A Physicist's Quest in Biology: Max Delbrück and "Complementarity"

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ABSTRACT Max Delbrück was trained as a physicist but made his major contribution in biology and ultimately shared a Nobel Prize in Physiology or Medicine. He was the acknowledged leader of the founders of molecular biology, yet he failed to achieve his key scientific goals. His ultimate scientific aim was to find evidence for physical laws unique to biology: so-called "complementarity." He never did. The specific problem he initially wanted to solve was the nature of biological replication but the discovery of the mechanism of replication was made by others, in large part because of his disdain for the details of biochemistry. His later career was spent investigating the effect of light on the fungus *Phycomyces*, a topic that turned out to be of limited general interest. He was known both for his informality but also for his legendary displays of devastating criticism. His life and that of some of his closest colleagues was acted out against a background of a world in conflict. This essay describes the man and his career and searches for an explanation of his profound influence.

KEYWORDS Delbrück; Luria; Hershey; complementarity; replication; bacteriophage; microbial genetics

MAX Delbrück was a genius, albeit an "ordinary genius" (Segre 2011)². James Watson described him as "the model for what I wanted out of my own life" (Watson 2001). His more enthusiastic acolytes consider him "the" father of molecular biology. He made major contributions but (almost) always in close collaboration with equally talented, but less remembered, colleagues. He seriously underestimated the possible contribution of biochemistry and spent much of his career searching for a likely nonexistent principle of complementarity in biology. It is reasonable to ask why he is guaranteed a place as one of the founders of molecular biology.

Delbrück's life has been described in two full-length biographies, a "Festschrift," and numerous obituaries as well as in a previous Perspective article (Fischer 2007). Why another? There are two reasons: First, as time goes on, Delbrück's work and these biographies are fading from view as far as the new generation of biologists is concerned. Second, I was a graduate student in Biology at the California Institute of Technology

(Caltech) from 1947 to 1950 at just the time of his arrival. I was not in the phage group, but Caltech was small and Delbrück was on my doctoral committee. I am therefore one of a dwindling group who can furnish a personal view of what he was like in his prime, though admittedly one filtered through memory many decades since.

What Was Caltech Like in the Late 1940s?

"The trouble with Caltech graduate students is that you all want to solve the secret of life." The speaker was Ray Owen (a pioneer immunologist who first recognized immune tolerance) and we were on a train returning to Pasadena after a meeting in New York in the late 1940s. Well, if he was correct about that, Caltech was the right place to be. I have my suspicions about the desires of a number of the faculty in this regard, but at least one was publicly committed to some such goal, namely Max Delbrück. This essay is my attempt to understand him after all these years. I still view Delbrück as a sort of superhuman intellect, different in kind from the other faculty members I encountered.

George Beadle and Norman Horowitz (my advisor) were superb scientists but one could readily relate to them. Delbrück was different. He gave the impression of seeing into things more deeply—and quickly. He not only drove the phage group but his comments on the *Neurospora* work, for example, were

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²Segre classifies Pauli, Heisenberg, and Einstein as extraordinary geniuses whereas Delbrück was only an ordinary genius "smarter and more imaginative than you and me, but not qualitatively different from us."

critically important (comment to Bonner 1946). In the mid-1940s, Beadle's group was busily isolating mutants of *Neurospora*, the great majority of which had single growth requirements. They used this impressive array to argue for the proposition that single genes controlled the production of single enzymes: "one gene—one enzyme." Delbrück pointed out that the method of selecting *Neurospora* mutants would automatically eliminate most mutants with multiple or complex functions because such mutations would generally be lethal. This comment prompted the experiments of Horowitz (Horowitz and Leupold 1951) who used temperature-sensitive mutants to show that in fact the majority of isolated mutants had single functions as postulated by the one gene—one enzyme hypothesis.

Delbrück was a charismatic teacher who made his material both clear and exciting, and he ran a miniature phage course (patterned after the famous summer course at Cold Spring Harbor) for a small group of Caltech graduate students. We were absolutely fascinated by him; and then one day he had to be away and his place was taken by a visitor who was mild mannered, mumbled, could not be understood, and in general confused us. As a teacher, this man was clearly no Delbrück. We learned later that his name was Al Hershey, and much later, he would share the Nobel Prize with Max Delbrück and Salvador Luria, of which more later.

In many ways, Delbrück's career parallels that of J. Robert Oppenheimer although, unlike Oppenheimer, his end was not tragic. They each had a brilliant beginning, became the intellectual leader of a group of extremely talented individuals, and then made a wrong decision. In Delbrück's case the decision was scientific and based on a long-standing preoccupation with Niels Bohr's thought that there might be a principle of complementarity operative in biology, analogous to that in physics. I believe that belief resulted in Delbrück's later years being relatively unproductive and it is therefore important to try to summarize the argument. In a much-referred-to lecture (Bohr 1933), Bohr started with the paradox that light was undoubtedly both a wave and simultaneously a particle. These two views had to be considered not antithetical but rather complementary, both describing aspects of the truth. He then argued that there might be a similar problem in biology. While admitting that "if we were able to push the analysis of the mechanism of living organisms as far as that of atomic phenomena, we should scarcely expect to find any features differing from the properties of inorganic matter," he also supposed that "we should doubtless kill an animal if we tried to carry the investigation of its organs in vital functions so far that we could describe the role played by single atoms in vital functions. . . *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. . . [my italics].*" It seems clear from the reminiscences of scientists close to Delbrück, e.g., Stent (1989), that he based his career on a search for biological phenomena that could only be accounted for by some principle akin to the complementarity Bohr

described for atomic physics. As of this date, no one has found such a paradox.

Delbrück's Early Training

In the current intellectual climate, today's biology students have little need to know how their science developed nor what part Delbrück played. His early life has been well described in *Thinking About Science*, a biography coauthored by a former student of his during the postphage years (Fischer and Lipson 1988), as well as in a comparison of his career and that of the physicist George Gamow by Gino Segre (Segre 2011). These biographies derive in large part from a series of oral interviews with Delbrück by Carolyn Harding (Harding 1978).

Delbrück's German origins are relevant to his history. He came from a respected intellectual, upper-class Protestant family in Germany. His father, Hans Delbrück, was a noted historian and distinguished university professor, and several relatives held high positions in the civil service. He grew up in a neighborhood surrounded by academics such as Max Planck. The family was liberal in a dignified sort of way, the father at one point in some (minor) trouble with the Kaiser. This was a family patriotically German and essentially apolitical, although Delbrück's sister married a Bonhoeffer and two of the Bonhoeffer brothers (Klaus, Delbrück's brother-in-law, and Dietrich) were executed by the Nazis for participation in the 1944 plot against Hitler.

Delbrück was first attracted to astronomy but then moved to physics in the mid-1920s. This was an exciting time in physics as the revolutionary implications of quantum theory were becoming fully apparent. He received his degree in physics and in the early 1930s took a position as theoretical physicist in the group in Berlin headed by Lise Meitner. His training also included what seems to the outsider as a mandatory period in Copenhagen under the direction of Niels Bohr, an icon of the new physics.

Radiation Biology

Although Delbrück was a member of the theoretical physics community at one of the most exciting times in the development of the subject, his interests had strayed to biology. He was working with Lise Meitner as her theoretical physicist but he, like many distinguished physicists, managed to avoid recognizing nuclear fission, probably because they were not chemists³.

Whatever the focus of his attention was supposed to be, Delbrück was moonlighting with a group of geneticists

³I recently was talking with a physicist friend and mentioned that I was interested in Max Delbrück. "Oh," he said, "Delbrück scattering." While working with Lise Meitner and Otto Hahn, Delbrück had written an article to explain some of the results of their irradiation with "hard" X rays produced by Thorium-C decay. The theory turned out to be correct but not relevant to the particular observations, but 20 years later was recognized by Hans Bethe as accounting for the scattering of gamma rays in the electromagnetic field of the nucleus. Bethe named the phenomenon "Delbrück scattering." Needless to say, my physicist acquaintance had no idea that Delbrück had done anything in biology!

studying the mutagenic effects of radiation. Just how this came about is not only interesting as it relates to Delbrück's career, but illustrates how interwoven the careers of scientists were with the tremendous political events of the times. Starting ~1933, a private discussion group started meeting in Delbrück's home. Here is how he describes it:

I don't know how this came about, but after a while there was a group of, as it were, exiled, internal exiled, theoretical physicists, I and five or six of them, who met fairly regularly and mostly at my mother's house to have private theoretical physics seminars among ourselves; at my suggestion we soon brought in also some other people, some biologists and biochemists. And one of the people we brought in was N. W. Timofeeff-Ressovsky, who was a staff member of a Kaiser Wilhelm Institute for Brain Research, which was located at the other end of Berlin—enormously far away, just about an hour and a half by various public conveyances, in Berlin-Buch, now East Berlin or maybe even in East Germany. Anyhow we had Timofeeff over at my house a number of times and we also went to his place just to see some flies, and talked about fly genetics and mutation research. His main line of research at that time was to study quantitatively the induction of mutations by ionizing radiations. In order to do this quantitatively, we had to have quantitative dosimetry of the ionizing radiation, and the person responsible for that was K. G. Zimmer. So out of that grew a rather lengthy paper, which summarized all the experimental data and methods, and then a big theoretical Schmus⁴ about interpreting it, for which I was mostly responsible (Harding 1978).

For anyone interested in the political events of the 1930s, this little group meeting at Delbrück's (parent's) house was interesting and one of the participants, Timofeeff-Ressovsky is absolutely fascinating (Box 1). While not exactly dissidents, the participants in the private seminar were clearly not favorites of the (Nazi) regime. What is important is that somehow Timofeeff and Delbrück became acquainted, and that Timofeeff and a physicist named Karl Zimmer became part of Delbrück's seminar.

The result was an article nicknamed the "Three Man Paper" and it had a major impact both on Delbrück's career and on thinking about the nature of the gene (Timofeeff-Ressovsky *et al.* 1935). The conclusion, based on the stability of the gene as measured by the mutation rate at different doses of ionizing radiation as compared to different temperatures was that the gene was likely to be a molecule. Delbrück put it as follows (Nobel lecture; Delbrück 1970):

A few years earlier H. J. Muller had discovered that ionizing radiations produce mutations and the work of the Berlin group showed very clearly that these mutations were caused either by single pairs of ions or by small clusters of them. Discussions of these findings within our little group strengthened the notion that genes had a kind of stability similar to that of the molecules of chemistry. From the hindsight of our present knowledge one might consider this

Box 1

Timofeeff's story is absolutely bizarre and illustrates the inherent ambiguity of life in central Europe. (According to Wikipedia) Timofeeff fought with the Green Army (midway between Reds and Whites!) during the Russian Revolution, but by the 1920s was a Soviet geneticist. In one of the strange features of that decade, the Russians and Germans participated in a variety of exchanges, as a result of which Timofeeff found himself working at an Institute of Genetics in Berlin. He stayed there for 20 years, disregarding an order to come home in 1937. His major contribution was in the field of radiation genetics. In 1945, as Germany was collapsing, he decided to stay in the East since there were plenty of scientists in the West and presumably the Russians could use him. He was promptly imprisoned, but then released because the Russians needed radiation biologists to help in the development of their nuclear weapons program. The story is even more complicated. At some point he was rearrested, spent a harrowing 2 years in prison and then was allowed, while still a convict, to resume his laboratory work. It was 11 years after his death that he was officially rehabilitated. This sketch does not do justice to an amazing career.

a trivial statement: what else could genes be but molecules? However, in the mid-thirties, this was not a trivial statement. Genes at that time were algebraic units of the combinatorial science of genetics and it was anything but clear that these units were molecules analyzable in terms of structural chemistry. They could have turned out to be submicroscopic steady state systems, or they could have turned out to be something unanalyzable in terms of chemistry, as first suggested by Bohr and discussed by me in a lecture twenty years ago (reprinted in Cairns *et al.* 1966).

It is difficult to appreciate the impact of the Timofeeff-Zimmer-Delbrück article without some understanding of the position of biologists in the 1930s. We are so accustomed to visualizing the double helix and thinking about the importance of DNA sequence and the interaction between structural and regulatory factors that it is hard to empathize with the view of many nongeneticist biologists; who still had to decide whether genes were involved in only relatively trivial traits and who had no good idea as to the relationship between a gene and the character it affected. The "theory of the gene," as described by the Morgan group, gave a detailed explanation of the modes of inheritance of these units but gave no hint as to what they were or how they worked. The position of the biochemists was not much better. A few proteins had been crystallized, but there was not even agreement that they were basically linear polypeptides. A few biochemical characteristics were inherited in Mendelian fashion, but on the whole, genetics was innocent of any contact with chemistry or physics. The field of biochemical genetics, a direct

⁴Schmus (German) is a word for nonsense, e.g., schmus erzählen: to talk nonsense. Possibly from Yiddish shmues (schmooze), idle talk.

precursor of molecular biology (Strauss 2016), was in its infancy and Beadle and Tatum had just published their initial work with *Neurospora* supporting the hypothesis of a direct relationship between genes and enzymes (Beadle and Tatum 1941).

Although the journal in which the article (Timofeeff-Ressovsky *et al.* 1935) was published is obscure (the English translation is found in Sloan and Fogel 2011), the article was influential. One of its illustrations takes up most of a page in Sturtevant and Beadle's classic 1939 genetics textbook (Sturtevant and Beadle 1939, 1962). More importantly, a reprint found its way to Erwin Schrödinger who used it as the basis for two chapters of speculation in his 1944 book *What is Life* (Schrödinger 1945).

One can understand an intelligent layman (albeit a Nobel laureate in physics in Schrödinger's case) being fascinated with the stability of the Hapsburg lip over generations and wondering about the nature of that stability (Schrödinger 1945). H. J. Muller's discovery of the mutagenic effect of radiation coupled with the quantitative analysis in the Timofeeff article along with Delbrück's analysis promised to provide some way to actually investigate the physical properties of this mysterious but clearly fundamental biological unit, the gene.

The main consequence for Delbrück was to make his name known to Schrödinger's readers, some of whom were energized to consider working in biology. Fischer and Lipson (1988) list Seymour Benzer, Francis Crick, Gunther Stent, and James Watson as being so motivated and prone to look at Delbrück as a leader. Not a bad quartet!

Bacteriophage

Physicists thinking about biology tend to look for simple systems that are amenable to analysis⁵. Delbrück was no exception.

He was looking for *the* simple system with which the fundamental problem of life could be elucidated. This was a big enough challenge in itself, but there were external ones as well. This was the 1930s in Germany after all, and the politics of that time and place affected even the most apolitical of men. Universities in Germany were government organizations. To be certified as a "Privatdozent," enabling one to teach, it was necessary to have not only certification of professional qualification but also proof of a pure Aryan (*i.e.*, non-Jewish) background and of political reliability. Delbrück could manage the first two. Certification of political reliability, however, required attendance at an indoctrination camp and it appears that he failed in two attempts (Fischer and Lipson 1988). My guess is that Delbrück, who was never one to suffer fools gladly, could not help but let his attitude show. As a result, the appropriate documents just never showed up

and it became clear that he had no academic future in Nazi Germany. He was allowed to continue working with Lise Meitner because the Kaiser Wilhelm Institut at which they worked was a private, not a governmental, institution. But Meitner was Jewish (notwithstanding a conversion) and her position was precarious.

It is at this point that the Rockefeller Foundation helped by providing a second fellowship. The first fellowship in 1931 had financed his stay in Copenhagen with Niels Bohr and with Wolfgang Pauli in Zürich. The foundation was actively engaged in trying to develop what one of their officers, Warren Weaver, had named molecular biology (Weaver 1970)⁶, as well as attempting to assist displaced scholars. The foundation's representative in Europe visited Delbrück in 1936, to see whether he was willing to leave Europe. Max picked on Caltech as an appropriate place and wrote to Morgan. As a result of the "Three Man Paper," T. H. Morgan invited Delbrück to Caltech as a Rockefeller Fellow (Summers 1993). At that time, this would have been considered a bold move: theoretical physicists were not usual features of biology laboratories. After a short stay at Cold Spring Harbor, Delbrück arrived at T. H. Morgan's department in 1937. Things went well (as discussed below) and the fellowship was renewed in 1938 but was due to expire in September 1939, which was, as it happened, the date of the German attack on Poland. Meanwhile the Rockefeller Foundation, aware of Delbrück's talents and the ambivalence of his situation in Germany, started looking for a permanent position for Delbrück in the United States. Morgan was now retired and unable to help, but by pledging salary support the foundation was able to secure Delbrück a job in the Physics Department at Vanderbilt University in Nashville, TN. It was then necessary for Delbrück, who was a "visitor" while on his fellowship, to formally enter the United States as an immigrant; so in the summer of 1940 he traveled to Mexico [with a stop at Caltech where he wrote an article on molecular interactions with Linus Pauling (Pauling and Delbrück 1940)] and then reentered the United States. He applied for immigrant status in December 1940 and was naturalized in 1945. Delbrück spent the war years in Nashville. In view of our current preoccupations with immigrants, it is interesting to consider that a German physicist was living and working a mere 165 miles away from Oak Ridge, a center of the Manhattan Project for development of the atomic bomb, but of course there is no connection.

In 1938, when he arrived at Caltech, Sturtevant assigned him a fairly intricate problem that, according to Delbrück, was staggering in its requirement for understanding the arcane terminology of *Drosophila* genetics. He was still looking around for something simpler. A well-argued article by William Summers (Summers 1993) suggests that before moving to Caltech, Delbrück had already decided that viruses were more likely to provide information about

⁵For example, in ~1962, many years later, after I had left Caltech, John Platt, a physicist/biophysicist at The University of Chicago dismissed the experimental system I was using, *Bacillus subtilis* transformation, as much too complicated.

⁶The role of the foundation in the development of molecular biology has been well documented by Kay (1993).

the basic structure of the gene than *Drosophila*. Summers traces this decision to earlier speculations by Muller (1922), the discoverer of the mutagenic effect of ionizing radiation. Muller had speculated that the viruses of bacteria, “bacteriophage,” and genes had identical properties.

Delbrück found that simpler system in the basement of the Kerckhof laboratories where a postdoctoral fellow named Emory Ellis was working on a bacteriophage, an infectious agent that destroyed (lysed or dissolved) bacteria. Phage had been discovered in 1915 by Twort and again in 1917 by d’Herelle (d’Herelle *et al.* 1922), but no one had been able to make it therapeutically useful as a bactericidal agent. Furthermore, it was far from clear that there were different kinds of phage specific to different bacterial species. Indeed, it was not even clear whether bacteriophage was a virus or some endogenous bacterial metabolic factor. The hopes that this virus of bacteria, as we now know it to be, had engendered for medicine are dramatically described in the novel *Arrow-smith* by Sinclair Lewis, a best seller in its time. Even today there continue to be attempts to put phage to clinical use, *e.g.*, Reindel and Fiore (2017).

d’Herelle and later Ellis had developed an assay in which bacteria were infected with phage and then plated on a lawn of uninfected bacteria, the result being that each infected bacteria produced more phage and these phage lysed the surrounding bacteria, which then liberated more phage, and so on for several cycles; the result being an apparent hole in the bacterial lawn. One could count the number of holes and, from that number and the dilution factor, calculate the initial concentration of virus particles. Delbrück was fascinated. Thinking about Bohr’s lecture had convinced him that reproduction of living things, a phenomenon with no clear parallel in physics, was the key problem in biology. Here was a simple system in which one could study a simple reproducing unit under controlled circumstances.

Ellis, however, had only been “sneaking” time to study bacteriophage when he should have been doing “cancer research,” so after one joint article with Delbrück (Ellis and Delbrück 1939) he had to go back to mice and cancer research, leaving Delbrück to continue. I am sure this was a high point of Delbrück’s life. Just reading his early articles on phage indicates how much fun it was. You could think up an experiment, do it, get the results the next day in quantitative terms, figure out the next experiment, and then do that.

Delbrück’s major experimental contribution to the development of molecular biology consists of a series of articles during the war years (Delbrück 1940a,b, 1945a,b,c; Luria and Delbrück 1943). The first problem had been to settle once and for all the question as to the nature of bacteriophage. We know too much today to appreciate how difficult and confusing that was. There were two major views: The first was that phage was a living organism, a virus that infected bacteria. The second was that phage was a product of bacteria that, when induced, produced enzymes that lysed the bacteria. This was the view espoused by John Northrop who had discovered that several proteolytic enzymes, such as

pepsin, were formed from an inactive precursor (*e.g.*, pepsinogen) that could be converted to active enzyme (pepsin) (Northrop 1939). The proponents of this view suggested that bacteria contained a similar phage precursor.

To understand the difficulty of this problem, one has to distinguish between lysogenic and virulent phage. A “virulent” phage infects a culture and results in lysis of the cells it infects. A lysogenic phage infects a culture but then integrates into the bacterial DNA, replicating along with the host. Occasionally, however, the incorporated phage will be activated and its host cell will subsequently lyse. As a result, a culture carrying a lysogenic phage will continually secrete some phage, as the Northrop theory would also suggest. To distinguish between the theories it was necessary to work only with virulent phage. Delbrück dealt with this problem by decree! He and his early recruits established a panel of unambiguously virulent phage (the T-phages of *Escherichia coli*, T standing for “type”) and essentially refused to read about experiments with anything else.

Second, there was the problem of lysis. Delbrück recognized that there were two ways that lysis could occur. One was by infection of cells with large numbers of phage particles, resulting in immediate lysis. The second, and more interesting, way was as a result of infection of a single bacterium with one or a few particles, after which there was a “latent” period and then a burst liberating many phage. Several cycles of this process resulted in clearing (lysis) of the culture or of a plaque in the bacterial “lawn” if the infected cell had been plated with host bacteria. Once this confusion was cleared up and the procedure for obtaining a “single-step growth curve” was established, one could start to consider the mysterious events during the latent period when one initial infecting particle had generated 20 or 60 or more.

During the next few years while the world was at war, a very few investigators started to work in concert to study bacteriophage. The growth of this phage group is readily conflated with the early development of molecular biology. It was the combined work of Salvador Luria, Al Hershey, and Tom Anderson along with Delbrück that indicated the promise of this new biological tool. One other important factor: the Cold Spring Harbor Laboratory that served as a boot camp for new phage workers.

With hindsight, Delbrück’s career seems blessed by the appearance of just the right person at the right time. Timofeeff appeared just as he started thinking about biology. Emory Ellis introduced him to phage. Then in 1940 Salvador Luria appeared (Luria 1984). Somewhat like that of Timofeeff, Luria’s appearance was in part a result of the upheaval in Europe in the first half of the 20th century. An Italian medical doctor who happened to be Jewish, Luria became interested in biophysics and learned of the Timofeeff article. He also, independently, had decided that bacteriophage would be ideal to test Delbrück’s ideas about mutations. He had obtained an Italian government fellowship to Berkeley, but this was abruptly withdrawn on the day Mussolini decided that Italians were Aryans. Luria was able to move to Paris and found

work studying radiation effects on bacteriophage. When France fell to the Nazis, he came to the United States (see below). He finally met Delbrück, with whom he had corresponded earlier, at a meeting in New York in December 1940, and then spent much of 1942 with Delbrück in Nashville. By 1943, Luria had a job at Indiana University but he and Delbrück remained in close contact.

Alfred Hershey (introduced earlier) had been working in St. Louis with Jacques Bronfenbrenner, the head of his department on phages, but apparently was unhappy since Bronfenbrenner's viewpoint was that the phages were byproducts of bacterial metabolism and he expected Hershey to find evidence to support that view. At some point Delbrück invited Hershey to Nashville for a seminar and that visit developed into a real collaboration (Fischer and Lipson 1988).

Another important figure to add to the triumvirate of Delbrück, Luria, and Hershey was Tom Anderson; who had the advantage of working with an early electron microscope. Anderson was a biology student who had received a fellowship from the RCA Corporation to come and explore (and presumably exploit) the biological applications of their new electron microscope. Luria contacted him to look at bacteriophage. This was in the winter of 1941 and Luria had to get clearance to come to the RCA laboratories because of the defense-related research being carried out there. It seems amazing today, but he did get clearance. In 1943, Luria, Delbrück, and Anderson published their pictures of phage (Luria *et al.* 1943). As Bronfenbrenner is reported to have said at his first look at the pictures, "Mein Gott, they've got tails!"

In 1943, Salvador Luria along with Delbrück made a spectacular contribution; one often cited as the actual start of microbial genetics (Luria and Delbrück 1943). An *E. coli* culture incubated with phage was wiped out, except that there were rare cells resistant to infection. What was the origin of these cells? Did treatment with phage induce a sort of (inherited) immune reaction or did any culture of *E. coli* include a very few preexisting mutant cells, which were then selected by the addition of phage as the only survivors? According to his autobiography, Luria (1984) thought of the answer to the question while observing the behavior of slot machines! He wrote to Delbrück who worked out a mathematical description that also showed how to calculate (bacterial) mutation rates. Fair slot machines will produce winners, but the distribution is very uneven. Most tries are failures but a few produce jackpots. Luria reasoned that under the hypothesis of preexisting resistant colonies produced by mutation, if one started a culture in a large pot and then tested many samples taken from the same pot for the number of phage resistant cells, all the samples would give about the same result. On the other hand, if new mutations originated at random and one started a large number of small cultures (adding to the same volume as the large pot) and then tested each separate culture for the number of phage resistant cells, there would be much greater variability. Most cultures would contain no or few resistant colonies, but a few would have jackpots of many colonies. The hypothesis of induced

resistance predicted that one would get the same results from both experiments. In fact, Luria found tremendous variability with some jackpots. Delbrück realized that application of the Poisson distribution to the fraction of subcultures that gave no resistant cells would permit calculation of a mutation rate. The mutation rates so calculated were of the order of 10^{-8} – 10^{-9} per generation, similar to those found in "real" organisms, *i.e.*, those reproducing sexually with genes recognizable by their segregation pattern.

The Luria–Delbrück experiment not only accounted for the presence of resistant cells, a phenomenon that appears again and again in biology when considering any sort of toxic factor; but also indicated that bacteria had genes, factors controlling specific traits and with orthodox mutation rates. This was a new and important idea. It might be noted that Beadle, when thinking about organisms to test his way of looking for biochemical mutants, rejected bacteria because they presumably did not have genes which, given the mindset of geneticists at the time, could only be detected in sexually reproducing organisms in which recombination could be detected. Only later did Ed Tatum extend their technique to *E. coli* (Tatum 1945), which was followed by Joshua Lederberg's discovery of sexual recombination in that organism (Lederberg and Tatum 1946).

The Nobel Prize 1969

When Hershey, Luria, and Delbrück were awarded the Nobel Prize in 1969, many experts asked why it had taken the Swedish Nobel Committee so long to recognize the three pioneers. In her book *Scientific Elite: Nobel Laureates in the United States*, Harriet Zuckerman (Zuckerman 1977) wrote that "before the prize finally came to the three founding fathers in 1969, it had gone to 15 molecular biologists and biochemists for investigations built on foundations the three pioneers had laid down." (Altman 1997). The citation for Delbrück, Hershey, and Luria is "for their discoveries concerning the replication mechanism and the genetic structure of viruses." But Delbrück's independent role in these discoveries was limited, albeit critical. He took d'Herelle's methodology and cleaned it up with the support of Ellis. The relatively few articles he did write are a pleasure to read and established a very neat system, but he did not pursue his stated primary problem: the mechanism of replication (which was left to a disciple, James Watson). Furthermore, he was not much interested in the details of genetic structure. The article with Luria showing that the development of bacterial resistance to phage is due to a mutation in a gene is convincing because of Delbrück's quantitative analysis. As in much of science, there had been a precursor observation—it had been shown that isolation of bacteria with altered colony morphology predicted phage resistance—but it was the quantitative analysis by Delbrück that convinced geneticists (if not all physical chemists). All the workers involved in these discoveries are agreed that Delbrück was the catalyst who led the group of phage workers and others to these discoveries, and that his

guardianship of their work was important. I suppose the answer is that the Nobel Prizes are given by real people, and their stated reasons need not be congruent with the actual reasons. The stricture in Nobel's will that the prize be given for a recent discovery has been ignored on other occasions as well.

Somewhere around 1950, Delbrück started to lose interest in the details of the phage experiments, possibly because the results required the introduction of biochemical detail. He published only two more experimental articles on phage, one in 1951 (Weigle and Delbrück 1951), the second in 1953. The Visconti and Delbrück (1953) article reflects an earlier interest in population genetics. This was the time when it was finally recognized that DNA was the critical genetic material, and when Hershey and Chase (1952) generalized the earlier findings of Avery (Avery *et al.* 1944) by showing that DNA could carry all of the genetic information of an organism, not only some. The Avery article had shown that DNA carried the information for polysaccharide-capsule specificity in pneumococcus. The interpretation of the Hershey and Chase experiment was that DNA carried *all* the information required to generate a phage.

I believe the final blow to Delbrück's interest in phage was the elucidation by Watson and Crick of the structure of DNA. Watson was a great admirer of Delbrück (Watson 2001) (see above) and Delbrück recognized immediately, and I think generously, the magnitude of Watson and Crick's achievement. But I suppose that the discovery of the double-helical structure of DNA along with its implications for replication, mutation, and gene function must have been a heavy blow. Delbrück had supposed that replication was the one area where Niels Bohr's concept of complementarity (no matter how fuzzy) might find its realization in some nonbiochemical way. But the DNA structure immediately showed that:

Everything was built in this wonderful way. . . that really a five year old can understand what's going on—that there was so simple a trick behind it. . . (Fischer and Lipson 1988).

For the coming few decades at least, biology was going to be explained by biochemistry and Delbrück was neither interested nor qualified to contribute much to that effort. However he had not given up on the hope, as expressed in a letter to Niels Bohr in 1954 (Fischer and Lipson 1988, p.242), that he might find a system that when analyzed sufficiently "will run into a paradoxical situation analogous to that in to which classical physics ran in its attempt to analyze atomic phenomena. *This, of course, has been my ulterior motive in biology from the beginning* [my italics]." The phenomenon he thought might lead to such paradoxes was phototropism in the fungus *Phycomyces*. This fungus is sensitive to "light, gravity, stretch and some unknown stimulus by which it avoids solid objects" (Bergman *et al.* 1969). Delbrück asked "How do a few quanta or a few molecules trigger macroscopic responses? Will we find ourselves confronted with devices wholly distinct from anything now known in biology?" (Bergman *et al.* 1969). Although he and his group published many articles on the

subject, the work is deemed not to have had a great impact, possibly because nothing wholly distinct was found.

Lest the above sound too much like an argument for the biochemical approach, I would like to consider one of Delbrück's lectures, "A Physicist Looks at Biology," delivered at a meeting of the Connecticut Academy of Arts and Sciences in 1949 (and reprinted several times) (Delbrück 1949). It gives a clear statement of why he thought the biochemical approach had its own distinct limitations. Delbrück concluded his talk with the following:

He (the Physicist) may be told that the only real access of atomic physics to biology is through biochemistry. Listening to the story of modern biochemistry he might become persuaded that the cell is a sack full of enzymes acting on substrates converting them through various intermediate stages either into cell substance or into waste products. The enzymes must be situated in their proper strategic positions to perform their duties in a well regulated fashion. They in turn must be synthesized and must be brought into position by maneuvers which are not yet understood, but which, at first sight at least, do not necessarily seem to differ in nature from the rest of biochemistry. Indeed, the vista of the biochemist is one with an infinite horizon. *And yet, this program of explaining the simple through the complex smacks suspiciously of the program of explaining atoms in terms of complex mechanical models. It looks sane until the paradoxes crop up and come into sharper focus* [my italics]. In biology we are not yet at the point where we are presented with clear paradoxes and this will not happen until the analysis of the behavior of living cells has been carried into far greater detail. This analysis should be done on the living cell's own terms and the theories should be formulated without fear of contradicting molecular physics. I believe that it is in this direction that physicists will show the greatest zeal and will create a new intellectual approach to biology which would lend meaning to the ill-used term biophysics (Delbrück 1949).

Surely Delbrück's scientific trajectory was built on the premise that some inexplicable peculiarity, unique to biological systems, might turn up. To date none has, nor is any in sight. Nonetheless, I think one can still sympathize with the unease experienced by Delbrück at the biochemists' certainty that there will always be another protein to account for any biological phenomenon. The chain of proteins leading to any biological effect grows with every seminar.

Personal Views

Any reminiscence of Delbrück needs to take into account the personal characteristics that set him apart from his colleagues. I include my own anecdotes but I am sure others of my generation have their own favorites. My scientific career might have progressed differently if I had learned to play tennis reasonably well. Delbrück scoured the floor in the Kerckhoff Biology Laboratories for someone to play tennis with. I did have a racquet given to me by a New York school friend before I left for Caltech so that I would do something besides science, but I was never, even barely, competent at tennis and was not asked again to play. Another interaction

I have never forgotten is that I was so pleased with myself on my 21st birthday, just because I was 21, that I went around the laboratories announcing the fact of my new status. Delbrück looked down his nose at me (I do not see how this could be since I am convinced I was taller, but in my thoughts he is always towering) and said: "Nonsense! No one is 21!" As the years go by, that has come to make more sense. Almost all of the reminiscences of Delbrück comment on his informality and his determination not to be a typical German professor, such as his insistence on being called Max. I must confess to never having done so—he was always Dr. Delbrück (though probably not "Professor"). But then I may have been the victim of East Coast habits. I did not call my advisor (Norman Horowitz) "Norm" until after I was married (though in retrospect it is hard to see why that should have made a difference). I do think there was an increase in informality as one proceeded westward across the United States at that time, but in my case that did not extend to Delbrück.

Delbrück ran a course or a journal club and was particularly interested in the problem of differentiation and control. Not in the details, but rather in the general mechanism that underlay it. One of the physiological problems that had to be solved dealt with the maintenance of the steady state and how organisms might switch from one stable steady state to another. A. C. Burton had written an article, "The properties of the steady state compared to those of equilibrium as shown in characteristic biological behavior" (Burton 1939), which attracted his attention and he assigned it to me. Delbrück discussed the articles with his students before the class and I remember two of his comments to me: (1) "Now keep me awake," as he sunk back in his deep yellow leather arm chair, and (2) "Little steps for little feet."

Delbrück was much given to leading excursions to the beach, desert, or mountains with his laboratory group plus hangers-on and ending up with a party. I remember coming down from a hike on Mount Wilson and going to his house. My wife, Carol, was with me and that was in her early teetotal phase. She refused the punch being served. We think that Delbrück just interpreted this refusal as good taste, and he kept urging more and increasingly exquisite (alcoholic) beverages on her, unfortunately to no avail.

I think the next anecdote needs to be read in connection with Delbrück's own statement about biochemistry recorded by Harding (1978):

Harding: Since we are on the subject of chemistry, a number of people have commented on your deprecation or even hostility towards chemistry in the investigation of biological systems.

Delbrück: I think what did happen was that I was impatient with biochemistry in the sense of metabolic pathways converting one small molecule into another, and with the idea that the further pursuit of this kind of biochemistry would lead to the understanding of the nature of the gene, and its replication, and its effects. It was obvious that you could do this kind of conventional biochemistry ad infinitum, and that it was enormously bewildering in the number of compounds that they handled; you had to learn a special

language for it, but you didn't really learn what I was interested in. Also the so-called biochemical genetics, the *Neurospora* genetics, that tied together genetics and biochemistry so beautifully, only highlighted the difficulty even more. You could learn an enormous amount about actual biosynthetic chains and their interrelations, but you did not learn at all how the enzymes came about; and if you say, "One gene, one enzyme," then the question remained, how does the gene make the enzyme, and how does the gene make the gene, and this was in fact not answered at all by any of the biochemical approaches. So in a sense I think my reservations about the powers of biochemistry were appropriate and if in addition I was glib and arrogant about it, then that was just a personality defect. I mean it was, of course, true that I had never learned any chemistry or biochemistry, and just did not want to take the time to do so. In recent years I have had to learn quite a bit more, and I wish I knew more, because it's all book learning. I still haven't mastered any of the elementary procedures used in chemistry and biochemistry, but I can at least talk to those who have in a meaningful way (Harding 1978).

These interviews took place in 1978 and provide Delbrück's own evaluation of his scientific bias. They indicate why he was unable to make significant progress on the problem that interested him most, the problem of replication. His intellectual heirs, Watson and Crick, succeeded but oddly enough also without too much initial knowledge of the biochemical details or indeed much curiosity; if either Watson's report of their meeting with Chargaff (Watson 1968) or Chargaff's response (Chargaff 1963) about molecular biologists "practicing biochemistry without a license" is to be credited.

Delbrück was on my thesis committee, probably because of his friendship with Norm Horowitz, my thesis advisor. I was absolutely petrified of what he could do to me in a question period. However, my thesis title "Vitamin B6 metabolism in pH sensitive mutants of *Neurospora*" had no interest for him and he announced to me ahead of time that he was just not going to read it, implying of course that it was much too boring. I confess to a tremendous surge of relief at the time since I was unlikely to be subject to some searching questions. On the other hand, it was a little hard on a 24 year old to have his work dismissed this way. I am told, however, that I recovered my self-esteem rather quickly. Delbrück's attitude toward biochemistry governed the very tepid (and I submit mistaken) response by Delbrück and his group to the early attempts of Seymour Cohen to ask (and answer) some fundamental questions about phage growth (e.g., does the phosphorus of the phage come from the bacterium or from the medium—that is, does it represent new synthesis?) (Cohen 1948).

My final contact with Delbrück was at the very first conference on DNA repair held in Chicago in 1966, which he attended. He moderated the final general discussion (Haynes *et al.* 1966) but seemed to me much calmer—I am not even sure why he attended other than his publication in 1962 of an article on the kinetics of formation of thymine dimers (Johns *et al.* 1962).

Others have reported a standard Delbrück comment on hearing of some new experiments, “I don’t believe a word of it.” Another reported comment was “That was the worst seminar I ever heard” (Fischer and Lipson 1988). I can only speak of the time when he first came to Caltech, but it is clear that all who knew him have similar stories. He would interrupt even the most distinguished speakers time and time again with “I don’t understand.” This comment, repeated often enough, drove strong men to tears and we, as graduate students, waited to see when it would come and how it would affect each speaker. I eventually realized that it could mean two things. The first was simply that he did not understand. Most of us, I think, are hesitant enough about ourselves that we remain silent in such situations rather than appear foolish in public. Not so Delbrück. He supposed (or acted as if he supposed) that he was so smart that if he did not understand, then the matter just had not been made clear enough. A more insidious reason was that he had detected a fault in the logic and then “I don’t understand” was a challenge.

It seems to me that this behavior was, at least in part, calculated and may even have been learned on Delbrück’s part. Niels Bohr was equally aggressive in seminars (Fischer and Lipson 1988) (Bohr’s typical opening to what could be a devastating comment was reported to have been “only to understand”), and given Delbrück’s admiration for Bohr, this may have been his model for this behavior. Another possible role model was Wolfgang Pauli, with whom Delbrück worked, and who is reported to have been even rougher in seminars (Segre 2011). His acolytes generally consider this trait either charming or at least excusable as a way to get to the truth. It was certainly educational to see the different responses to the onslaught.

The most charitable, and possibly even correct, view of this behavior is that Delbrück was interested in scientific truth and that the way to get at the truth was by rigorous questioning of all assumptions. According to this interpretation, being gentle or overlooking a defect in reasoning did no one any favors. Delbrück’s view coincided with that of Harry Truman: “If you can’t stand the heat, stay out of the kitchen.” This view implies that the pursuit of science is (or should be) without regard for frail human egos.

In thinking about Delbrück’s career, it is important to remember the political events that were occurring during the years of Delbrück’s greatest productivity. In some ways his immigration to the United States was an accident. He was here on a fellowship in 1938–1939, the war broke out and he could not easily return to Germany. The Rockefeller Foundation helped him find a place at Vanderbilt University and he spent the war years in Nashville. His oral interviews indicate his ambivalence at not having gone back to Germany:

Harding: What was the psychological state of the scientists that you met at that point? So many people had emigrated during the Nazi period, and of course the whole status of Germany during the war ... was there much guilt among the scientists that you met? How did they feel about this experience of the last fifteen years?

Delbrück: It depended on who. No, I have explained earlier that if anybody feels guilty, I feel guilty of not having stayed, because I had so many friends who I admire for having stayed, and having tried to save what was to save, rescue it across this disaster. I have seen many of those; Karl Friedrich Bonhoeffer was one of them, Hans Kopfermann was another one, and many others for whom I have the greatest admiration—Von Laue, Heisenberg, too; Otto Hahn certainly (Harding 1978).

It is clear that he was no supporter of the Nazi regime. His major collaborator in the war years was Salvador Luria, who was Jewish. I think that we need to remember that he came from a distinguished intellectual family who were proud of their country and its contributions. Those were difficult times.

Some Final Thoughts

Delbrück enforced his will and intellect on a group of individuals, each of whom was a major intellectual figure in his own right. But his prejudices against the details of biochemistry led him to make mistakes. When his studies were overtaken by biochemistry, he moved on. In his later career he was much honored both in this country and in his native land. His brusqueness was proverbial but not personal. It was not always easy to take, but his impression was indelible.

Max Delbrück was not like less-assured talents who are threatened by the presence of equals. He thrived in the presence of colleagues who were (arguably) as creative (Timofeeff, Luria, Hershey, Watson) and fostered their productivity. I suggest that it was this ability to recognize and foster creativity at the highest level that persuaded the Nobel Committee to award Delbrück a share of their Prize. How could they recognize Luria and Hershey and not Delbrück?

The most creative period of Delbrück’s career came in the midst of a period of world upheaval, but that is not commented upon in any of the published biographies. Indeed, it might not have happened without the turmoil that uprooted so many scientists and brought the lucky ones to places where they could work. The Russian Revolution and the defeat of Wilhelminian Germany at the end of the first World War led to a strange (to my eyes) cooperation between Germany and Russia, and the transfer of Timofeeff to Berlin (Box 1). The rise of Hitler and the demand for Nazi orthodoxy led Delbrück to establish his “seminar in exile” and eventually to his migration to the United States. That same political turmoil led Schrödinger to Dublin—who knows whether *What is Life?* would have been written had he stayed in Graz, Austria? Salvador Luria moved from Italy to France as a result of the official anti-Semitism resulting from the Mussolini–Hitler alliance. In 1940, as the Nazis approached Paris, he made his way first to Marseilles and then to Lisbon, and a short while later was in New York working at Columbia University and connecting with Delbrück. (Writing about this in February 2017, this feat of immigration seems almost miraculous.) Over much of this nascent stage of molecular biology hovers the guiding hand of the Rockefeller Foundation, helping Delbrück leave Germany and finding him support first at

Caltech and then at Vanderbilt, helping Luria by finding him support (based on a laconic recommendation from Fermi) for work at Columbia, all without formal applications, Committee review, and other bureaucratic devices. It all sounds too improbable but is perhaps an example from real life of the kind of jackpot phenomenon that Luria recognized and that Delbrück, with the eye of a physicist, managed to quantitate.

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