Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

Max Delbrück

Ernst Peter Fischer[1]

University of Konstanz, D 78457 Konstanz, Germany

MAX DELBRÜCK (1906–1981) played a crucial role in getting molecular biology as we know it on its successful way. Thus, in the 1940s, after emigrating to the United States, he started a new science. However, he had begun in the oldest science as a student of astronomy in the 1920s while still in his native country, Germany. He soon left this field since it was during those student years that the lasting revolutionary science of quantum mechanics made its debut. Thus, Max eagerly switched to theoretical physics in which he obtained his Ph.D. in 1929. From then on he tried to find out if the new understanding of the stability of atoms and the properties of matter could help in explaining the nature of genes. This quest led to developing what the famous Austrian Nobel laureate Erwin Schrödinger called "Delbrück's model." In his influential book, *What is Life?* (1944), Schrödinger contributed to Max's fame by expressing the following opinion: "If the Delbrück picture should fail, we would have to give up further attempts" (Schrödinger 1944, p. 61), meaning further attempts in using physics to understand what genes are and how they act.

In the years during the Second World War Max discovered—with a little help from a lot of friends—how to do genetics with bacteria and their viruses (bacteriophages). After 1945 he helped to spread the news by setting up phage courses, still running today, at the Cold Spring Harbor Laboratory on Long Island, New York (see Susman 1995). These activities were instrumental in creating the molecular biology that exploded in the years following the Second World War (Stent and Watson 1966). When the new science of life reached its first epochal breakthrough with the discovery of the structure of DNA in 1953, Max was Professor of Biology at the California Institute of Technology in Pasadena. At that time, he left genetics and turned to the analysis of sensory behavior that he pursued till the end of his life. During the early 1970s I became one of his last graduate students, thereby repeating on a small scale what Max had done decades earlier: shifting from the physics that one had studied to the biology in which one wanted to work. It is perhaps this parallel move that brought Max to ask me, shortly before his death in March 1981, to write his biography. I accepted this challenge and eventually produced two versions of his life, one in German (Fischer 1985) and one in English written with the help of Carol Lipson who also knew Max personally (Fischer and Lipson 1988). This *Perspectives* essay frequently refers to these sources, and I finish this introductory section with a quote from p. 7 of the English version of the biography, entitled *Thinking About Science—Max Delbrück and the Origin of Molecular Biology*:

> In 1969, Max shared the Nobel Prize for Physiology and Medicine with Salvadore Luria and Alfred Hershey. Since they were the first to publish on bacterial genetics, their work opened the field. Yet even as the object of highest recognition possible in the scientific world, Max remained totally unpretentious. He always directed friends and coworkers to call him Max; anyone referring to him as Dr. Delbrück or Professor Delbrück would have been rebuked. This essay, then, will refer to him as he wished to be addressed.

Max was born in Berlin in 1906 as the seventh child of the famous historian Hans Delbrück and his wife Lina. There, he was raised in the upscale suburb of Berlin called Grünewald, where today one can find a street named after Max's father. The neighbors of the Delbrücks consisted mainly of distinguished academic families with famous names like Bonhoeffer (a professor of psychiatry) and Harnack (a professor of theology). It was a marvelous life until in 1914, when "the dam broke and swept away four decades of peace," as Max put it, adding that "my memories start with the war years: hunger, cold, substitute teachers, social pressure to engage in dismal patriotic war games."

[1]*Address for correspondence:* University of Konstanz, P.O. Box 65, D 78457 Konstanz, Germany. E-mail: epfischer@t-online.de

After 1918 and during the following years at high school Max began looking for a field that was new both to neighbors and to family, to achieve a name for himself. Thus, he picked astronomy as his topic and selected Johannes Kepler as his hero. He would study Kepler's original writing in the rare book collection of the university library:

> To see and handle these old books, 300 years old, was a tremendous experience, especially when I found in one of them speculations about the celestial harmonies expressed in terms of musical notes. (Fischer and Lipson 1988, p. 23)

Despite experiences like this, Max's choice of astronomy turned out to be a bad one since the exciting science being developed in the mid 1920s was quantum mechanics. In the spring of 1925, 23-year-old Werner Heisenberg had conceived of a totally new way of describing atoms and their particles. In the next year Erwin Schrödinger followed suit with his version of the new physics called wave mechanics. In early 1926, Heisenberg came to Berlin to give a seminar that Max attended. Although he did not understand a word of it, Max realized by picking up remarks from Albert Einstein, who was sitting in the first row, that he had witnessed a very important scientific development. Therefore, Max switched fields to study the new quantum theory. He went to Göttingen as a graduate student of Max Born, eventually completing a "rather dull" Ph.D. thesis on the lithium molecule. While working on this he started to wonder about the relevance of the new revolutionary insights into the nature of matter and light.

One of the puzzling insights physicists had to face was the fact that two classical concepts were needed to describe or understand light as well as matter—the concept of a wave and the concept of a particle. The great Danish physicist Niels Bohr called pairs of concepts like this complementary. By this, he meant that they together provide a complete description of the phenomena under consideration, while the use of one of them excluded the simultaneous application of the other. Bohr considered it likely that the idea of complementarity would eventually pervade all of science. He believed that a deep understanding of nature would come about by using complementary concepts and/or arguments. He repeated and restated this suggestion in the early 1930s in many lectures, including the 1932 opening lecture of an International Congress of Light Therapists that Max attended.

At that time, with the help of a fellowship from the Rockefeller Foundation, Max was doing some postdoctoral studies in Bohr's institute in Copenhagen. He was not really happy to be in physics since the days of great discoveries seemed to have ended in 1928 when Paul Dirac managed to fuse quantum mechanics and relativity theory. Of course, there were many details left to be worked out, but Max had not switched from the stars to the quantum to do that. He was looking for a field that needed new ideas and he saw his chance when he attended Bohr's 1932 lecture entitled "Light and Life."

There is a printed version of this lecture (Bohr 1933) but it is likely that a reader will not find what Max learned during the talk itself. The closest we can get to the real events is quoting what Max remembered having heard in Bohr's lecture:

> In physics it is obvious that even in the simplest case such as an electron running around a proton one can do classical physics until one's dying day and never get a hydrogen atom out of it. In order to achieve this, one has to use the complementary approach. If one looks at even the simplest kind of cell, one knows it consists of the usual elements of organic chemistry and otherwise obeys the laws of physics. One can analyze any number of compounds in it but one will never get a living bacterium out of it, unless one introduces totally new and complementary points of view. (Fischer and Lipson 1988, p. 82)

The idea of complementarity has been described in such detail because of its importance to Max's thinking: "It has through the years provided the sole motivation for my work," as Max wrote in 1962 when he invited Bohr to deliver another lecture about light and life 30 years after the influential first one (Bohr 1963).

When one tries to reconstruct the ideas that emerged in Max's thinking while listening to Bohr we are led to a view of his future research, summarized below.

The new physics had started by analyzing the interaction of light and matter and realizing that it occurs in quantum jumps. These quanta helped to explain the stability of atoms (and thereby of matter), which was discovered with the help of a simple system, namely the hydrogen atom consisting only of two elements—an electron and a proton. To get a new study of biology one had to start by analyzing the interaction of light and life. Further, one needed to find a simple system that allowed investigation of the basic property of living systems: their reproduction and the generation of stable variants (mutations). Thus, Max started to look for the "hydrogen atom" in biology, *i.e.*, a living entity that did little more than replicate. But first, he had to learn to do biology!

After working with Bohr, Max returned to Berlin to become assistant to Lise Meitner. There, his main goal of learning biology was pursued in private. He contacted the Russian geneticist Nicolai Timoféeff-Ressovsky, who was working with Drosophila, studying the genetic changes induced by different wavelengths of radiation. The two men collaborated with the physicist K. G. Zimmer to eventually produce an article, "About the nature of the gene mutation and the gene structure" that was published in 1935 and contained what was already referred to above as Delbrück's model of the gene (Timoféeff-Ressovsky *et al.* 1935). After presenting quantitative results of the effects of ionizing radiation on mutation frequency, in a separate chapter Max worked out a quantum mechanical model of the gene, calling it an "Atomverband"—a collection of atoms—thereby connecting genetics with physics and chemistry and opening the abstract gene for a concrete analysis using the exact sciences.

In 1937 Max was offered another fellowship by the Rockefeller Foundation to continue his biological work in the United States. He chose the California Institute of Technology where Thomas H. Morgan had set up his Drosophila laboratory. After Max quickly discovered that the fruit fly could not fulfill his dream of connecting physics to biology, he feared that he would be a failure. At that point, Max was saved by meeting Emory Ellis, who was analyzing bacterial viruses. Max immediately identified them as "something like atoms in biology" (Fischer and Lipson 1988, p. 113).

At this point, the reader should recall that in 1937 it was impossible to distinguish the terms "phage," protein," or "gene." Genes were assumed to be proteins, some of which were known to be autocatalytic enzymes. This was one way to interpret the multiplication of phage. To Max, it was of no importance to distinguish between phage, protein, and gene as long as he could study the key properties of a reproducing biological system that allowed easy quantification. He was not interested in genes but in replication as the basic property of life (compared to physical stability as the basic properties of atoms).

Max collaborated with Ellis to investigate "The growth of bacteriophage" (Ellis and Delbrück 1939). This article describes the beginning of modern phage work: presenting one-step-growth curves and a way to determine the concentration of bacterial viruses in solution. It makes use of statistical arguments from physics, thereby creating a first quantitative basis of genetic analysis.

Since Ellis was paid to follow up other lines of research Max continued with phage all by himself when he transferred to Vanderbilt University in Nashville after the beginning of World War II. Then, in December 1940 he met Salvadore Luria at a meeting of the American Association for the Advancement of Science in Philadelphia. Although the two differed in their goals, they agreed to join forces. Max wanted to study and understand replication while Luria was interested in the gene. Since, in the early 1940s, the known laws of inheritance were valid only for organisms that reproduced sexually, no one knew for sure if these creatures even had genes.

Nevertheless, both scientists wanted to see what a virus was doing in the black box of a bacterium. When they discovered that two phages acting upon the same host strongly interfered with each other's multiplication, Max was very excited. He saw a chance to apply physical terms like interference and the idea of mutual exclusion that characterizes a complementary situation to a biological process. In 1947 he wrote about "the principle of mutual exclusion" (Delbrück 1947) and he experienced a letdown when it turned out that the real explanation resulted from recombination. While every other biological scientist was happy to see that phages fit into the general genetic framework Max was disappointed that his dream of finding a definite complementarity in biology did not come true. Finally, in 1953 the double-helical structure of DNA was discovered and Max gave up research in genetics altogether. The model proposed by James Watson and Francis Crick (Watson and Crick 1953) achieved for biology what physics had missed in the early decades of the 20th century: a molecular model that would explain basic phenomena in classical terms without reference to complementarity. Max felt that genetics had been reduced to chemistry, a field in which he was not really interested.

By fast-forwarding to the early 1950s we have slipped over Max's most important contribution to the rising science of genetics (Luria and Delbrück 1943). During his collaboration with Luria, in the war years, the German–Italian pair had observed a phenomenon they called secondary growth. It had to be due to resistant strains that appeared a few hours after a susceptible culture of *Escherichia coli* had been lysed. In April 1941 Max sent a note to Luria, telling him that he felt "that the rise of the secondary culture would be an interesting and attackable problem for future collaboration." As they started working on it, Luria discovered first to his annoyance that the number of resistant *E. coli* cells was subject to great day-to-day fluctuations. After observing a slot machine it occurred to Luria that he was analyzing the wrong numbers. Instead of thinking about the number of resistants, he felt he should look at the fluctuations (Luria 1984). Max, the physicist, immediately recognized which statistical distribution could be applied to the phenomenon, and he worked out a theoretical explanation. Together, they created the famous fluctuation test that led to two important insights. First, it made clear that phage-resistant mutants originated by spontaneous mutation (as Darwinian evolution would expect) and, second, that a mathematical analysis of the fluctuations allowed the precise determination of mutation rates. The joint article by Max and Luria provided statistical evidence for the existence of genes in bacteria and allowed the calculation of their rates of spontaneous mutation. Thus, the field of bacterial genetics was begun, and this science exploded when in 1946 Edward Tatum and Joshua Lederberg discovered that bacteria had a sex life after all (Lederberg and Tatum 1946).

As mentioned above, in the year that saw the discovery of the double helix, Max began a new scientific life by starting to investigate another basic property of life: sensory perception and adaptation. After identifying phage as the hydrogen atom of genetics Max was now looking for the phage of vision and he picked a small fungus named Phycomyces. He explained this choice in a 1954 letter to Bohr (quoted in Fischer and Lipson 1988, p. 242):

> Max considered *Phycomyces* "as something analogous to a gadget in physics" which he wanted "to analyze in great detail" thereby hoping "when this analysis is carried sufficiently far, it will run into a paradoxical situation analogous to that into which classical physics ran in its attempts to analyze atomic phenomena. This, of course, has been my ulterior motive in biology from the beginning. What I have in mind is an application of the complementarity principle not in a form which is just vaguely analogous to the dividing line between observer and object, but something much more closely related to the physics situation, springing directly from the individuality and indivisibility of the quantum processes."

Unfortunately, once again Max's dream did not come true (see Cerdà-Olmedo and Lipson 1987). We leave the research on Phycomyces in the hands of the scientists still working at it and conclude by mentioning some of Max's influence on modern science. With this I do not mean the functioning of Cold Spring Harbor Laboratory or the Genetics Institute in Cologne or the University of Constance, which he helped to get underway in the late 1960s. Rather, I suggest that genetics is still a science that can be treated as physics. Max was proud to tell everybody that modern biology was the result of what physicists did.

One might question if this is good for science in the sense that the people who work in this field try to understand life solely by looking "for other physical laws," as Schrödinger put it (Schrödinger 1944, p. 73). With these other laws still being laws of physics scientists may miss out on explanations of another kind, *e.g.*, explanations that are genetical in the sense that they describe the creation of form. One cannot expect to be able to explain the shape of an earlobe or a nose by physical causality alone, since one cannot explain a work of art such as a painting by the force an artist applied or the chemical composition of the colors used. There is more to a shape than physical causality and the science of genetics has to rise to this challenge if it wants to explain the properties of life. Today's molecular biologists should be reminded that already the pioneers of atomic physics (personally known to Max) realized that even atoms cannot be fully understood by physical causality alone. You have to start with the existence of a stationary state—*i.e.*, a form—to explain the behavior of the basic building blocks of matter. So the question is: How will the appropriate morphogenetic reasoning be incorporated into the modern genetics that at the present is mainly busy sequencing genomes and considering them as physical causes?

To use an expression Max liked: We are still waiting for a "Niels Bohr" in biology as Max used to say, recognizing that in James Watson, we already have had an "Einstein of biology." As I have discussed, Bohr introduced what became Max's favorite idea into science: the idea of complementarity, which at this point should be stated in a general way.

Complementarity means that for each description of reality there is another one that is equally justified although it contradicts the first one. The classical example is the wave-particle duality of atoms and light. Another complementarity can be found if you look at the ways Newton and Goethe describe color, concentrating on what they meant by "simple." For Newton light was simple when it consisted of a single wavelength after passing through a prism. For Goethe that light was complicated because it needed an instrument for its production before being seen. Instead, for the German poet the light that came from the sun was simple: It was generated that way and our eyes then made direct use of it from a phenomenological point of view.

Max was convinced that science would achieve a deep understanding of its objects only if it arrived at a complementary description. How can we apply this idea to genes, development, genomes and the like? Max suggested that as along as complementarity is not on the horizon we are not even close to an understanding.

Is there anything else that can we learn from Max's life in science? With respect to the responsibility of researchers, I like Max's idea that a scientist can bring much more change into the world than any politician or military leader and he can do so by just sitting in his office and thinking. And Max loved to do this all his time.

LITERATURE CITED

Bohr, N., 1933 Light and Life. Nature **131:** 421.

Bohr, N., 1963 Licht und Leben—noch einmal. Naturwissenschaften **50:** 725.

Cerdà-Olmedo, E., and E. D. Lipson (Editors), 1987 *Phycomyces.* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.

Delbrück, M., 1947 Über Bakteriophagen. Naturwissenschaften **34:** 301–306.

Ellis, E. L., and M. Delbrück, 1939 The growth of bacteriophage. J. Gen. Physiol. **22:** 365–384.

Fischer, E. P., 1985 *Licht und Leben—Max Delbrück als Wegbereiter der Molekularbiologie.* Konstanzer Universitätsverlag, Konstanz, Germany.

Fischer, E. P., and C. Lipson, 1988 *Thinking About Science—Max Delbrück and the Origin of Molecular Biology.* W. W. Norton, New York.

Lederberg, J., and E. Tatum, 1946 Novel genotypes in mixed cultures of biochemical mutants in bacteria. Cold Spring Harbor Symp. Quant. Biol. **XI:** 113–114.

Luria, S. E., 1984 *A Slot Machine, A Broken Test Tube.* Harper & Row, New York.

Luria, S. E., and M. Delbrück, 1943 Mutations of bacteria from virus sensitivity to virus resistance. Genetics **28:** 491–511.

Schrödinger, E., 1944 *What is Life?* Cambridge University Press, Cambridge, UK.

Stent, G. S., and J. D. Watson (Editors), 1966 *Phage and the Origin of Molecular Biology.* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.

Susman, M., 1995 The Cold Spring Harbor Phage Course (1945–1970): a fiftieth anniversary remembrance. Genetics **139:** 1101–1106.

Timoféeff-Ressovsky, N., K. G. Zimmer and M. Delbrück, 1935 Über die natur der genmutation und der genstruktur (about the nature of the gene mutation and the gene structure). Nachrichten der Gesellschaft der Wissenschaften zu Göttingen, Math.-Phys. Klasse. Fachgruppe **6**(13): 190–245.

Watson, J. D., and F. H. C. Crick, 1953 A structure for deoxyribonucleic acid. Nature **171:** 737–738.