1

What is Life? *The next fifty years. An introduction*

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This book is the result of a conference held in Trinity College, Dublin in September 1993 which commemorated the fiftieth anniversary of a series of lectures entitled *What is Life?*, given in Trinity College in 1943 by Erwin Schrödinger. Schrödinger, a Nobel-prize-winning physicist and one of the founders of quantum mechanics, had come to Dublin in 1939 at the invitation of Éamonn de Valera, the Taoiseach (Prime Minister) of Ireland to take up a Chair of Theoretical Physics at the newly founded Dublin Institute for Advanced Studies (Moore, 1989; Kilmister, 1987). The invitation followed his dismissal from the Chair of Theoretical Physics at the University of Graz after the *Anschluss*. Dublin suited Schrödinger and he fitted in well, becoming a leading personality in the intellectual life of the city. He remained in Dublin until his return to Austria in 1956, where he died five years later.

Schrödinger had broad intellectual interests and while in Dublin he explored areas of philosophy and biology as well as continuing to work in theoretical physics. In this volume we are concerned with Schrödinger's thinking on biology. In *What is Life?* Schrödinger focused on two themes in biology: the nature of heredity and the thermodynamics of living systems. Delbrück was an influence on Schrödinger's views on heredity while Boltzmann stimulated much of his work on the thermodynamics of living systems. For the first presentation of his thinking on biology Schrödinger chose a public lecture. An annual public lecture is a statutory obligation of the Dublin Institute for Advanced Studies and in February 1943 Schrödinger gave a series of three lectures to a general audience at Trinity College, Dublin. These lectures were popular with Dubliners and over four hundred stayed through the entire series. No doubt part of their popularity was the provocative title and the restricted entertainment available during the 'emergency', as the Second World War was called in neutral Ireland, but in addition Schrödinger was a gifted public speaker who could captivate an audience.

After their publication by Cambridge University Press (Schrödinger, 1944) these lectures had considerable impact internationally. The book was widely read and became one of the most influential 'little books' in the history of science (Kilmister, 1987). Surprisingly, in spite of the widely acknowledged influence of this book on the founders of molecular biology (Judson, 1979), the precise role played by *What is Life?* is still disputed (Judson, 1979; Pauling, 1987; Perutz, 1987; Moore, 1989). Undoubtedly, part of the appeal and influence of the book was its clear prose and the persuasiveness of the arguments. Schrödinger, portraying himself as a 'naive physicist', made it clear how living systems could be thought of in the same way as physical systems. Clearly this approach was already widespread, but *What is Life?* popularized it and encouraged physical scientists that the time was ripe to consider biological problems.

What about the actual ideas expressed in the book? Schrödinger discussed two themes based on his thinking on heredity and thermodynamics. In one of these themes, usually termed the 'order from order' theme, Schrödinger discussed how organisms pass on information from one generation to the next. As a basis for this discussion about the gene he used the well-known paper by Timoféeff-Ressovsky, Zimmer and Delbrück (1935) on mutation damage to fruit flies from which the size of the gene was calculated to be about 1000 atoms. The problem faced by the cell was how a gene this size could survive thermal disruption and still pass on information to future generations. Schrödinger proposed that to avoid this problem the gene was most probably some kind of aperiodic crystal which stored information as a codescript in its structure. As is well known, this prophetic statement has been shown to be true by work on the structure of DNA which led to the central dogma of molecular biology. The second theme covered by Schrödinger was 'order from disorder'. The problem faced by organisms was how to retain their highly improbable ordered structure in the face of the second law of thermodynamics. Schrödinger pointed out that organisms retain order within themselves by creating disorder in their environment. However the term 'negentropy', which he coined for this process, has not been well received by other scientists (e.g. Pauling, 1987).

In the fifty years since Schrödinger's lectures we have become accustomed to the 'order from order' theme and much of the astonishing success of molecular biology over the past fifty years can be seen as working out the implications of this idea. It is on this that much of the reputation of *What is Life?* is based. The 'order from disorder' theme has generally been considered of less significance. However, now that work on the thermodynamics of systems removed from equilibrium and dissipative structures is being applied to living systems the importance of this theme may reassert itself. Perhaps fifty years from now *What is Life?* will be seen as prophetic for its treatment of the thermodynamics of living systems rather than for the prediction of the structure of the gene.

While the influence of *What is Life?* is acknowledged, the ideas expressed have been criticized as unoriginal or wrong (Pauling, 1987; Perutz, 1987) by some while defended by others (Moore, 1987; Schneider, 1987). It is true that much that was explicit in *What is Life?* was implicit in earlier work. However, these criticisms perhaps miss a major aspect of the uniqueness of *What is Life?*: that a physicist straying from his area of expertise into a field not his own could stimulate research. This interdisciplinary posing of provocative questions is not usual in science and in *What is Life?* the musings of a physicist have acted as an inspiration to subsequent researchers. It is in this spirit that we commemorate the lectures fifty years ago of Erwin Schrödinger. In doing this we have gathered together a number of articles in which scientists speculate on the future of biology. Much expressed in this volume may turn out to be wrong; however, we believe that this exploratory spirit is the best way to commemorate the publication fifty years ago of *What is Life?*

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2

What will endure of 20th century biology?

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'QUO VADIS HUMANITAS?'

We find ourselves in the last decade of this century; no previous century has had such a profound effect on human life. Perhaps no century has produced such a level of apprehension and fear, anchoring them in the consciousness of man. One has become mistrustful. When a discovery becomes known nowadays, the first question is not, 'Of what use will it be to mankind?' (as in earlier times) but, 'What damage will it cause, and how will it diminish our well-being and health?' Our present state of well-being is bestowed upon us mainly owing to scientific knowledge; this has brought life expectancy up to 75 years, approaching the biologically natural age limit. At the beginning of this century, life expectancy was a mere 50 years and at the beginning of the previous century it was only about 40 years. In developing countries, the curve of life expectancy is also rising, although it lags about 50 years behind ours; meanwhile, our life expectancy is approaching an upper limit. Yet, as never before, we peer apprehensively into the future. This is despite the fact that in the political sector, some of the gravest and most grotesque developments instigated by humanity in this century appear to be in the process of rectification. It is unlikely to be decided in this last decade whether these changes are really for the better.

This decade not only brings the century to a close; it ushers in a new millennium. We feel impelled to reflect on the way we have come and on the road ahead. Our predicament becomes conscious in the question: 'Will humanity even survive to the end of the coming millennium?' Of the thirty or so generations that span a thousand years, we already have direct experience of two or three. These thirty generations may be listed with space to spare on a printed page; but, nonetheless, a thousand years defies our comprehension. What indeed could Charlemagne have predicted about our times? Proper experience of the past is essential for any extrapolation to the future but, even then, what is really new remains a surprise. In basic research, the situation is no different. New insights can open up whole continents of new opportunities. Moreover, all the things that shape our daily life depend essentially on discoveries and insights from the most recent past. All that we can really say about the future is almost a truism: changes in our way of life will be yet more radical in the coming millennium than they have been in that which is drawing to a close.

The world population is currently growing hyperbolically. How does hyperbolic differ from the exponential growth that is usually referred to in publications on this subject? Well, the latter involves successive doublings at equal intervals of time; with hyperbolic growth, these intervals become steadily shorter. A constant percentage rate of birth already yields exponential population growth, but, over and above this, an increasing percentage of people reach sexual maturity as a result of improved hygiene and medical care of infants and children in developing countries. The most recent doubling of the world population took only 27 years. There are now 5.5 billion of us on earth. If things continue according to the hyperbolic law, which has accurately described the increase of the past 100 years, there will be 12 billion people in 2020 and in 2040 the growth curve will tend asymptotically to infinity! I can see myself being quoted in the media: 'Scientist prophesies growth catastrophe in the year 2040.' Steady on now: the only prediction that I can make with certainty is that this will not take place; it cannot, since the resources of the earth are limited. We do not know where the coming century will lead us. Nevertheless, the really uncanny aspect of our predicament is not this fatalistic nescience. Much more disconcerting is the fact that we cannot derive anything from the present growth behaviour, not even in principle. Near such a singularity, even the smallest fluctuations can be amplified and come to have an enormous effect. Catastrophes, on a small scale or even of a global character, will limit the growth of world population. Such catastrophes are certainly not new to us. We know too that we stand helpless before them in their path. There is something amiss with our ethics, which is still matched to an epoch where human survival (or that of smaller demographic units) had to be secured through numerous offspring.

You may wish to interject that the population of industrial nations long ago reached equilibrium. In some countries it is even declining. Nonetheless, our population density is so great that, if it were to spread to the entire land mass, there would be a population of 30 to 40 billion people. According to a study by Roger Revell, that would be about the maximum number that could be maintained by mobilizing all conceivable planetary resources. An increase in food harvests over the entire earth to the local maximum when he wrote (corresponding to the corn harvest of the state of Iowa in the USA for instance) would be necessary just to barely feed such a population. There could be no prospect of general prosperity. The number calculated by Revell allows perhaps for a few regions of ample production, but in most regions there would be a catastrophic deficit. In this analysis, I have not even mentioned the environmental problems that are already getting out of control. Neither has mention been made of bottlenecks in the exploitation of resources and in energy production, nor of sanitation or medical emergencies.

This must suffice for an introduction. I wanted to describe the backdrop before which humanity's development will be played out. We should not lose sight of it when considering the future of science and our associated expectations, fears and hopes.

Turning now to the main topic, I will begin my exposition by taking stock of the current situation.

THE BIOLOGY OF THE 20TH CENTURY

One is indeed justified in proclaiming the second half of this century as the era of molecular biology, analogously to the first half as the age of atomic physics. In fact it was physicists who first took up the analysis of the concept of life, even if this initially led in the wrong direction. Pascual Jordan's *Physics and the Secret of Organic Life* from the year 1945 and most notably Erwin Schrödinger's 1944 book *What is Life?*, the event we are celebrating in this volume, are characteristic examples. Schrödinger's text was epoch-making, not because it offered a useful approach to an understanding of the phenomenon of life, but because it inspired new directions of thought.

Much of Schrödinger's prophetic content had long since been resolved by biochemists, but no one had previously so openly delved for basic principles. Nonetheless, it was not pure theoreticians who initiated the turn of the tide in biology and established the new science of molecular biology. They stood helpless in the face of the complexity of living things. Rather it was physicists who began to experiment in a radically new way, using our basic knowledge of the chemical nature of life processes as a springboard. There was Max Delbrück, a theoretical physicist of the Göttingen school who, inspired by Niels Bohr's complementarity principle, decided to investigate the molecular details of inheritance. This was the foundation of phage genetics. And then there was Linus Pauling, a physicist of Sommerfeld's school who sought a deeper understanding of the nature of proteins, the molecular executive of living cells. He discovered in the process essential structural elements, forming figuratively a seam between chemistry and biology. Most conspicuously, there was Francis Crick, a technical physicist who had been involved in problems of radar during the war, who together with James Watson in 1953 reconstructed the double helical structure of DNA from X-ray reflections. In the process, and this is what really made the discovery important, he concluded how genetic information could be stored and transferred from generation to generation. In Cambridge there was also Max Perutz, working in the Cavendish Laboratory under Sir Lawrence Bragg, whose method of X-ray interference patterns he applied to such complex molecules as the red blood cell dye, haemoglobin, elucidating together with John Kendrew for the first time the detailed design of a biomolecular machine. That was the birth of molecular biology.

Today we have a broad appreciation of the molecular design of living cells, including detailed mechanisms of the molecular processes lying at the basis of cell functions. We know about perturbations and breakdowns of such functions, as expressed in the most diverse sets of clinical symptoms; how parasites in the form of bacteria, fungi and viruses destroy the life cycle of an organism. Indeed, we can even go so far in regulating these life processes as to permanently alter their genetic program. Increasingly, the currently more chemically oriented pharmaceutical industry is exploiting our detailed knowledge of molecular biology and the associated technical opportunities. It is basic research, paramountly, that has irrevocably embraced the so-called recombinant DNA technology. What would we know about the molecular structures of the immune system, or about oncogenes or AIDs without this technology?

But I do not wish to bombard you with a quasi-alphabetical list of all the highlights of molecular biology, nor to confront you with a list of the names of those, from Avery, Luria and Delbrück to Neher and Sackmann, who excelled in creating them. Neither in my account do I want to deal with the biology of the first half of this century more specifically, other than to say that it was not just a completion of the grand concepts of the 19th century, of the ideas of Charles Darwin and Gregor Mendel, the insights of Louis Pasteur, Robert Koch, Emil von Behring and Paul Ehrlich. The first half-century established primarily a chemical foundation, through the work of Otto Warburg, Otto Meyerhof, his students Hans Krebs and Fritz Lipmann and many others, upon which the molecular biology of the second half-century could develop. I would much rather focus on the fundamental questions of biology. Answering them has only entered the realms of possibility through the compilation of detailed molecular knowledge in the 20th century. In doing so, we will cross the threshold into the 21st century and cast a glance into the future. Many questions that we can formulate today will only find a satisfactory answer in the coming century.

WHAT IS LIFE?

Not only is this a difficult question; perhaps it is not even the right question. Things we denote as 'living' have too heterogenous characteristics and capabilities for a common definition to give even an inkling of the variety contained within this term. It is precisely this fullness, variety and complexity that is one of the essential characteristics of life. Possibly it will not take very much longer until we know 'everything' about the *Escherichia coli* bacterium, perhaps even about the fruitfly *Drosophila*. But what will we then know about humans?

It is certainly then more sensible to ask: how does a living system differ from one that is not alive? When and how did this transition take place during the history of our planet or of the universe as a whole?

As a chemist I am often asked: what is the difference between a coupled chemical system albeit arbitrarily complex, and a living system in which we again find nothing other than an abundance of chemical reactions. The answer is that all reactions in a living system follow a controlled program operated from an information centre. The aim of this reaction program is the self-reproduction of all components of the system, including the duplication of the program itself, or more precisely of its material carrier. Each reproduction may be coupled with a minor modification of the program. The competitive growth of all modified systems enables a selective evaluation of their efficiency: 'To be or not to be, that is the question.'

There are three essential characteristics in this behaviour which are found in all living systems yet known:

1 Self-reproduction – without which the information would be lost after each generation.
2 Mutation – without which the information is 'unchangeable' and hence cannot even arise.
3 Metabolism – without which the system would regress to equilibrium, from which no further change is possible (as Erwin Schrödinger already rightly diagnosed in 1944).

A system that shows these properties is predestined to selection. I mean that selection is not an additional component to be activated from outside. It would be meaningless to ask who does the selecting. Selection is an inherent form of self-organization and as such, as we know today, a direct, physical consequence of error-prone self-reproduction far from equilibrium. Equilibration would only select the most stable structure. Selection – an alternative category incompatible with equilibrium – chose instead a sufficiently stable structure which is optimally adapted for certain functions which ensure the preservation and growth of the organism. Evolution on the basis of natural selection entails the generation of information.

In order to fix information structurally, defined classes of symbols are required, like the letters of an alphabet or the binary symbols of a computer code. Additionally, we need the connecting relations between symbols for forming words and the syntax rules which combine words into sentences. Facilities to read the sequences of symbols are admittedly also necessary and, ultimately, information is only that which may be understood and evaluated. The ability to deal with information in our language is coupled with the existence of a central nervous system.

What form does this take in the case of molecules? Information storage in molecules is subject to the same prerequisite that the information be 'readable' and subject to evaluation. Only with nucleic acids did molecules learn to read. Complementary interaction, an inherently specific association between two matching pairs of nucleic acid building blocks, underlies this ability of nucleic acids. So the basis of molecular information processing is base pairing, as discovered by Watson and Crick. This at first purely chemical