That Was the Molecular Biology That Was

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The first attempts to write the history of a scientific discipline often presage its imminent senescence. And so the appearance a year ago of the collection of autobiographical essays entitled, *Phage and the Origins of Molecular Biology* (*1*) is probably symptomatic of the approaching decline of molecular biology, only yesterday an avant-garde but today definitely a workaday field. The essays in this book were written by some 30-odd actual or former bacteriophage workers who, at one time or another over the past 30 years, had been associated with Max Delbrück, to whom this book is dedicated on his 60th birthday. My decision to continue the historiographic celebration of the decline of molecular biology was prompted by reading some, in the main very friendly, reviews of this book. For these reviews revealed to me that, though the names of its leading figures and their achievements are now known to most schoolboys, the genesis and nature of molecular biology, and particularly its philosophical origins, deserve more extensive discussion.

Among these reviews was one written by John C. Kendrew (*2*), who offers some deep insights into the nature of our field. Kendrew, supremely legitimated for this reviewing assignment as editor-in-chief of the *Journal of Molecular Biology*, begins his appreciation of *Phage and the Origins of Molecular Biology* by asking what molecular biology actually *is*. He points out that he is aware of the biochemists' view that so-called molecular biology is naught but the unlicensed practice of biochemistry. But, Kendrew writes, "molecular biologists themselves are by no means unanimous about the nature of their subject. To anyone brought up in the British school of molecular biology, as the present reviewer was, it is a little odd to find in nearly every contribution to this book the explicit or implicit assumption that molecular biology had its only real beginnings with the phage group, and that the central theme of the subject is biological information." This emphasis on information, particularly on genetics, is odd because W. T. Astbury, one of the originators and first propagandizers of the term *molecular biology*, defined it as follows (*3*):

> It [molecular biology] is concerned particularly with the *forms* of biological molecules and with the evolution, exploitation and ramification of these forms in the ascent to higher and higher levels of organization. Molecular biology is predominantly three-dimensional and structural—which does not mean, however, that it is merely a refinement of morphology. It must at the same time inquire into genesis and function.

Thus, Astbury's definition does not even mention biological information or genetics. But, by the time the term *molecular biology* had become popular, in the 1950's, and many a research institute and university department had been organized under that name [though, as Astbury wistfully reported later (*4*), never his own], its meaning had evidently widened to include also molecular genetics. And, as Kendrew points out, though molecular geneticists are interested in such matters as the DNA double helix, their interest in the structure is not "geometrical so much as topological: the one-dimensional [rather than three-dimensional] nature of the information store and the role of the specific pairs of nitrogenous bases in replication." Thus there have existed, and there still exist, two schools of molecular biologists—structurists and informationists, three-dimensionists and one-dimensionists, who, "although they listen politely enough to each other's seminars, have less to say to each other in terms of real intellectual communication than one might expect."

The Structural School

The best explanation for why both schools ultimately came around to adopting the neologism *molecular biology* seems to have been offered by Francis Crick (*5*):

> I myself was forced to call myself a molecular biologist because when inquiring clergymen asked me what I did, I got tired of explaining that I was a mixture of crystallographer, biophysicist, biochemist, and geneticist, an explanation which in any case they found too hard to grasp.

Thus there is probably little point in now arguing about any precise a posteriori definition of molecular biology. But, its schism into two main schools, to which Kendrew drew attention in his excellent review, *is* worth reflecting on. It is my opinion that this schism was immanent in a profound difference in attitude of the founders of the two schools toward the relation of physics to biology, a difference which was to engender also a highly differentiated attitude towards biochemistry. Not only did the one-dimensional, or informational, school have nothing in common with biochemistry but its early practitioners were positively hostile to biochemistry. The three-dimensional or structural school, however, *can* be properly thought of as a branch of biochemistry, whose basic working assumptions concerning biology it shared. This structural or, according to Kendrew, British, school, corresponding to Astbury's definition of molecular biology in the strict sense, can be considered to have descended from W. H. Bragg and W. L. Bragg. The Braggs, father and son, had invented x-ray crystallography in 1912 and then founded a school of crystallographers that made Britain the home of molecular structure. As success came in the determination of the structure of ever more complicated molecules, these crystallographers became sufficiently emboldened to train their x-ray cameras also on molecules of biological importance. For they had acceded to the idea that the physiological function of the cell can be understood only in terms of the three-dimensional configuration of its elements. Among the first of the Bragg pupils to enter this line of work were Astbury and J. D. Bernal, who, in the late 1930's, began to tackle the structural analysis of proteins and nucleic acids—that is, of molecules con-

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taining thousands of atoms, and of nucleoproteinic aggregates at an even higher level of organization, such as viruses. Some of this work provided insights that were to prove most useful at a later time, such as Bernal's recognition in 1939 that the tobacco mosaic virus represents an assemblage of hundreds of identical protein subunits, and of Astbury's discovery in 1945 that in the DNA molecule the purine and pyrimidine bases of successive nucleotides form a dense stack perpendicular to the long axis of the molecule, with one base occurring every 3.4 angstroms along the stack. Elucidation of the true helical nature of these two structures did not, of course, come until the 1950's.

However, the first great triumph of structural molecular biology was achieved, not by a member of that British school, but by a Californian, Linus Pauling, when in 1951 he proposed the α-helix as the secondary structure of the polypeptide chain. Pauling's success was due in part to a novel approach to structure determination, in which guesswork and model building played a much greater role than they did in the more straightforward, analytical procedure of more conventional crystallographers. Pauling had decided some years earlier that it ought to be possible to deduce the secondary structure of the polypeptide chain from a knowledge of the exact spatial coordinates of the peptide bond, and he had, therefore, concentrated his x-ray crystallographic analyses on the structural determination of simple oligopeptides. And once the exact structural coordinates of these peptides were at his disposal, Pauling worked out the α-helix from first principles. Great triumph that it was, the discovery of the α-helix did not immediately suggest to anyone very many new ideas about proteins—how they work, or how they are made. It did not seem to open new vistas to the imagination, or to suggest many experiments, other than to show how very far one can go by use of the methods of structural analysis that Pauling had employed.

Meanwhile, in W. L. Bragg's laboratory in Cambridge, Max Perutz and Kendrew had been working on the structures of the two proteins hemoglobin and myoglobin. Their progress had been rather slow, since, in view of the rather limited tools available at that time, the task they had cut out for themselves was immensely difficult and complex. Pauling's brilliant success is said to have come as a bit of a shock to the Cambridge molecular biologists, but they continued on undeterred. The application of the heavy-atom isomorphous replacement technique to the analysis of protein structure and the availability of ever more potent computers for mathematical analysis of the x-ray photographs presently allowed Perutz and Kendrew to work out the complete tertiary structure of their respective proteins.

Without wishing in the least to minimize the magnitude of these extraordinary achievements of structural molecular biology, I give it as my view that their influence on general biology was not revolutionary. It was most important to learn, of course, that the polypeptide chain really does fold in such a way as to bring its hydrophobic amino acids into the inside, and its hydrophilic amino acids to the outside, of the molecule. Furthermore, knowledge of the spatial arrangements of the atoms of these two respiratory proteins will undoubtedly be of enormous help in future efforts to understand the physicochemical basis of the still rather mysterious interaction of the oxygen molecule with the heme iron of the two proteins. Indeed, a detailed understanding of the catalytic action of any enzyme will most probably issue from the precise determination of tertiary and quaternary structures of its polypeptide chains.

After the fact and in retrospect it seems plausible to conclude that the largely nonrevolutionary influence of the structural school on general biology derived from its preoccupation with structure rather than information. It is my belief that this preoccupation reflected a down-to-earth view of the relation of physics to biology—namely, that all biological phenomena, no matter what their complexity, can ultimately be accounted for in terms of conventional physical laws. For, since the study of molecular structure was obviously one domain in which physics *could* make significant contributions to biology, the decision to focus on structure was an eminently rational one 30 years ago. In contrast, working on the physical basis of biological information must have seemed more of a pie-in-the-sky activity, for there was then hardly any common ground between genetics, on the one hand, and physics and chemistry, on the other. And so the choice of genetics as the focal point of the informational school turns out to have had a rather different, or even diametrically opposite, intellectual origin. Whereas the structural molecular biologists operated under the entirely reasonable assumption that physics can make many significant contributions to biology, some of the early informational molecular biologists were motivated by the fantastic and wholly unconventional notion that biology might make significant contributions to physics.

The Informational School

For just when old-fashioned vitalism was rapidly disappearing from intellectually enlightened circles, the idea that some biological phenomena might turn out to be *not* accountable wholly in terms of conventional physical concepts was fashioned by Niels Bohr. In the wake of the formulation of the quantum theory of atomic structure Bohr developed the more general notion that the impossibility of describing the quantum of action, and hence what he called its "irrationality," from the purview of classical physics is but a heuristic paradigm illustrating how the encounter of what appears to be a deep paradox eventually leads to a higher level of understanding. He presented these views in an address, "Light and Life," before the International Congress of Light Therapy in 1932 (*6*).

> At first, Bohr said, this situation [the introduction of an irrational element] might appear very deplorable; but, as has often happened in the history of science, when new discoveries have revealed an essential limitation of ideas the universal applicability of which had never been disputed, we have been rewarded by getting a wider view and a greater power of correlating phenomena which before might even have appeared contradictory.

In particular, Bohr thought it would be well to keep this possibility in mind in the study of life:

> The recognition of the essential importance of fundamentally atomistic features in the functions of living organisms is by no means sufficient for a comprehensive explanation of biological phenomena. The question at issue, therefore, is whether some fundamental traits are still missing in the analysis of natural phenomena, before we can reach an understanding of life on the basis of physical experience.

The difficulty inherent in trying to understand life in physical terms is, according to Bohr, "that the conditions holding for biological and physical researches are not directly comparable, since the necessity of keeping the object of investigation alive imposes a restriction on the former, which finds no

counterpart in the latter. Thus we should doubtless kill an animal if we tried to carry the investigation of its organs so far that we could describe the role played by single atoms in vital functions." Thus there seems to exist for the living animal an "uncertainty principle" formally analogous to that of the electron, in that "there must remain an uncertainty as regards the physical condition to which [the organism is] subjected, and the idea suggests itself that the minimal freedom we must allow the organism in this respect is just large enough to hide its ultimate secrets from us. On this view, the existence of life must be considered as an elementary fact that cannot be explained, but must be taken as a starting point in biology, in a similar way as the quantum of action, which appears as an irrational element from the point of view of classical mechanical physics, taken together with the existence of the elementary particles, forms the foundation of atomic physics. The asserted impossibility of a physical or chemical explanation of the function peculiar to life would in this sense be analogous to the insufficiency of the mechanical analysis for the understanding of the stability of atoms." These ideas of Bohr's would evidently put the relation of physics to biology on a new footing.

That *genetics* was, in fact, a domain of biological inquiry in which physical and chemical explanations might turn out to be "insufficient" in Bohr's sense was spelled out in 1935 by Bohr's pupil Max Delbrück (*7*). Delbrück points out that "whereas in physics all measurements must in principle be traced back to measurements of place and time, there is hardly a case in which the fundamental concept of genetics, the character difference, can be expressed meaningfully in terms of absolute units." Thus, Delbrück thought, one could take the view "that genetics is autonomous and must not be mixed up with physicochemical conceptions." Admittedly, "the refined [genetic] analysis of *Drosophila* has led to [estimates] of gene sizes which are comparable to those of the largest known molecules endowed with a specific structure. This result has led many investigators to consider that the genes are nothing else than a particular kind of molecule, except that their detailed structure is not yet known." But, Delbrück continued, one must remember that there exists here a significant departure from the chemical definition of the molecule.

> In chemistry we speak of a certain kind of molecule when we are faced with a substance which reacts uniformly to chemical stimulation. In genetics, however, we have, by definition, only a single representative of the relevant "gene molecule," in a chemically heterogeneous environment; and we ascertain its identity with a gene of another individual only on the basis of its similar ontogenetic effect. Thus there could be no question of a uniform chemical reaction, not even in a Gedankenexperiment, unless we conceive of the relevant gene as being isolated from a large number of genetically identical organisms and would make a chemical study of the behavior of the ensemble of these isolated genes.

In any case, the main basis for thinking of the gene as a molecule in the first place is its evident long-term *stability* in the face of outside influences.

> Hence, when we speak of [genes as] molecules we are not so much thinking of their similar behavior but more generally of a well-defined union of atoms, supposing that the identity of two genes represents the same stable arrangement of the same atoms. The stability of this configuration must be especially great *vis-à-vis* the chemical reactions that normally proceed in the living cell; the genes can participate in general metabolism only catalytically.

This stability, Delbrück thought, can be accounted for only if each atom making up the gene "molecule" is fixed in its mean position and electronic state, so that only discontinuous, saltatory changes do occur in this arrangement, whenever an atom of the ensemble happens to acquire an energy superior to the activation energy required to change its particular state. These changes evidently correspond to gene mutations, whose spontaneous frequency, Delbrück reckoned, could be as low as one per atom per 30,000 years if the activation energy exceeded kT by a factor of 60.

In 1945, immediately after the conclusion of World War II, a little book appeared which popularized these hitherto rather esoteric views and secured for them a much wider audience. This was *What is Life?* (*8*), written by Erwin Schrödinger, then living as an anti-Nazi emigré in Ireland. In *What is Life,* Schrödinger heralded the dawn of a new epoch in biological research to his fellow physicists, whose knowledge of biology was generally confined to stale botanical and zoological lore. Having one of the inventors of quantum mechanics ask "What is life?" now confronted them with a fundamental problem worthy of their mettle. Since many of these physical scientists were suffering from a general professional malaise in the immediate postwar period, they were eager to direct their efforts toward a new frontier which, according to Schrödinger, was now ready for some exciting developments. In thus stirring up the passions of this audience, Schrödinger's book became a kind of Uncle Tom's Cabin of the revolution in biology that, when the dust had cleared, left molecular biology as its legacy.

Schrödinger opens with the comforting statement that "the obvious inability of present-day physics and chemistry to account [for the events which take place in a living organism] is no reason at all for doubting that they can be accounted for by those sciences." Since, as Schrödinger points out next, organisms are large as compared to atoms, there is no reason why they should not obey exact physical laws. And even the peculiar quality of living matter—namely, that it "evades decay to equilibrium"—does not put it beyond the pale of thermodynamics, since organisms evidently feed on "negative entropy," whose ultimate source is the sun. No, the *real* problem requiring explanation is the physical basis of genetic information. For, while the genes are evidently responsible for the order that an organism manifests, *their* dimensions are not very large relative to those of atoms. How, then, do the genes resist the fluctuations to which they should be subject? How, wonders Schrödinger, has the tiny gene of the Hapsburg lip managed to preserve its specific structure, and hence its information content, for centuries while being maintained at a temperature 310°K above absolute zero? Following Delbrück's then 10-year-old proposal that this stability derives from the atoms of the gene "molecule" staying put in energy wells, Schrödinger proposes that genes preserve their structure because the chromosome that carries them is an aperiodic crystal. These large aperiodic crystals are composed of a succession of a small number of isomeric elements, the exact nature of the succession representing the hereditary code. Schrödinger illustrates the vast combinatorial possibilities of such a code by an example in which the two symbols of the Morse code are used as isomeric elements. Schrödinger thinks that "we may safely assert that there is no alternative to [Delbrück's] molecular explanation of the hereditary substance. The physical aspect leaves no other possibility to account for its

permanence. If the Delbrück picture should fail, we would have to give up further attempts." Furthermore, "from Delbrück's general picture of the hereditary substance it emerges that living matter, while not eluding the 'laws of physics' as established up to date, is likely to involve hitherto unknown 'other laws of physics,' which, however, once they have been revealed will form just as integral a part of this science as the former."

It requires no deep psychological insights to appreciate that the sort of romantic who would be attracted to working in biology because of the opportunity to search for "other laws of physics" is a rather different type from the sort of solid citizen who is confident that everything, however complex, can be eventually explained within the framework of conventional physics.

The philosophy of the search for "other laws" was spelled out in further detail by Delbrück (*9*) in a speech he gave in 1949, entitled "A Physicist Looks at Biology." Delbrück explains, first of all, what he believes to be a fundamental difference between physics and biology. Whereas the aim of physics is the discovery of universal laws, biologists cannot reasonably aspire to any such aim, since "any one cell, embodying as it does the record of a billion years of evolution, represents more an historical than a physical event. . . . You cannot expect to explain so wise an old bird in a few simple words." After discussing the relation of classical physics to quantum physics as an object lesson for biology, Delbrück states Bohr's (and his) belief that, "just as we find features of the atom—its stability for instance—which are not reducible to mechanics, we may find features of the living cell which are not reducible to atomic physics, but whose appearance stands in a *complementary* relation to those of atomic physics." Delbrück admits that he is aware that these views might be considered very dangerous, since they are susceptible to naive misinterpretation and could inspire either unnecessary defeatism or wild and unreasonable vitalistic speculations. Nevertheless, he asserts, they can be justified on the grounds that the suggestion of a complementarity situation in biology has been the prime motive for the interest in biology of "at least *one* physicist." Delbrück concludes his speech with a homily that accounts for the, at first sight, surprising tendency of the early molecular geneticists to look down on biochemistry. Biochemistry, Delbrück thought, is not likely to be very useful for gaining an understanding of the really important matters in biology:

> He [the physicist] may be told that the only real access of atomic physics 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 the 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. . . . 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 paradoxes crop up and come into sharper focus, and this will not happen until the behavior of living cells has been carried into far greater detail. This analysis should be done on the cell's own terms and 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*.

The Romantic Phase

In 1938 Delbrück started his work with bacteriophages, because he had realized that bacteriophages should make ideal objects for the study of biological self-replication, and hence of the physical basis of heredity. And thus opened the first of three phases in the history of the informational school of molecular biology—the romantic phase, whose spiritual hallmark was to be the quest for the physical basis of the gene. Delbrück soon met Salvador Luria and Alfred Hershey, and with this meeting the American phage group came into being. The members of this group were united by a single common goal—the desire to understand how, during the brief half-hour latent period, the simple bacteriophage particle achieves its own hundredfold self-reproduction within the bacterial host cell. The initial growth of this group was rather slow, but after Delbrück organized the first annual summer bacteriophage course at Cold Spring Harbor to spread the new gospel among physicists and chemists, growth was more rapid. Nevertheless, by 1952, which was to be the last year of the romantic phase, the phage group still numbered only three or four dozen people.

Delbrück, Luria, and Hershey dominated this first, romantic phase, though during that same period several other people had, of course, made discoveries which equaled in importance anything that these three had found (*10*). When one looks back now on that first phase, a curious fact emerges: though the immediate conclusions drawn from the results of the experiments of the romantic phase were almost always right, the more general and really interesting speculations built upon these first-order conclusions were mostly wrong. Thus the outstanding accomplishment of the romantic phase was the introduction into microbial genetics of previously unknown standards of experimental design, deductive logic, and data evaluation. These procedures had led to final and definitive settlement of matters that had been under dispute for 10 or more years, such as whether phages are really viruses that multiply autonomously within their bacterial host cells, whether bacteria and phages really sport spontaneous hereditary variants, whether phages really enter a noninfectious eclipse phase during their intracellular growth, and whether lysogenic bacteria really perpetuate hereditarily the capacity to produce infective phage. They had also led to the discovery of important new phenomena, such as multiplicity reactivation of irradiated phage genomes and genetic recombination in phage and bacteria. Insofar as the new theories and working hypotheses of that phase were concerned, however, we see that such ideas as the bacterial "key enzyme" for which infecting viruses were supposed to compete, the multiplication of the viral genome by independent subunits, genetic recombination in phage by "partial replicas" or "copy choice," and bacterial recombination by cell fusion and postzygotic elimination of genetic material did not stand the test of time. The last mistaken idea to be produced in the romantic phase, based not unreasonably on the finding of proteinaceous, DNA-free phage precursors during the eclipse period of phage growth, was that *protein* is the viral genetic material. This idea arose just a few months before Hershey and Martha Chase showed that the oppo-

site is actually true—that the phage DNA is the viral genome. This demonstration ushered in the end of the romantic phase, since it presaged ominously that, in the study of phage, no paradoxes might crop up and come into sharper focus after all. For the fundamental problem of self-reproduction could now be restated in terms of two functions, "autocatalytic" and "heterocatalytic," of the phage DNA. By means of the former, the phage DNA replicates itself several hundredfold to generate the genome of its progeny, and by means of the latter, the phage DNA induces, or presides over, the synthesis of the virus-specific proteins that govern the reactions of vegetative phage growth and furnish the soma of its progeny.

The Dogmatic Phase

The successful elucidation of these two functions of the DNA was the work of the second, or dogmatic, phase of the informational school, which lasted from 1953 to about 1963. By the end of that decade the number of working molecular geneticists had to be reckoned by the hundreds, rather than the dozens; nevertheless, two men can be clearly identified as having dominated that second phase: James Watson and Francis Crick. At first sight, their discovery, at the outset of that second phase, of the double-helical, self-complementary structure of DNA resembles Pauling's then 2-year-old discovery of the α-helix, from which they had undoubtedly drawn their inspiration for training Pauling's methods on what had meanwhile been shown to be the hereditary substance. But, on second sight, the discovery of the double-helical structure of DNA emerges as an event of a qualitatively different heuristic nature. First, in working out the structure of the double helix, Watson and Crick had for the first time introduced genetic reasoning into structural determination, by demanding that the evidently highly regular structure of DNA be able to accommodate the informational element of arbitrary nucleotide base sequence along the two paired polynucleotide strands. Second, unlike the discovery of the α-helix, the discovery of the DNA double helix opened up enormous vistas to the imagination. It provided the highroad to understanding how the genetic material functions. Watson and Crick then formulated the central dogma of molecular genetics, which asserted that DNA achieves both autocatalytic and heterocatalytic functions by serving as a template for the synthesis of replica polynucleotide chains, through formation of complementary hydrogen bonds—DNA chains for the autocatalytic and RNA chains for the heterocatalytic function. To complete the heterocatalytic function, the replica RNA chains are translated into polypeptides by way of a genetic code, under which any given short permutation of three nucleotides along the RNA chain represents one of the standard 20 amino acids. Since Crick thought it unlikely, from first principles, that amino acid side chains could undergo specific interactions directly with the nucleotides of the RNA template chain, he proposed the idea of an oligonucleotide adaptor, by means of which the standard amino acids are recognized in the decoding, or translation, process.

It is the existence of the central dogma that sharply distinguishes the second phase of the informational school from the first. For whereas the romantic phase involved groping for the still unimaginable, test and elaboration of the clearly stated central dogma characterized the dogmatic phase. The only hope now left the veterans of the first phase was the hope that the central dogma might somehow prove to be untrue after all, in which case quest for the paradox could be resumed. But, as the work of that decade was to show, the central dogma is essentially correct. No paradoxes had come into focus, no "other laws of physics" had turned up (*11*). Making and breaking of hydrogen bonds seems to be all there is to the workings of the hereditary substance.

Though Watson and Crick were to play important roles in the experimental testing and elucidation of their central dogma, the success of the dogmatic phase depended on the appearance on the molecular biological scene of many other highly intelligent and gifted experimentalists, not a few of whom had recourse to the recently despised methods of biochemistry. But, though numerous initially unknown and unsuspected details of the processes covered by the central dogma were discovered during the dogmatic phase, only one great theoretical extension of that dogma was made during that decade: François Jacob and Jacques Monod's idea of the messenger RNA and of the operon. I think it fair to say, by way of appreciation of the dogmatic phase, that there have been only two great theories in the history of biology that went more than a single step beyond the immediate interpretation of experimental results; these were organic evolution and the central dogma.

The Academic Phase

About 1963 the last, or academic, phase of the informational school began. By that time many of the details of the genetic code were known, the colinearity of nucleotide sequence in DNA and amino acid sequence in protein had been finally proved, the structural details of the transfer RNA (Crick's postulated adaptor) and the mechanism by which it combines with its cognate amino acids had been worked out, and the general enzymatic and informational mechanisms connected with the synthesis of DNA, RNA, and protein had been elucidated. All hope that paradoxes would still turn up in the study of heredity had been abandoned long ago, and what remained now was the need to iron out the details.

Some of these details still represent formidable problems, such as that of understanding the processes responsible for the orderly morphogenesis of the fertilized egg into complex and highly differentiated multicellular organisms. But now that some reasonable molecular mechanisms for cellular differentiation can at least be *imagined,* the likelihood that the explanation of development of the embryo will lead to the "other laws" seems to have greatly diminished, and with this denouement has diminished also the appeal of embryology as an area of romantic strife. Indeed, we now seem to be close to an understanding of one special case of cellular differentiation, that of the antibody response of vertebrates (*12*), thanks to the application of the notions of the central dogma. There also still remains the matter of the origin of life, which, as we now see, could not possibly have been solved prior to the promulgation of the central dogma. Though there is no guarantee, of course, that the first self-reproducing genetic materials formed in the primordial soup of ancient oceans were nucleic acid, or any polymers even resembling polynucleotides, it has now become clear at least that probing into the origin of the genetic code—into ways in which it could have arisen

without, like Athena, having sprung full-blown from Zeus's head—is likely to be a most profitable attack on this problem. Perhaps a paradox may still be hidden here, but unless extraterrestrial life becomes available for study, it is difficult to see how such a paradox connected with the origin of life could ever come into sufficient focus to reveal "other" physical laws.

The Last Frontier

There now seems to remain only one major frontier of biological inquiry for which reasonable molecular mechanisms still cannot be even imagined: the higher nervous system. Its fantastic attributes continue to pose a problem as hopelessly difficult and intractably complex as the hereditary mechanism did a generation ago. And the higher nervous system does, of course, present the most ancient and best-known paradoxes in the history of human thought: the relation of mind to matter, or of free will to determinism. Bohr had thought that the principle of complementarity would be of help in fathoming the nature of this relation also (*6*):

The recognition of the limitation of mechanical ideas in atomic physics would much rather seem suited to conciliate the apparently contrasting points of view which mark physiology and psychology. Indeed the necessity of considering the interaction between the measuring instruments and the object under investigation in atomic mechanics corresponds closely to the peculiar difficulties, met with in psychological analyses, which arise from the fact that the mental content is invariably altered when the attention is concentrated on any single feature of it. . . . Indeed, from our point of view, the feeling of the freedom of the will must be considered as a trait peculiar to conscious life, the material parallel of which must be sought in organic functions, which permit neither a causal mechanical description nor a physical investigation sufficiently thoroughgoing for a well-defined application of the statistical law of atomic mechanics.

Victor Weisskopf (*13*) recently summarized Bohr's attitude in the following terms:

The awareness of personal freedom in making decisions seems a straightforward factual experience. But when we analyze the process, and follow each step in its causal connection the experience of free decision tends to disappear. . . . Bohr, an enthusiastic skier, sometimes used the following simile, which can be understood perhaps only by fellow skiers. When you try to analyze a Christiania turn in all its detailed movements, it will evanesce and become an ordinary stem turn, just as the quantum state turns into classical motion when analyzed by sharp observation.

This attitude would mean nothing less than that searching for a "molecular" explanation of consciousness is a waste of time, since the physiological processes responsible for this wholly private experience will be seen to degenerate into seemingly quite ordinary, workaday reactions—no more and no less fascinating than those that occur in, say, the liver—long before the molecular level has been reached. Despite this simple, though psychologically possibly unsatisfying, resolution of the mind-matter paradox, increasing numbers of veteran molecular biologists of the informational, but few of the structural, school are now turning toward the nervous system in the hope that its study may soon enter a romantic phase, similar to that which attended the birth of molecular genetics. Thus, now that the success of the informational school has made molecular genetics an academic discipline, one can expect that in the coming years students of the nervous system, rather than geneticists, will form the avant-garde of biological research. And the inability to even imagine any reasonable molecular explanation for conscious life still offers some hope that some "other laws of physics" may yet turn up through study of the nervous system. But it is also possible that study of the nervous system is bringing us to the limits of human understanding, in that the brain may not be capable, in the last analysis, of providing an explanation for itself. Indeed, Bohr ended his 1932 lecture with the thought,

. . . without entering into metaphysical speculations, I may perhaps add that any analysis of the very concept of an explanation would, naturally, begin and end with a renunciation as to explaining our own conscious activity.

Perhaps *this* then is the paradox: there exist processes which, though they clearly obey the laws of physics, can *never* be explained.

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8. E. Schrödinger, *What is Life?* (Cambridge Univ. Press, New York, 1945).
9. M. Delbrück, *Trans. Conn. Acad. Arts Sci.* **38**, 173 (1949).
10. Some of my friends, to whom I had presented an earlier version of this lecture, demanded that I ascertain whether, in fact, *anyone* besides Delbrück among the workers of the romantic phase was motivated by the search for the paradox. Accordingly, I asked Luria, Hershey, James Watson, and Seymour Benzer about their own views. Luria replied as follows: "I had been exposed to some [ideas about complementarity in biology] in Rome, although Fermi took a rather dim view of such speculations. Later I became suspicious of Bohr's ideas, of which I had read some in Paris, as being tainted with idealism. I believe my position was a more strictly biological one, which made me expect that new levels of integration would reveal unexpected sets of rather simple relations rather than epistemological or physical surprises. In fact, I remember finding Schrödinger's book exciting for the formulation of 'aperiodic crystal,' not for the speculations on new laws of physics." Hershey replied, in part, that "whereas I never liked the complementarity double-talk, I think I did consciously recognize *some* qualitative difference between what the phage people aimed at, and the goals of, say, the structural and biological chemists in general." Both Watson and Benzer, though admitting to having been influenced by Schrödinger's book, deny having been motivated by the complementarity idea. There is, however, definitely at least one other person who *was* captivated by the search for the paradox—namely, myself.
11. In commenting upon an earlier version of this lecture Delbrück pointed out to me that at least one paradox had come into focus—the "enzyme cannot make enzyme" paradox, described in J. D. Watson's *The Molecular Biology of the Gene* [(Benjamin, New York, 1965), p. 179]. "You might as well say," Delbrück writes, "that the resolution of this paradox by the reduction in dimensionality from 3-dimensional-continuous to 1-dimensional-discrete in the genesis of proteins is a new law of physics, and one that nobody could have pulled out of quantum mechanics without first having seen it in operation." Just in case I should feel let down by the revelation that *this* is the kind of "new law" we were looking for, Delbrück quotes Bohr as telling of the man who, upon seeing a magician sawing a live woman in two, rises excitedly in the audience and shouts: "It's all a swindle!"
12. *Cold Spring Harbor Symp. Quant. Biol.* **32** (1967).
13. V. Weisskopf, *New York Rev. Books* **7**, 26 (20 Apr. 1967).

14. I am indebted to numerous friends for their vigorous comments on this manuscript and for their help in calling factual errors to my attention. That is not to say, however, that the present version necessarily meets with their approval. I also express my appreciation to the Assembly of Professors of the Collège de France for inviting me to deliver a series of lectures under a visiting professorship.