PERSPECTIVES

Physics and the origins of molecular biology

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Bohr, Delbrück and Schrödinger were physicists who had important influences on biology in the second half of the twentieth century. They thought that future studies of the gene might reveal new principles or paradoxes, analogous to the wave/particle paradox of light propagation, or even new physical laws. This stimulated several physicists to enter the field of biology. Delbrück founded the bacteriophage group which provided one of the roots of molecular biology. Another was X-ray crystallography which led to the discovery of DNA structure. The strength and success of molecular biology came from the many interactions between geneticists, physicists, chemists and biochemists. It was also characterized by a powerful combination of theoretical and experimental approaches.

Max Delbrück was trained in physics and after obtaining his Ph.D. in 1930, he went to study for six months with Niels Bohr in Copenhagen during the spring and summer of 1931. Bohr was interested in the relation between life on the one hand and physics and chemistry on the other. He wondered whether the complementarity principle in physics, as demonstrated by the dual nature of the propagation of light, might be applicable to biology. Thus, light can be defined as a continuous propagation of electromagnetic waves, or as individual quanta of energy: the two expressions of reality stand in mutually exclusive but complementary relation to one another. In a comparable way life could be viewed as a jumble of molecules, or as a living organism; you could make observations that tell you where the molecules are, or you could make observations that tell you how an animal functions, and these might have the same mutually exclusive features that are found in atomic physics. Bohr was not particularly knowledgeable about biology, but his interest provided the spark that stimulated Delbrück to involve himself in biological problems (Hayes 1982).

After Copenhagen, Delbrück moved to Berlin where he first worked as research assistant to Lise Meitner. He organized a small private group of theoretical physicists to join in fairly regular discussions, often at his mother's house. Later some biochemists and biologists joined this group, including K. G. Zimmer, whose interest was in the effects of ionizing radiation on living systems. By that time H. J. Muller had demonstrated that ionizing radiation induced mutations in *Drosophila*, and similar work was being done by L. J. Stadler using maize. Nikolai Timofeeff-Ressovsky was a Russian geneticist who had moved to the Kaiser Wilhelm Institute for Brain Research as part of a scientific exchange programme between the Soviet Union and Germany before Hitler's rise to power. However, when this occurred in 1933, Timofeeff-Ressovsky continued to work in Berlin in close association with Zimmer. Delbrück joined in the discussions and theoretical work. One upshot was a paper on the nature of gene mutations and gene structure, which proved to have a seminal influence on future biology (Timofeeff-Ressovsky *et al*. 1935). Genetics had demonstrated that genes are very stable structures, which can occasionally mutate to a new stable form. The paper proposed that the high energy of radiation could shift one stable state of a gene to another with different properties, with a much higher frequency than would occur spontaneously.

This paper may not have had much impact on geneticists, but it was read by the theoretical physicist Erwin Schrödinger. In his influential book *What is life?*, which was published in 1944, Schrödinger discussed the apparent paradox between the statistical laws of thermodynamics and the stability of the gene. In this discussion he included the Delbrück–Timofeeff–Zimmer model of the gene and the means by which it might mutate. (Schrödinger refers to it as 'Delbrück's model', assuming it was due mainly to him.) There has been much discussion concerning Schrödinger's conclusions about physics and biology, but it does seem clear that he proposed that the paradox between disordered and ordered states might lead to the formulation of new laws capa-

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ble of explaining the unique behaviour of genes. He referred to the gene as an aperiodic crystal: stable as a chemical crystal, but also containing the information essential for living organisms. He also pointed out that organisms 'feed on negative entropy', by which he meant that they could create order from the intake of energy and disordered molecules, and thus contradict the second law of thermodynamics. Another very significant insight was the suggestion of a genetic code, analogous to the symbols of the Morse code.

The impact of *What is life?*

There has been just as much debate about the influence Schrödinger's book had on physicists, and to what extent it stimulated physicists to enter the field of biology after the Second World War (Witkowski 1986; Perutz 1987; Symonds 1986, 1987, 1988; Dronamraju 1999). Gunther Stent (1966) expressed one fairly extreme view: 'Having one of the Founding Fathers of the new physics put the question What is Life? provided them with an authoritative confrontation with a fundamental problem worthy of their mettle. Since many of these physical scientists were suffering from a general professional malaise in the immediate post-War period, they were eager to direct their efforts towards a new frontier which, according to Schrödinger, was now ready for some exciting developments.' In the same article, Stent writes: 'Schrödinger states an important credo which, as can be inferred from the article 'A physicist looks at biology', had been embraced also by Max Delbrück (1966). In fact, this credo probably was the most important psychological incentive for physicists to turn to biology in the first place: "From Delbrück's general picture of the hereditary substance it emerges 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." Thus it was the romantic idea that 'other laws of physics' might be discovered by studying the genes that really fascinated the physicists.' (Stent's quotation is from *What is life?*.) Francois Jacob (1974) wrote: 'To hear one of the fathers of quantum mechanics ask himself What is Life? and to describe heredity in terms of molecular structure, of interatomic bonds, of thermodynamic stability, sufficed to draw towards biology the enthusiasm of young physicists and *to confer on them a certain legitimacy*. Their ambitions and their interests were confined to a single problem: the physical nature of the genetic information.'

Who are all these physicists? According to James Watson (1965), reading the book had been a 'major factor' in Francis Crick's decision to leave physics and develop an interest in biology. However, Crick (1988) wrote: 'It was only later that I came to see its limitations – like many physicists, he knew nothing of chemistry – but he certainly made it seem as if great things were just around the corner.' He told Max Perutz that he found the book interesting, but he would have switched to biology anyway (Perutz 1987). Seymour Benzer (1966) wrote: 'Delbrück first entered my life in the form of a chapter heading 'Delbrück's model' in Schrödinger's book *What is Life?* I read that book at an impressionable age, while still a graduate student in solid state physics.' He and others were more impressed by the fact that a bacteriophage could infect a bacterial cell and in just twenty minutes its lysis released up to 200 new phage particles. Delbrück himself was much influenced by this striking example of biological replication, which he first learned from Emory Ellis at the California Institute of Technology (Caltech) (Hayes 1982). Delbrück had gone there in 1937 to learn more about *Drosophila* genetics, but when he encountered bacteriophages, he went on to found a whole school of phage genetics, and this was where Benzer carried out his first experiments. Maurice Wilkins (2003) is more positive: 'I was attracted to Schrödinger's thinking in *What is Life?* because he linked the extremely important biological idea of a gene with the rather strange world of electrons moving in crystals. He wrote about the gene being an aperiodic crystal, and that connected directly with my Ph.D. research where electrons moved freely in perfect crystals but could be slowed down and trapped when the crystal had irregularity. It seemed to me that 'aperiodic' referred to the local irregularities in which the genetic message was written, against a periodic background. But the main impact of Schrödinger's book was that it set me in motion. It was not just what he wrote, but how he wrote it. Schrödinger used the language of physicists and that stimulated me, as a physicist, to persevere with his book, and its introduction to genetics, and to decide that this was the general area I wanted to explore, as a 'biophysicist'.'

In contrast, and much later on, Perutz (1987) is quite dismissive. He wrote: 'A close study of the book and of the related literature has shown me that what was true of the book was not original, and most of what was original was known not to be true even when it was written.' Also: 'The apparent contradictions between life and the statistical laws of physics can be resolved by a science largely ignored by Schrödinger. That science is chemistry.' Neville Symonds (1986, 1987, 1988) takes issue with Perutz, and outlines the real importance of Schrödinger's contribution to biology. However, he was a physicist who was not influenced by *What is life?* to enter biology. He is instead an important example of a scientist with many connections to influential laboratories.

After graduating in physics at the University of Melbourne, Australia, Symonds went to London early in 1946 to study for a Ph.D. at London University under the supervision of H. T. Flint. He then went to work with Schrödinger in 1948, studying unified field theory, and stayed until 1950. The best brains in physics were making little progress in this area, and Schrödinger, with his interest in biology, suggested to Symonds that he should consider entering that field. Warren Weaver of the Rockefeller Foundation was supporting physicists to move into biological research. Symonds met

Weaver in Dublin and later in Paris. He had read the book *Mathematical biology* by the Russian scientist N. Rashevsky, then in Chicago, and who later founded the 'Committee on Mathematical Biology'. Symonds went to work with him for six months, again got in touch with Weaver and went to see him in New York. On this occasion Weaver explained the significance of the work of Aaron Novick and Leo Szilard, and also that of Salvador Luria and Delbrück. As a result, Symonds went in the spring of 1951 to the Cold Spring Harbor Laboratory on Long Island, and had long discussions with Delbrück, Luria and Alfred Hershey. Subsequently he joined Delbrück's phage group at Caltech. Raymond Appleyard, who also had a background in physics, was in the phage group, and he later became first executive secretary of the new European Molecular Biology Organisation (EMBO). Symonds later joined Bill Hayes's MRC Unit of Microbial Genetics at Hammersmith, and then became professor of microbial genetics at the University of Sussex.

It is surprising that Delbrück in his publications appears not to have mentioned Schrödinger's book. For example, there is no citation of it in the posthumously published *Mind from matter*, based on a course of twenty lectures, in an article 'A physicist looks at biology', or in a related later article (Delbrück 1966, 1970, 1986). He was however attracted to biology in the first place for much the same reason as Schrödinger, namely: Were there new physical laws to be discovered that would explain life? Were there paradoxes to be resolved?

It is possible that the influence of *What is life?* was largely educational, because it informed physicists and others about the gene, heredity and genetics. Watson (1995) was a biologist when he read Schrödinger's book in 1946: '... the gene had suddenly come to the forefront of my attention through reading *What is Life?* The gene's being the essence of life was clearly a more important objective of study than how birds migrate, the scientific topic that previously I could not learn enough about.' Watson also learned about the experiments of Oswald Avery, Colin Macleod and Maclyn McCarty which strongly indicated that genetic tranformation in bacteria depended on pure DNA. This in turn impinged on Crick when they met at Cambridge in 1951.

Biophysics, genetics and chemistry

In 1966, many of Delbrück's former colleagues and associates published a book, *Phage and the origins of molecular biology*, on the occasion of his 60th birthday (Cairns *et al*. 1966). The title is misleading, because the genetic studies of bacteriophage pioneered by Delbrück, Hershey and Luria provided only one of the roots of molecular biology. Indeed, It could be argued that the importance of the phage group before the structure of DNA was published, with two important exceptions, was its influence in promoting the future potential of genetic-molecular experiments using phages. The most significant exception was the Hershey–Chase experiment that produced new evidence for the identity of genes and DNA (Hershey and Chase 1952). The other is the discovery of host-induced modification of bacteriophages (Luria and Human 1952). There is not much doubt that the courses on phage genetics held at the Cold Spring Harbor Laboratory, and also at Caltech, were instrumental in training many scientists who then entered the field of phage genetics and went on to do important research. Long before the discovery of the structure of DNA, George Beadle and Edward Tatum (1941) had pioneered biochemical genetics, with the isolation of nutritional mutants in *Neurospora* and the development of the one-gene-one-enzyme concept. This was confirmed in the early 1950s and became another cornerstone of molecular biology.

The use of X-ray crystallography was just as important as phage and biochemical genetics. The techniques had been developed by W. H. Bragg and W. L. Bragg to unravel the three-dimensional structure of small inorganic molecules. The dream was to use it to study macromolecules. William Astbury was a pioneer who obtained the first X-ray diffraction data for nucleic acid and keratin. Dorothy Hodgkin and colleagues published in 1955 the first complete structure of a complex organic molecule, vitamin B_{12}. Wilkins, Rosalind Franklin and their colleagues obtained much improved results on the A and the B forms of DNA, and all the world knows how this led to the structure proposed by Watson and Crick. Subsequently Wilkins checked all the atomic coordinates of DNA, whilst Franklin in J. D. Bernal's laboratory obtained the three-dimensional structure of tobacco mosaic virus. W. L. Bragg was director of the MRC Laboratory for Molecular Biology at Cambridge. One of the research aims was to work out the three-dimensional structure of globular proteins using X-ray crystallography. Perutz was working on haemoglobin and John Kendrew on myoglobin, whilst their colleague Crick made important theoretical contributions. There were many difficulties, but finally success, with the Nobel prize to follow. Nowadays, with powerful computers and many improved methods, the elucidation of protein structure is one of the standard procedures in molecular biology. Another early contribution of physics to molecular biology was the density-gradient centrifugation of DNA (Meselson *et al*. 1957). Matthew Meselson and Frank Stahl (1958) used this to demonstrate semiconservative replication of DNA, as predicted by the Watson–Crick structure. This and other methods of centrifugation of macromolecules were widely applied in molecular biology. Autoradiography is another powerful biophysical technique which soon had very important biological applications, for example in the study of DNA replication in the bacterium *Escherichia coli* (Cairns 1962) and also in the chromosomes of higher organisms (Taylor *et al*. 1957) The electron microscope provides yet another example of an essential biological technique derived from physics, and so do many other instruments of research.

Chemists and biochemists also made essential early con-

tributions to molecular biology. Erwin Chargaff demonstrated the equivalence of adenine and thymine, and guanine and cytosine in DNA. Linus Pauling discovered the protein alpha helix, and Fred Sanger obtained the sequence of insulin. Protein sequencing was used in many contexts, but when Sanger and Walter Gilbert were successful in sequencing DNA, the open reading frames of genes provided the protein sequence, since the genetic code had been worked out in the later 1960s. The elucidation of the triplet DNA code illustrated the interdependence of theory and experiment that was an essential characteristic of early molecular biology. It was one of the greatest achievements of science in the twentieth century. With the sequencing of the human genome, it is unfortunate that the media are now referring to this as the genetic code, thus confusing the true definition of the genetic code.

Interconnections and interactions

Timofeeff-Ressovsky was more interested in science than in politics, and he continued to work in Berlin throughout the War. He was then arrested as a Nazi collaborator and sent to one of the Gulag labour camps. At that time, the USSR was beginning to develop the atomic bomb, and the field of radiation biology became very important. Timofeeff-Ressovsky might have perished, had it not been realized that he was one of the world leaders in the field. He then worked at a prison research institute near Sverdlovsk. He was released in 1955, but continued to work at Sverdlovsk until 1964. He then obtained a senior position in the new Institute of Medical Radiology at Obninsk (Ratner 2001). One of his colleagues was Zhores Medvedev, who was a radiation biologist also interested in genetics and ageing. Medvedev (1982) wrote: 'For me, the work under Timofeeff was a great and unforgettable experience. His competence in many fields of genetics and biology, his great dynamism and personal magnetism were enormously stimulating factors in the work of the entire department.' Medvedev was a pioneer in the technique of autoradiography, and was one of the first scientists in the USSR to realize the significance of the new field of molecular biology. His book that exposed the false claims of Trofim Lysenko was published in Russia and in the West (Medvedev 1969) and was largely responsible for his being categorized as a political dissident. Medvedev came to work in my laboratory, the Genetics Division of the National Institute for Medical Research, Mill Hill, London, in 1973, as a visiting scientist. In the same year he lost his passport and his citizenship, so continued to work at Mill Hill on ageing until his retirement.

My interests and contributions to the field of genetic recombination led to an invitation to organize an EMBO workshop, whilst Appleyard was secretary, and this was held in 1971 at the Villa Serbelloni in Bellagio, Italy. Symonds attended, and so did Meselson and Stahl. This meeting was the first one in which scientists who worked on bacteria (prokaryotes) and their viruses intermingled, in presentations and discussion, with those who worked on fungi or higher organisms (eukaryotes). This synergistic interaction was judged to be a success and eight further EMBO workshops on genetic recombination were organized along the same lines by Symonds and myself in Scotland. (They continue to this day in France.)

In the history of molecular biology there is therefore an interesting cycle of connections: Delbrück and Timofeeff-Ressovsky – Schrödinger and Symonds – Delbrück, Meselson, Stahl and Symonds – Timofeeff-Ressovsky and Medvedev – Medvedev, Holliday and Symonds. There are of course many many others not mentioned here.

Conclusion

We now know that the new laws of physics that might govern the behaviour of the gene—the aperiodic crystal discussed by Schrödinger—never materialized, and there are no paradoxes to be resolved. This is the triumph of molecular biology: the behaviour of large complex molecules can be explained according to established principles of chemistry. The complementarity between DNA strands depends on hydrogen bonds. The specificity in replication is not absolute because mistakes in base pairing occur. We now know that most of these mistakes are recognized and repaired. The repair is carried out by many enzymes, the properties of which are determined by their polypeptide chains and their folding into three dimensions. The innumerable metabolic reactions in cells are catalysed by specific enzymes and other proteins, and much is known about the regulation of all these reactions. We now know how energy is generated and used for the creation of ordered systems. 'Feeding on negative entropy' is a correct concept because all organisms depend on energy obtained from the environment, which is essential for the formation of life forms capable of replication. The evolution of these new life forms is expensive because it depends on the natural selection of the fittest, that is those that produce the most progeny which are also capable of reproduction. The cost of evolution is enormous because in almost all species a large proportion of the progeny are eliminated. Organisms today are highly accurate in the synthesis of DNA, RNA and proteins, but this would not always have been the case. Primitive organisms would have been less accurate, but accuracy and all other features of contemporary living organisms evolved over long periods of time by natural selection. However, complete accuracy would be a dead end in evolutionary terms, because it would eliminate the rare mutations that provide the genetic variability on which Darwinian selection can act.

Some have speculated that the uncertainty principle of quantum mechanics might be applicable to biological systems, and that such indeterminacy might have far-reaching implications, for example in brain function. This is an illusion, because the chemical laws that govern the behaviour of

large and small molecules in living systems are not subject to uncertainty and indeterminacy. Some are statistical, such as the law of mass action applied to enzymes and their substrates, others are ordered, such as the pairing between the complementary bases of DNA.

Physics has contributed in a variety of ways to modern molecular biology, but not perhaps as Bohr, Delbrück and Schrödinger envisaged. Nevertheless they were responsible for issuing challenges that were met by geneticists, biochemists, chemists, as well as by physicists, and the result is that we now know that in elucidating the fundamental features of living cells no new laws of physics have emerged. There were no paradoxes, but instead, much light and understanding. It is not easy to define life, but it is very reasonable to conclude that scientists at the end of the twentieth century had provided an anwer to Schrödinger's question. Crick has said that the ultimate aim of the modern movement in biology is to explain it all in terms of physics and chemistry (Crick 1966). There has already been spectacular success.

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