Founder of phage genetics

Max Perutz

Licht und Leben: Ein Bericht über Max Delbrück, den Wegbereiter der Molekularbiologie.* By Peter Fischer.
Universitätsverlag Konstanz, Postfach 6632, 7750 Konstanz, FRG:1985. DM 34.80.

THE EARLY conceptual development of molecular biology was dominated by two physicists: Max Delbrück and Francis Crick. Both owe their fame to a small number of seminal papers and their influence to their formidable powers of imagination and argument. Peter Fischer's carefully researched biography explains Delbrück's scientific work in words and diagrams intelligible to the layman, and paints a vivid, thoughtful, affectionate, humorous and balanced portrait of the man. It is to be hoped that the book will soon appear in English, and thus be known to a wider audience.

I learnt much that I had not known, such as Delbrück's early association with Otto Hahn and Lise Meitner, who engaged him as a theoretician to help them interpret their bombardment of uranium with neutrons. Delbrück failed to grasp the meaning of their results, but he applied the target theory learnt from them to the Russian geneticist Timoféeff-Ressovsky's mutagenic quantum yield of X-rays and calculated that the gene must be a molecule containing no more than a few hundred atoms. Even though his estimate was wrong because he neglected the effects caused indirectly by the generation of free radicals in the surrounding medium, the paper secured him a Rockefeller Fellowship to go and study in Pasadena; it also stimulated Schrödinger to write his influential book *What is Life?*, published by Cambridge University Press in 1946, in which he predicted the gene to be a molecule with an aperiodic structure; and it made a young medical graduate learning physics in Enrico Fermi's laboratory in Rome decide to work with Delbrück on the nature of the gene. His name was Salvatore Luria.

Fischer recounts that Delbrück's entry into biology was inspired by a lecture, "Light and Life", by his teacher Niels Bohr. Bohr predicted that the study of life at the atomic level would lead to a paradox similar to that posed earlier by atomic spectra, a paradox that was resolved only by the new quantum mechanics:

> The existence of life must be considered as an elementary fact that cannot be explained, but must be taken as a starting point in biology, in a similar way as the quantum of action, which appears as an irrational element from the point of view of classical mechanical physics, taken together with the existence of elementary particles, forms the foundation of atomic physics. The asserted impossibility of a physical or chemical explanation of the function peculiar to life would be . . . analogous to the insufficiency of the mechanical analysis for the understanding of the stability of atoms [Niels Bohr, *Nature* **131**, 458 (1933)].

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

Fruitful partnership — Salvador Luria (standing) and Max Delbrück at Cold Spring Harbor Laboratory in 1953.

CHSL Library Archives. Reproduced from *The DNA Story* (W.H. Freeman, 1981).

Delbrück himself has described the search for this "Elementary Fact of Life" as the sole motive behind all of his work. He should have listened instead to Linus Pauling, with whom he actually published a joint paper in 1940, and who realized that the biological "quantum of action" is the hydrogen bond, which accounts for most biochemical reactions without having to invoke any new "Elementary Facts".

In 1937, for scientific rather than ideological or racial reasons, Delbrück left Berlin for T.H. Morgan's laboratory at the California Institute of Technology. He hoped to reduce the genetics of *Drosophila* to simple physical principles, but was disappointed to find no quantitative data susceptible to theoretical interpretation. He was about to give up when he discovered that in the basement of the same building another biologist, E.L. Ellis, was working on bacteriophages in *Escherichia coli*. A glance at Ellis's plaques convinced Delbrück that the bacteriophage was the hydrogen atom of biology for which he had been looking, and that study of it might lead him to the "Great Paradox of Life". He and Ellis soon discovered that a single phage adsorbed to a single bacterium multiplies "upon or within" that bacterium until it bursts with the release of an average of 60 progeny phages; such a mechanism had been proposed by d'Herelle, but never proved, while others thought they had found evidence in favour of continuous release of phage by infected bacteria. By clear thinking and application of the simple theory of exponential growth, Delbrück and Ellis opened up the pathway to the analysis of phage genetics. Delbrück soon attracted an enthusiastic band of disciples, who formed the flourishing phage school that met each summer at Cold Spring Harbor in New York state.

In 1938, Luria obtained an Italian government fellowship to work with Delbrück in Pasadena, but Mussolini's racial laws annulled that, and it was not until September 1940 that Luria reached New York, now as a refugee. He sought out Delbrück, who had become an instructor at Vanderbilt University in Nashville, Tennessee. They first worked together on interference between two bacterial viruses acting on the same host, where Delbrück hoped to find something analogous to Pauli's exclusion principle in physics. The paper which was to earn them the Nobel Prize 26 years later was conceived in 1942, after Luria had found a job at Bloomington, Indiana. Luria tried to discover whether bacterial resistance to phage infection was caused by an adaptive change, as many believed, or whether it arose from mutations. He was perplexed by the extreme variability of the numbers of resistant bacteria present in different cultures of the same organisms, until the correct explanation dawned upon him one night at a dance while watching a game machine. If the change from susceptibility to resistance was a random event due to mutations, then a mutation occurring early in the life of a culture would give rise to a large clone of resistant bacteria, while several mutations arising later would each produce only small clones. Luria wrote to Delbrück, telling him of his idea; Delbrück put it into mathematical form and proved rigorously that the distribution of resistant bacteria in Luria's different cultures was consistent only with their being due to random mutations, and that these mutations occurred with a constant frequency of 2.45×10^{-8} per bacterial div-

---

**Light and Life: An Account of Max Delbrück, Pioneer of Molecular Biology.*

ision. These results opened up the field of bacterial genetics. Just like Delbrück and Ellis's earlier results on phage, they involved nothing that could not have been found out years earlier; the only new ingredient was clear thought.

In the ecology of science the opening of a new habitat immediately attracts a crowd. Delbrück escaped from it by switching to phototropism of the fungus *Phycomyces*, hoping again that simple experiments and clear thinking would lead him to a breakthrough. Twenty years of work, however, failed to bring the solution of this very difficult problem any nearer.

Fischer's biography reveals Delbrück as a German Romantic searching for the Holy Grail, which for him was Bohr's "Elementary Fact of Life". To those like myself, who have tried to understand the workings of large biological molecules in terms of simple chemical laws, Bohr's and Delbrück's belief in some mystical principle looks like vitalism, but this book has led me to understand the motive behind Delbrück's proverbial and often misplaced scepticism of new work. For example, he objected to Beadle and Tatum's one-gene-one-enzyme hypothesis on the ground that it could not be falsified by experiment; he dismissed Lwoff's lysogeny of phage as a non-phenomenon; and he disbelieved Meselson and Stahl's demonstration of the semi-conservative replication of DNA. Fischer writes that Delbrück wanted to model himself on his two great teachers by combining Bohr's insights with Pauli's mordant criticism, or, as he put it, by becoming God and Mephisto all in one. But I have the impression that Delbrück really wanted to disbelieve any advance that removed the elusive "Elementary Fact" further from his grasp. □

Double Max — Max Perutz (right) with Delbrück at a birthday party for Linus Pauling.

Max Perutz is at the Medical Research Council's Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK.

Explanation for the amiable physicist

Horace Freeland Judson

The Problems of Biology. By John Maynard Smith. *Oxford University Press: 1986. Pp. 134. Hbk £12.95, $19.95; pbk £4.95, $6.95.*

WHAT are "the problems of biology"? The notion is ambiguous. We could mean the next unanswered but perhaps accessible large questions — in effect, the list we would offer of the most promising lines of research on which a graduate student in biology might found a prize career. Or we could mean the approaches and constraints that distinguish biology from other sciences — in other words, the considerations we would explain to an amiable theoretical physicist who asks (as some still do) why biology doesn't provide real answers, why the ratio of theory to data seems so inordinately low. The latter sense of the problems provoked Ernst Mayr to the declaration of biology's epistemological independence with which, four years ago, he opened *The Growth of Biological Thought* — three chapters that together ran to nearly twice the length of the entire book in which John Maynard Smith now marshals the problems of the former sort, the questions biologists are getting on with.

Yet the semantic fork has a handle. The fundamental problem of biology in either sense is the presence, in systems of immense complexity, of the element of the contingent — of the accidents of history. That is, in everything that is to be explained, whether we are considering, say, the nature of mutations in regulatory genes, or the behaviour of a given mammal, or the array and interrelationships of all species surviving at a given moment, we confront phenomena shaped by uncountably long sequences of past events, many of them random. Contingency characterizes life from its origin. Darwin put history into biology and we're still working out the consequences.

Contingency, for many biologists, is normally an aspect of the background; but for the biology Maynard Smith practises it's up front. He is, after all, a population geneticist (and the recent target of a *Festschrift*) who has written a long-running paperback on evolutionary theory and who has in this past decade been modelling theorems of sociobiology as simple games. He says he agreed to write this new book for two reasons. He was flattered by the opportunity to measure himself against Bertrand Russell's *The Problems of Philosophy*. More important, he had been brought up on "the popular books of Eddington, Jeans, Einstein, Haldane and Wells" to believe that "the fundamental ideas of science can be explained to anyone willing to make the effort needed to understand them". *The Problems of Biology* has most of the virtues of that splendid tradition. It is sensible, colloquial, bracingly lucid, and stripped, sometimes daringly, to essentials. The comparison that sprang to my mind is Lawrence J. Henderson's *The Fitness of the Environment* — a classic (incidentally American) that pre-dates that (chiefly British) line Maynard Smith recalls. One rises from each of these lean volumes with a sense of the world not merely clarified but put in order; one leaves the table with an appetite.

The definition of life is not now a real problem, as it was even four decades ago when Erwin Schrödinger's *What Is Life?* was attracting physicists into biology; but Maynard Smith takes it as an obligatory starting point. He re-states the two characteristics that we have come to recognize as definitive. First, living organisms, always in populations, reproduce, and not simply by multiplication — as does a fire — but by means of a hereditary mechanism such that like begets almost-like and the population evolves individuals successively more adapted for survival. Secondly, an organism is "a complex structure which is maintained by the energy flowing through it". Maynard Smith calls these two aspects of what we want to understand about any living creature or process the "ultimate and the proximal causes", adopting terminology that Mayr, for one, used. Ultimate causes are evolutionary, proximal causes functional in the sense that they answer the question "how?" in terms of immediate process. Heredity, which in the narrow sense of genetics has become "perhaps the best understood and least problematic area of biology", Maynard Smith considers to be the necessary prelude to the cluster of ultimate problems: the evolutionary process, the origins of sexual recombination, the levels of life and the patterns of nature (the species and their interactions) that have resulted from evolution. He starts the proximal problems with the organism's methods of achieving stability and controlled responses at the biochemical level, and goes on to animal behaviour, neurobiology, and the development and differentiation of the organism. He gives his tenth and final chapter to the origin of life. The list is canonical, the particular questions within these categories incisively posed, the examples apt.

Yet a book both brief and universal also requires an organizing principle. The right one was to hand in the all-pervasive

---

• Also published in this series (OPUS) are *The Problems of Evolution* (by Mark Ridley) and *The Problems of Chemistry* (by W. Graham Richards).