base; enzymically catalyzed metabolic processes), reflecting common origins, evolution has transformed life into a highly multivariate phenomenon, in terms of its expression and its complexity. Complexity arises not just from the number of different components that constitute a living system, but also from the potential for those interacting components to do so synergistically, thus going far beyond the capabilities of the individual parts. The power of such synergy, extended to the n^{th} degree, is exemplified by the development of the human brain, the mind, self-awareness, creativity, and the ability to marvel at, and perhaps ultimately to understand, all the phenomena of life itself.

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