Delbrück's Publications in Biology

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Max Delbrück (1906–1981) was a German theoretical physicist who, stimulated by the speculations of Niels Bohr on the nature of life, developed an abiding interest in biology. After moving to the United States in 1937 he went on to become one of the most influential biologists of his time. The aim of this article is to survey a set of Delbrück's publications in biology. Most of them fall in the area of molecular biology, the field that he was instrumental in founding. The selection is subjective but not unrepresentative. Matters of related interest are highlighted in the boxes; these include a few items of historical and biographical information and can be read independently. The article ends with an overview.

Molecular Biology

On the Nature of Gene Mutation and Gene Structure (1935). Ever since the rediscovery of Mendel's laws of heredity in 1900, the science of genetics had flourished inspite of the fact that no one knew exactly what genes were. There were hints: genes were associated with chromosomes, chromosomes were rich in nucleic acid, and nucleic acid appeared capable of transforming non-virulent bacteria into virulent forms. Muller had shown in 1928 that X-rays could cause mutations, meaning hereditary changes in genes. But how did the X-rays do this? An answer was provided in this work, carried out in Berlin by Timoféef-Ressovsky, Zimmer and Delbrück. Delbrück provided the theory. It was his first publication in biology and was announced as 'representing a cooperation between genetics and physics'. The experimental results, in particular the manner in which the outcome depended on the dose of the radiation, were explained by a simple hypothesis.

The hypothesis, which came to be called 'target theory', was that the effect of X-rays and other forms of ionising radiation was concentrated within a very tiny volume inside the cell. Indeed, the volume was so small, typically about 10^{-17}cc, that it was of no more than molecular dimensions. In short, the target of the X-rays, genes, could be molecules. The fact that genes remained stable over many generations of reproduction, even when the cells in which they were housed were exposed to high temperatures, was pointed out as a puzzle that demanded a solution. Delbrück offered one by saying that genes were stable because they were in quantum mechanical stable states. A mutation was analogous to a quantum transition and carried a gene from one stable state to another.

Today the 'three man work', as it became popularly known (multiply authored publications were unusual then), is primarily of historical interest. The way in which it treats the concepts of genes and mutations has long disappeared. One knows that genes remain unchanged through generations because there are enzymes that safeguard the fidelity of the copying process. Uncorrected mistakes in copying, and insertions of movable genetic elements, are the main causes of mutations. Also, the hope embodied in the work, that the methods of radiation genetics might help in unravelling the chemical nature of the gene, remained unfulfilled. Nevertheless, the work was momentous in more than one sense. By endowing genes with physical dimensions, it suggested that they were things that one could get hold of, so to speak. It was the first occasion on which 'hard' physics had been applied to solve a fundamental problem in genetics (it may also have been the last). And not least, the popularization of this piece of research by Erwin Schrödinger in his book '*What is Life?*' (Cambridge University Press, 1944) influenced many physicists to move into biology, though not necessarily with the same motives as Delbrück (see *Box* 1).

An interesting but mostly forgotten spinoff of target theory was a calculation by Timoféef-Ressovsky and Delbrück of the rate at which cosmic rays could cause mutations. The idea – possibly based on a confusion between mutation rates and evolutionary

Box 1

Delbrück always thought of himself as a physicist on loan to biology; it might even be said, on loan from Niels Bohr. He states as the prime motive behind his move from physics 'Bohr's suggestion of a complementarity situation in biology, analogous to that in physics'. The motive was phrased differently by Schrödinger in *What is Life?*. He called it the search for 'other laws of physics' that, in addition to those already known, might apply to living matter. At least in an operational sense, the motive does not appear to have lasted very long though towards the end of his life Delbrück wondered whether an explanation of the mind might not require radically new ways of thinking. He found biology both fascinating and depressing, depressing because the analysis of biological phenomena seemed to have stalled in a semi-descriptive state without noticeably progressing towards a radical physical explanation. Not least among the varied ways in which Delbrück influenced biology was that thanks to him – and so, thanks to Bohr – many physicists entered the field. This was partly due to his direct influence and partly indirectly, because of the manner in which the work he did with Timoféef-Ressovsky and Zimmer was popularised by Schrödinger in his book. Schrödinger made Delbrück's role, and biology itself, appear fashionable to a great many physicists and thereby instigated the birth of molecular biology. However, his understanding of biology was out of date even then, and the reason for the book's fame has puzzled many. Perhaps Francis Crick's explanation comes closest to the truth: "... it suggested that biological problems could be thought about in physical terms – and thus it gave the impression that exciting things in this field were not far off". S Sarkar (*Bioscience*, Vol.41, No.9, 631–634, 1991) says that the book deserves to be remembered because in it Schrödinger clearly enunciated the hypothesis of a genetic *code*. It is unlikely that the original publication by Timoféef-Ressovsky, Zimmer and Delbrück would have been read, or if read, understood by many biologists. Salvador Luria, who was trained in medicine, was at first sight a prominent exception among those who actually read the paper. And he too immediately acquired a vocation, in his case of working towards 'open[ing] the way to the Holy Grail of biophysics'. But this is the exception that proves the rule. Luria's getting to see the paper can be traced to a series of events, some of them accidental, originating from his close association with physicists when he was a student in Rome (especially with Ugo Fano and through him, with the group around Enrico Fermi).

It is worth noting, by the way, that anyone who talked about 'the problem of life' – whatever *that* means – in the light of the complementarity principle would sound ridiculous today. One might say that the problem has disappeared. This is an interesting example of how the advance of science sometimes disposes of what seem to be pressing issues; it simply bypasses them.

change – was to see whether they might have been instrumental in the origin of species. Disappointingly, the outcome was that just one tenth of one percent of the spontaneous mutation rate could be ascribed to cosmic rays (*Nature*, Vol. 137, 358–359, 1936).

The Growth of Bacteriophage (1936). Sorry at having missed a seminar on bacterial viruses by Emory Ellis in Caltech (where he was a visiting Rockefeller Fellow), Delbrück dropped in later on Ellis to find out what these viruses were all about. The upshot was that he found his life's work. Ellis and Delbrück begin the paper with the arresting statement "Certain large protein molecules (viruses) possess the property of multiplying within living organisms". They go on to characterise the process as one that "is at once so foreign to chemistry and so fundamental to biology". The point under discussion is the manner in which a bacterial virus, or bacteriophage (or simply phage), grows; in this work they established the growth of phage under a well-defined set of cultural conditions. The outcome was a piece of original research; also, it was an improvement on the unsatisfactory state in which the earlier workers Krueger and Northrop had left the problem. It marks the beginning of the subsequent career of bacteriophage as, one might say, the hydrogen atom of molecular biology. Note the implied belief that viruses were proteins. It needed many years before it was realised that they were not made up of proteins alone and that their hereditary properties resided in the nucleic acids they contained.

This publication is notable for its approach to experimental method, for its spare elegance – visible already in the first two sentences – and finally, for three observations. The first, in confirmation of a finding by d'Herelle, was that the phage lay hidden inside the bacterium until, after about 30 minutes, it was suddenly liberated in a burst. The implication was that growth occurred in a single step and not continuously. Each burst was made up of an average of 70 progeny. Secondly, bacteria that adsorbed several phage particles behaved as if only one of them had been effective in sustaining the infection. This was true in terms of the burst size, the number of phage particles liberated from a single infected bacterium, and the latency, the period between adsorption and bursting. And finally, the burst size resulting from infection by a single virus varied enormously from one experiment to the next. As few as 5 to as many as 190 phages could be released in a burst: "The cause of the great

Box 2

Delbrück was not the first well-known physicist to have drawn the correct conclusions from the behaviour of bacteriophages. Phages had been first reported by F W Twort in 1915 as agents that could continue to infect and kill bacteria even after being passed through the finest porcelain filters. Twort ended his account by stating that financial considerations prevented him from carrying the research any further. F d'Herelle, who was then at the Pasteur Institute in Paris but later worked in many places (including India), succeeded in doing so. The basic facts concerning phage infection were discovered by d'Herelle. In particular, he observed that the end point of an infective cycle was reached when the bacterium burst open or lysed and released a large number of infective units. He immediately deduced that the units must be particulate. To his evident delight, the very same inference struck a distinguished colleague at the University of Leiden, 'Professor Einstein, [who] ... told me that, as a physicist, he would consider this experiment as demonstrating the discontinuity of the bacteriophage'.

fluctuation in burst size is therefore still obscure". Clearing up the obscurity was to occupy Delbrück for years to come (see *Box* 2).

Statistical Fluctuations in Autocatalytic Reactions **(1940).** Here Delbrück carries out a theoretical analysis of the spectrum of fluctuations that can occur in chemical reactions in which the product, initially at a very low level, catalyses its own formation. Examples of such processes are the production of a protein-cleaving enzyme from a precursor protein and the increase in the number of bacteriophages arising after infection by a single phage. The average outcome of the process can be predicted accurately, this being the usual law of exponential growth. But that average is more or less useless for making predictions. The reason is simple. Because of the positive feedback inherent in the process, individual experiments vary enormously in their outcomes; one does not get the familiar bell-shaped distribution in the number of product molecules. If there is just one molecule at the start, the shape of the distribution is exponential or 'long-tailed'. Similarly, if the time taken for the product, or number, to attain a certain level is measured, that too will show large fluctuations. In relation to the work discussed previously, this means that the huge variation in bacteriophage burst sizes, far from being an experimental anomaly, is just what ought to be expected.

One can draw a more general inference. Suppose that one or more autocatalytic processes are important for determining the properties of a cell or organism. If so, even individuals of the same hereditary constitution, meaning those that are genetically identical, can differ significantly in respect of their traits. For example, the swimming responses of bacteria that are attracted by chemicals display a large degree of variability from one bacterium to another. A question of interest is whether this sort of variation can have any evolutionary consequence. (The immediate answer would be no, because the basis of the variation is not genetic; that is, specific variants do not have progeny that exhibit the same kind of variation. But recent research shows that non-genetic variation may have indirect evolutionary effects.)

Mutations of Bacteria from Virus Sensitivity to Virus Resistance **(1943).** Gunther Stent, a close associate of Delbrück, dates the birth of molecular biology to this publication. The experimental part was contributed by Luria and the theory by Delbrück. The problem that it attacked was one that had plagued biology since the days of Darwin. Where did the heritable differences between individuals, on which natural selection was supposed to act, come from? Answers were offered by two rival schools. One, associated with the name of Darwin's predecessor Lamarck, held that just like physiological adaptations (for example, a strengthening of the muscles caused by exercise), hereditary variations too were initially responses to specific environments. The other, 'Darwinian', view was that elementary variations, mutations, occurred spontaneously and at random. They bore no relation to whether the environment favoured them or not. If the result of a mutation was helpful, the descendants of an individual that happened to carry it would increase in number. If the result was harmful, the descendants would eventually be weeded out.

Luria designed an elegant experiment to distinguish between these two hypotheses. He picked the case of a bacterium that, after mutation, became resistant to a previously virulent phage. He realised that if the mutations were acquired as a result of exposing a growing culture of bacteria to phage, the number of resistant individuals would vary very little from one experiment to the next. In fact, they would vary in the same haphazard manner as the number of bacteria that would be found when repeated samples of the same volume were drawn from a culture. The observed number would fluctuate slightly about the average: it would be above the average sometimes and equally often, at other times, below the average. On the other hand, if a mutation could occur even before the bacterium was confronted with phage, the number of resistant bacteria would depend on when – in other words, on how long ago in the past – the mutation had occurred. But then the number of resistant individuals would show very large fluctuations in the positive direction. The reason is that the total number of bacteria in the culture, which is growing all the while, keeps increasing exponentially.

For example, by the time that the test was carried out, a bacterium that had mutated 10 generations ago would have had 2^{10} or about 1,000 progeny. However, a bacterium that had mutated two generations ago would have given rise to just 2^2 or 4 progeny. Early mutations are on the whole less common, because the number of bacteria available to mutate is small in the beginning. Later, as growth proceeds, a mutation becomes more likely. What this means is that corresponding to those rare instances in which the mutant came into being long ago, at the time of the test one would find a huge number of resistant progeny. Luria carried out the experiment and observed large fluctuations in the outcome exactly as expected on the assumption of spontaneous mutations. Not being mathematically inclined, he remained unsure of the soundness of his conclusions. Delbrück was appealed to; in reply, a postcard arrived saying "I believe you have something important. I am working out the mathematical theory". The theory duly followed a few days later. It did not stop at deriving a formula for the distribution of mutants to be expected on the basis of the two rival hypotheses. There was a bonus: the fluctuations could be used for estimating the average value of the spontaneous mutation rate and its variance. However, difficulties with the mathematics prevented Delbrück from obtaining the distribution itself. Many attempts have been made to tackle this problem since then, including one by J B S Haldane.

The importance of this experiment, which came to be known as the fluctuation test, cannot be overestimated. By showing that a mutation rate could be measured, it made it plausible that bacteria had genes, an issue that was heatedly disputed at the time. Next, by demonstrating that the spectrum of variations about an average quantity was crucial, rather than the average itself, it introduced an unprecedented degree of quantitative rigour into the field of experimental genetics.

The Burst Size Distribution in the Growth of Bacterial Viruses (Bacteriophages) **(1945).** This contains a more careful examination of the high degree of variability in the number of phage particles released after an infective cycle and confirms the basic finding. Delbrück points out that the theory of autocatalytic reactions, worked out by him previously (1940), predicts exactly such large fluctuations in the outcome. He leaves it at that and does not attempt to make a detailed comparison between theory and experiment. But he draws attention yet again to two features of the phenomenon of bursting. One, the period between infection to lysis does not depend on whether a bacterium is infected with one or many particles. And two, bacteria that are multiply infected by the same phage yield the same distribution of burst sizes as singly infected bacteria. There seems to be a form of 'self-interference' at work here, with only one of the many infecting phages actually contributing progeny.

Induced Mutations in Bacterial Viruses (1946). This work by Delbrück and Bailey set the seal on the recognition of bacteriophages, and by extension all viruses, as a form of life: they were shown to be capable of genetic exchange (recombination), the essential feature of sexual reproduction. The paper reads like a detective story with a twist at the end, the twist emerging through a serendipitous discovery. Delbrück and Luria had found previously that when a bacterium was simultaneously infected by two different kinds of phages, after lysis it yielded only one of the two infecting types. Clearly, this 'mutual exclusion' resembled self-interference. Was self-interference too a form of mutual exclusion? To get an answer, it was necessary to devise a means for distinguishing between the progeny of essentially identical phages: "One is thus naturally led to the study of mutual exclusion between a virus and one of its mutants".

The findings were in one sense a disappointment; they showed that mutual exclusion did not hold after all. Nearly every infected bacterium yielded virus particles of both types. The earlier results were seen to be an artefact caused by the lack of a sufficient number of markers to enable different infecting phages to be told apart. A slight modification of the set-up led to a completely unexpected outcome. The modification was to use, not just a phage and its mutant, but pairs of closely related and more easily distinguishable phages instead. When this was done, it turned out that a burst yielded viruses of the two original types along with others which exhibited traits of both. For example, a bacterium that was simultaneously infected by two phages of types T2r– and T4r+ gave rise, upon lysis, not only to the original types T2r– and T4r+, but also to T2r+ and T4r– (T stands for 'type', 2 and 4 for two strains, and r+ and r– for whether a lysed bacterial colony has a clear or mottled appearance on a plate). On their own, all these types bred true.

The most straightforward resolution of the puzzle was the one implicit in the title of the paper: one of the infecting phages had induced a mutation in the other. A more exciting inference was drawn with some circumspection: "A discussion of the possible theoretical interpretations of these findings does not seem warranted at this point, since our studies are far from complete. Perhaps one might dispute the propriety of calling the observed changes 'induced mutations'. In some respects they look like transfers, or even exchanges, of genetic materials". A similar study, leading to the independent discovery of recombination in viruses, had been made slightly earlier by A D Hershey, with whom Delbrück and Luria were always in close touch.

Biology and Physics, Sensory Biology and other Areas

A physicist looks at biology **(1949) and *A physicist's renewed look at biology: twenty years later*** (1970) should be read together. Both are texts of lectures. They bracket the beginning and the end of the first great phase in molecular biology and provide insights into the mind of someone who shaped the field in between. The first talk shows how much of a physicist, how much of a disciple of Bohr, Delbrück still was in 1949. Four years earlier, he had reviewed *'What is Life?'* in The Quarterly Review of Biology (Vol.20, pp.372-374). The review made no mention of his own central role in the book and, at best, can be called cool (the title – "What is Life? And What is Truth?" – is a pointer). He did not take kindly to the assertion that "... contrary to the opinion upheld in some quarters, quantum indeterminacy plays no biologically relevant role [in the cell]", an obvious reference on Schrödinger's part to Bohr's views. In 1949 Delbrück continued to be sufficiently convinced of the general validity of Bohr's principle of complementarity to wonder, wistfully, whether a similar principle might not underlie the mystery of life. In other words, might the attempt to define ever more precisely some aspect of the living state make others recede beyond our reach? This possibility had been raised by Bohr during a public lecture that he gave in 1932 in Copenhagen (on an improbable-sounding occasion, the opening meeting of the International Congress on Light Therapy). The lecture gripped Delbrück, who was then a physicist visiting Bohr's institute, and it was decisive in inducing him to turn to biology. One reason why he persisted with the notion of complementarity for many years thereafter was that he was bothered by the seemingly tautological nature of the only unifying principle that biology contained, the theory of evolution by natural selection. All the same, Delbrück's preoccupation with this issue did not carry over into an attempt to 'do physics in biology'.

By 1970 Delbrück no longer feels compelled to appeal to physics as the ultimate arbiter of biology, going so far as to say, 'Molecular genetics, our latest wonder, has taught us to spell out the connectivity of the tree of life in such palpable detail that we may say in plain words, "The riddle of life has been solved" '. He acknowledges that the focus of interest among those wanting to reduce the phenomena of life to cellular and sub-cellular levels has shifted from molecular biology to neurobiology. Complementarity is hardly a bugbear any more but he sees a new problem looming ahead, the problem that "the eagerness with which we plunge into neurobiology overlooks an essential limitation – the *a priori* aspect of the concept of truth". What he seems to be saying is that any system which we use to assess the validity of our discoveries (in the ultimate analysis, language) must itself be subject to validation. But how is this to be done without getting trapped in a self-referential loop? According to Delbrück, the second step of validation is carried out implicitly on the basis of principles that "cannot be conceived as an emergent property [of nerve nets], of a biological evolution". In other words, we know certain things *a priori* all right, but that knowledge is not a consequence of our status as products of evolution. Considering the eagerness with which Delbrück embraced Konrad Lorenz's hypothesis of how *a priori* concepts are no more than a form of phylogenetic or evolutionary learning, internalisations of experience gained during the course of evolution, this attitude is difficult to understand (see *Box* 3).

Around the 1950s Delbrück started drifting away from an active involvement in molecular biology; as he put it, the field was in good hands. His published work thereafter continued to cover the wide range of his intellectual interests.

Adam and Delbrück (1968) carried out an interesting theoretical calculation of the possible consequences of reducing the number of dimensions in biological diffusion processes. They were able to demonstrate that a huge advantage can be gained by a chemical sensor if it first binds the species to be sensed at a site removed from the receptive site proper, and then allows the chemical to diffuse on its surface until it reaches the receptor. The underlying principle is a consequence of the statistical theory of random

Box 3

The philosopher Immanuel Kant drew attention to the fact that the brain interprets sensory data in terms of a certain framework of concepts – 'categories' – that it possesses from birth. He termed these *a priori* concepts. The brain does not need experience in order to acquire the categories. For example, babies are born with the notion of depth; they instinctively recoil from the edges of surfaces on which they are sitting. The ethologist Konrad Lorenz is generally credited with being the first to assert that this is because we are the products of evolution by natural selection. Thereby Lorenz is thought to have founded the field of evolutionary epistemology, a theory of knowledge based on evolutionary principles. Delbrück believed so too. It turns out that the 19th century physicist Ludwig Boltzmann had anticipated Lorenz. As he put it: "How will one now treat what one calls, in logic, the laws governing thinking [the formal principles of reasoning]? Well, in the Darwinian sense, these laws of thought will be [regarded as] nothing other than inherited habits of thought ... since, if we did not bring these laws of thought with us [as part of our heredity], all knowing would cease and the [process of] perception would be without any context." Lorenz himself mentions Boltzmann's claim to priority in his book '*The Waning of Humanness*' (Unwin Paperbacks, London, 1989).

walks. A random walk in 1 or 2 dimensions is spatially restricted in a sense that a random walk in 3 dimensions is not, and this makes the strategy outlined above an efficient one. An unexpected application of the theory has emerged subsequently. It concerns the problem encountered by a protein that is present at a very low concentration inside the cell to home in on, and bind to, a small stretch of DNA within the chromosome. In at least one case it has been shown that what the protein does is to first diffuse in three dimensions and bind weakly to the chromosome wherever it happens to hit it. Thereafter the protein diffuses *along* the chromosome – in one dimension – until it finds the correct target.

In another theoretical paper Saffman and Delbrück (1975) calculate an approximate solution to the mathematically intricate problem of surface diffusion in an anisotropic environment. The example in their minds is the 2-dimensional membrane of living cells. The conclusion is that relative to diffusion in an isotropic medium, translational diffusion is faster than rotational diffusion by a factor of about 4. To put it simply, a protein molecule tends to maintain its polarity in the plane of the membrane to a greater extent than it would if the cell membrane had been much wider, and therefore more isotropic, than it is.

Delbrück's dominant interest after his molecular biology days was the study of the fungus *Phycomyces*. During its growth phase the spore-containing body or sporangiophore formed by this fungus displays a variety of behaviours, primarily movements. In many respects these appear to be primitive versions of the motor movements exhibited by higher organisms in response to various sensory stimuli. His hope was that *Phycomyces*, even though it lacked any semblance of a nervous system, might become the bacteriophage of sensory biology and provide insights into how sensory information is processed in higher organisms. It is not unfair to say that the hope was largely belied. Innovations in technique and experimental design made it possible for many of the relevant questions to be posed directly at the level of groups of nerve cells if not whole organisms. The 1975 paper by Cohen and others provides a revealing example of the systematic approach he adopted in his attempt to understand the behaviour of *Phycomyces*. The 'avoidance response', in which the growing sporangiophore moves away from nearby objects, remains a puzzle to this day.

How Aristotle discovered DNA (1976) is the text of a part-serious, part-facetious talk given at a symposium to honour the physicist V F Weisskopf. Delbrück offers for our consideration two ideas discussed by Aristotle in *De Partibus Animalium*. Firstly, Aristotle talks about heredity and how the expression of hereditary traits can sometimes skip generations; secondly, he suggests an analogy between the generation of a living animal and the making of a bed. In doing so he draws the distinction between 'the carpenter and the wood'. Both are essential for making a bed but their contributions are qualitatively different. Delbrück's point is that when Aristotle discussed heredity he noted the contrast between a 'mover', that remained unmoved itself, and the 'moved'. Or, one might say with some licence, to the fundamental distinction (as we know today) that exists between the information carrier and the information carried. He adds that as a philosophy Aristotle's approach ran counter to the (future) Newtonian principle of a symmetry between action and reaction. In Delbrück's opinion, the overwhelming success of the Newtonian method had blinded people to Aristotle's significance as a biologist.

In ***Was Bose–Einstein Statistics Arrived at by Serendipity?*** **(1980)** Delbrück concurs with the opinion of most physicists that S N Bose's derivation of his famous statistical formula looks like a conjurer's trick. And like the others, he too is bothered by the unprecedented method invented by Bose for counting the number of ways in which photons can be distributed so as to occupy a set of energy levels. The salient feature of Bose's technique was that he counted states, not photons, a step which elicits from Delbrück the comment "At this point Bose's mind goes foggy". (One can draw an analogy. Consider the problem of enumerating the number of ways in which a given number of children can be put into a certain number of rooms. The natural method would be to decide in which room the first child can be put, then the second child, etc.. Instead, Bose asks, How many rooms contain no children? How many contain one child? and so on.) The piece is worth reading for the nuggets of history and opinion that it contains. Also, it conveys a marvellous picture of the whirl in which wave mechanics developed.

The justification for its inclusion here is different. At the end of the essay Delbrück expresses his dismay at the price to be paid in exchange for using quantum mechanics – the abandonment of truths gained by practical experience, the abandonment of common sense: "our intuitive understanding of the events in our environment balks at this demand of [quantum mechanics]". The difficulty stems from the fact that many of our intuitions are based on a deeply internalised notion of objective reality, and from birth at that – we possess them *a priori*. But how can that be? The explanation, according to Lorenz, was that their existence was '*a priori* for the individual, but *a posteriori* for evolution' (see *Box* 3). At its deepest, says Delbrück, the reason why we find it difficult to reconcile the validity of quantum mechanics with our intuitive beliefs is because of a situation that Bohr kept emphasising: "we (the human mind and experimenter) play a dual role as 'actor' and 'onlooker' in the drama of existence". He ends by asking whether, "armed with new insights on the origin and evolution of life, on the structure and evolution of our cognitive capabilities", we should not try to "take a new look at this question and perhaps formulate it in somewhat less of a defeatist style". The theme of mind recurs in the book *Mind From Matter?*[1] a somewhat unevenly edited and posthumously published text of the lecture notes for a course on evolutionary epistemology given by Delbrück in 1974–1975.

[1] Reviewed in this issue.

Overview and Concluding Remarks

The molecular biology revolution occurred with astonishing rapidity. It took no more than a decade or two, or less than one human generation, for classical, path-breaking experiments to be duplicated in high school and college laboratories. This makes it easy to adopt the vantage point of the present and, from it, underestimate the significance of what the pioneers did and the difficulties that they faced. There is another mistake that historians warn us about, the temptation to read history as a sequence of deterministic events through which a single causal thread runs. In studying the past, especially a heroic past, one is tempted to see prophecies of the future embedded in it. This particular pitfall is not a serious one in the present instance. To a large degree, the major advances in molecular biology have come about by way of surprises.

In one sense 'molecular biology' stands for biological phenomena reduced to the level of molecules; in another sense it means the study of the properties of DNA, RNA and proteins, the special molecules that are found in living beings. According to the historian H F Judson, molecular biology arose as a synthesis of five distinct disciplines: genetics, microbiology, biochemistry, physical chemistry and X-ray crystallography. Oddly enough, though Max Delbrück epitomised what molecular biology stood for more than anyone else, his contributions cannot easily be identified as falling within any of these areas (except, perhaps, microbiology to some extent). His one known attempt to learn formal genetics was not a success and he did not care much for biochemistry (see *Box* 4). Linus Pauling, the preeminent physical chemist of the day, may have been too close to make Delbrück think of becoming one himself. And he cannot be called a biophysicist either – though one must concede that to this day 'biophysics' has remained a name without a defining theme.

Delbrück was the person primarily responsible for ensuring that bacteriophage was used as a tool for research. The annual phage courses organised by him made the Cold Spring Harbor Laboratory in New York the Mecca of molecular biology. But the work with Luria on the fluctuation test – which established the nature of mutations in bacteria – remains his best-remembered contribution to biology. Ironically, the logic used in alluding to the fluctuation test is often of doubtful validity. The finding was that bacteria that were susceptible to a lethal viral infection mutated spontaneously and thereby became resistant to the virus. This inference was generalised beyond its immediate scope and assumed to hold good universally. In other words, it

Box 4

Delbrück was dubious about using biochemistry to address the problems of biology, adducing as a reason his feeling that though 'the vista of the biochemist is one with an infinite horizon', the biochemical approach 'smacks suspiciously of the program of explaining atoms in terms of complex mechanical models'. Just as the hope of usefully applying the logical strength and formal austerity of theoretical physics acted as a strong motivation for physicists to get into molecular biology, the empiricism, overwhelming detail and general 'messiness' of biochemistry appears to have persuaded some who were already working in molecular biology not to become biochemists. In one place Delbrück's associate Seymour Benzer says, presumably when the implication of what he is doing dawns on him, 'I had almost gone down the biochemical drain'. Considering how deeply the methods of biochemistry permeate all of biology today, it is a wonder that they were held at bay for so long, first by classical genetics and then, approximately until the breaking of the genetic code, by molecular biology itself. The irony is that the very success of molecular biology made it difficult for the more reductionist-minded to avoid becoming biochemists. As molecular biology turned increasingly biochemical, many of those who were not comfortable with the trend turned to neurobiology.

was taken for granted, from insufficient evidence, that all mutations, whether in bacteria or higher organisms, occurred randomly – meaning in a direction that was not influenced by environmental cues; a conclusion that has since been amply buttressed, of course. Thus, on the basis of a finding limited to microbiology – "the last stronghold of Lamarckism" according to Luria – the fluctuation test was turned into a general vindication of Darwinian theory over Lamarckian conjecture.

The reasons for Delbrück's fame are not easy to decipher. Significant as his publications are, none of them contains a path-breaking finding that can be attributed solely to him; there is no famous discovery associated with Delbrück's name. By present standards he did not publish all that much, and what he did publish came out in journals with a varied reputation. Indeed, of his very first work in biology, the one that made him known outside the charmed circle of theoretical physicists of which he formed a part, he said – referring to the journal in which it came out – that it got a first-class state funeral. (Nevertheless, its impact was considerable. Clearly, in those days what you published mattered more than where you published it.) An assessment of his stature in biology made solely on the basis of his publications would be mistaken. His influence had much to do with the rigour, integrity and discernment, not to speak of a style, that characterised his approach to science. He did not merely try to make sense of the facts as they were available, but instead, being convinced of what the important questions were, set out to search for, and if necessary build, a system that was suited to answer them. He was uncompromising in discriminating between the trivial and the important. But there was an element of abrasiveness as well; and that too had an influence, on the whole an unfortunate one (see *Box* 5).

According to Stent, his role in the birth of molecular biology was seminal yet elusive. In certain respects it was similar to the role played by Bohr in making his disciples, of whom Delbrück was one, come to terms with quantum mechanics. Among contemporaries, his habit of relentless questioning has been described as

Box 5

Towards the culmination of the first phase of molecular biology, approximately 30 years ago, one aspect of the long-lasting quest for the 'secret of life' ended with the deciphering of the genetic code. Since then, it has become increasingly obvious that life is yet another property of matter. The accompanying message has been that *in principle*, the problem of understanding living systems can be reduced to sets of problems in physics and chemistry. This was a major triumph of human understanding. But it extracted a price. The spectacular success of molecular biology led some molecular biologists to adopt an aggressively hostile stance towards all biology that was not 'molecular'. Old fashioned botany and zoology – not to mention old-fashioned botanists and zoologists – were looked down upon, even derided. In his autobiography E O Wilson gives a vivid impression of what it felt like to be at the receiving end (*Naturalist:* Warner Books, New York, 1995). He uses the metaphors of conquest and cultural domination to describe what transpired and refers to this phase of biology as 'The Molecular Wars'.

On top of that, almost the entire emphasis of the molecular biology approach was on what might be called the internal world. The fact that plants and animals functioned in an environment, that there was an external world, was lost sight of. In consequence, bright young men and women started to think that certain areas of biology – among them natural history, morphology and systematics – were unfashionable. Starved of fresh inputs, the level of activity in these fields began to decline. The price is being paid today. We live at a time when fear of environmental destruction runs deep. Also, evolutionary questions dominate research in all of biology. Enormous amounts of data are being churned out, not least with the help of molecular biological techniques. There is an urgent need for making sense of all the data, but that requires 'a feeling for the organism'. Sadly, the very people whose help has become essential for addressing these concerns are in short supply. The making of this situation is in no small measure due to the manner in which molecular biology dominated biological thinking for so long.

Socratic, and a pithy description of Socrates' attributes may be a good way to end. " ... his mind, though not creative, was exceptionally clear, critical and eager. He tolerated no pretence; and since his will was as strong as his convictions, his conduct was as logical as his thinking."

Suggested Reading

H F Judson has written an excellent account of the rise of molecular biology in *The Eighth Day of Creation* (Jonathan Cape, London, 1979). *Phage and the Origins of Molecular Biology* (J Cairns, G S Stent and J D Watson, eds., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1966), from which I have also quoted, is a useful work of reference pertaining to Delbrück's work and influence. Max Delbrück, 1906–1981 (G S Stent,

Genetics 101: 1–16, 1982) is an insightful obituary. The description of Socrates is from H Tredennick's Introduction to Plato's *The Last Days of Socrates* (Penguin Classics, U.K., 1975). The following is the list of Delbrück's publications discussed in the text. In the case of the very first one I was unable to get hold of the original and had to depend entirely on secondary sources.

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[13] M Delbrück, How Aristotle Discovered DNA, in K Huang (ed.), *Physics and Our World: A Symposium in Honor of Victor F Weisskopf* (American Institute of Physics, New York, 1976).

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