

# Book Reviews

## The Origins of Molecular Biology

**The Path to the Double Helix.** ROBERT OLBY. University of Washington Press, Seattle, 1975. xxiv, 510 pp. + plates. \$23.50.

Robert Olby is a lecturer in the department of philosophy at the University of Leeds, specializing in the history of science. He has previously written *The Origins of Mendelism* (Schocken, 1966) and *Charles Darwin* (Oxford University Press, 1967), as well as articles on the origins of molecular biology with particular emphasis on the chemical and physical nature of genetic material. One of these articles, published in *Daedalus* (fall 1970), contains a short biography of Francis Crick, who has now contributed a brief foreword to the present volume. Praising Olby's work as a professional historian, Crick has described this book as "the first full scholarly account of how the structure of DNA was discovered, set against its proper historical background." But Olby, who knows something more of the problems of historians attempting to sort out even relatively recent events from the "vantage" point of accepted contemporary viewpoints, is less confident in his own introduction, and refers to his work "not as a definitive account but as a first attempt which will stimulate others to do better." In qualifying the extent of his considerable efforts to provide a guide to the source material in this area, Olby refers to various omissions of relevant materials and notes deficiencies in his treatment of such important topics as the history of the chemistry of the nucleic acids.

Historians of science are greatly concerned with the question of how science advances. A serious and extensive discussion of this topic has developed in recent years as a result of the work of T. S. Kuhn, who has considered mainly the nature of theoretical revolutions in physics and cosmology. Kuhn conceived of science as moving

from paradigm to paradigm, "paradigm" being a term devised to denote the definite theoretical framework or model within which scientists develop their ideas. In a scientific revolution such a framework is rejected or replaced in significant measure or *in toto*, and scientists plan their experiments within the new conceptual structure. It is clear that in the two decades since the proposal of the double helix as a model for the nature, synthesis, and behavior of genetic material biologists have found it to provide the core of a new and useful theoretical framework, within which they have been able to develop many significant experiments. The recognition of the physical reality of this structure has indeed helped to initiate a revolution in biological thought. Although both the term "paradigm" and the enterprise of clarifying the process of scientific revolutions have become popular, little has been done to analyze the development of biology in these terms. As a professional historian, then, Olby has both the opportunity and the responsibility to clarify the nature of a crucial advance in a science relatively unexplored by other historians. For example, we can ask whether this scientific revolution is also characterizable as moving from one paradigm which determined the quality of past biological experimentation to another representing the theoretical structure in which we now operate.

In approaching the problems of recent scientific history, Olby has been able to interview some of the individuals who contributed to the solution of the structure of DNA. The professional historian working on contemporary problems has devised "oral history," in addition to the gathering, sifting, and evaluation of written records and other materials. He interviews the individuals who have participated in the events under investigation and

records their versions of the remembered past. However, as Saul Benison describes in his classic oral history memoir *Tom Rivers: Reflections on a Life in Medicine and Science* (MIT Press, 1967), the process of extracting reliable and useful accounts from such survivors is complicated and arduous. The historian must be prepared to see and define the problems and to remind and even spur as well as to check and supplement the forgetful subject. In short, a tape recorder does not of itself make an "oral historian." Olby learned some of these problems in his years of work on this book. For example, he has discovered that the date reported for the correct pairing of cut-out model bases by Watson in February 1953 was not quite as described in 1968 (and in the 1970 *Daedalus* article). The book contains evidence of such advances in his technique, as well as a profusion of quotations from the interviews, letters, and other documents.

The book is organized in five sections, the first, fourth, and fifth of which trace what constitutes a central theme. This may be described as the development of the work and ideas of the polymer chemists and physicists who forged our knowledge of the structure of long-chain macromolecules, advancing slowly with insights concerning certain natural polymers, polysaccharides, proteins, and eventually DNA. I will discuss separately the other two sections, which are on more biological and chemical themes, because I believe they are less well done and dilute the quality of the work. Although Olby suggests that the central theme of the book is the development of the molecular theory of the gene, the contributions of genetic experiments to the analysis of gene structure receive little discussion. Nineteen of 26 illustrative plates show diffraction patterns and, of about a hundred figures and tables, fewer than ten relate to genetics as such whereas some 75 are concerned with the physical chemistry of polymer structure. The emphasis in the distribution of explanatory material defines Olby's most consistent efforts, if not his stated intent.

The first section, *From Colloidal Particles to Long-Chain Molecules*, describes the evolution of the recognition of the existence of very large molecules from the beginning of the 20th century until the beginning of World War II. In this portion Olby presents the achievements and debates of the German organic chemists and

physicists on this problem. Here also we find the contributions of the physical chemists, such as Svedberg and Staudinger, who affirmed the existence of such molecules. A description of the early development of x-ray analysis in determining the size and shape of such substances is also presented. The rise of the school of Astbury in Leeds is described in great detail, from Astbury's studies on keratin and rubber to the surprising detection of regularity in the stretched fibers of DNA. The weaknesses in Astbury's interpretations of his x-ray analyses are characterized very sharply. At the very end of the book Astbury's role in coining the term "molecular biology" is set straight by reference to the earlier contribution of Warren Weaver, then of the Rockefeller Foundation, who in 1938 used this term to describe the newly emerging dynamic and structural biology.

In the fourth section, Intellectual Migrations, the now familiar story of the growing interest of the physicists and physical chemists in biology and in natural polymers is told in perhaps too great detail. In an introductory chapter which Olby calls "The informational school," the path of the physicist Delbrück is traced from pre-war Europe to an intellectual haven in the United States where he and an early segment of the phage group could concentrate on the biology of phage. In my opinion, Schrödinger's book on biology did not contribute greatly even to the early development of work on phage and does not warrant the space Olby gives it. Two vivid chapters describe the development of a "structural school" concerned with the biophysics of proteins, in England including Bragg, Needham, Bernal, and Perutz and in the United States Pauling, Corey, and Huggins. This section also summarizes the early careers of Watson and Crick and indicates how these two elements, mildly radioactive in isolation, began to implode when brought together at the Cavendish Laboratory in Cambridge.

In an attempt to define the intellectual milieu from which Watson had emerged in the United States, this section presents an inadequate and occasionally inaccurate discussion of the development of the biochemistry of phage until 1950-51. If it is true, as I believe, that the development of phage biochemistry not only prepared Watson and a large number of other biologists and biochemists for acceptance of the role of DNA as the genetic material but

also pointed to phage as a model system for work on the nucleic acids, that history might have been given a bit more space, time, and work than are Watson's efforts to obtain and retain a fellowship in Europe, which are described at length. The section concludes with an analysis of the Hershey-Chase experiment. Watson's apparently ready acceptance of that experiment as showing that phage DNA alone is the genetic material contrasted with the hesitancy of most phage workers in this regard.

The fifth section, Hunting for the Helix, is an instructive treatment of the tortuous path to the solution of the structure of DNA. There were three laboratories competing actively on this problem, one at King's College in London, that of Crick and Watson in Cambridge, and Pauling's in California. The research unit at King's College was split internally and was self-defeating, whereas the approach and model of the California group were simply wrong. Watson and Crick not only were fired by insights into both the biological significance of DNA and the potentialities of x-ray analysis and model building but were also the center of an active communications network which assured knowledge of almost all the data and thoughts of their competitors in London and Pasadena. Further, they pumped key colleagues and numerous visitors, such as Chargaff and Donohue, who supplied them with crucial knowledge. Nevertheless, after two years of work and travel, Watson and Crick had not solved the DNA problem. It is demonstrated unequivocally in three long chapters that they had made all the possible incorrect choices for the structure of DNA and had eliminated these from consideration. In going off on these wrong tracks, all three of the laboratories had not heard of or had actively repressed the two-year-old crucial analytical data of Chargaff concerning the equivalence of purines to pyrimidines, adenine to thymine and guanine to cytosine. Only when these rules had been recognized and an elementary knowledge of the chemistry of the bases obtained were Watson and Crick able to build a reasonable approximation of the double helix. This event took about three weeks after the structure was conceived to be of this form.

Despite their settings in major universities with excellent libraries and the presence of groups and occasional

visitors familiar with the chemistry and biochemistry of the nucleic acids, all these laboratories had worked on a crucial polymer without any effort to learn of the "recent" developments pertaining to its composition and biochemistry. It may be noted that as early as 1943 Mirsky had reported that purine deoxyribose was half the total deoxyribose in DNA. This reviewer had confirmed this in 1945 and in 1946 had reported an equivalence of purine and pyrimidine deoxyribose in phage DNA. It appears that after the paper on the "double helix" had been sent to *Nature* Watson accidentally met Wyatt in Paris and even then wished to be reassured of the equivalence of a number of bases, as obtained by Chargaff for DNA in 1950 and in 1953 by Wyatt and the reviewer for phage DNA. What is the significance of such specialization and intellectual isolation, which led to fumbling for two years in our best laboratories? Is the question trivial, since a reasonable structural model was eventually devised by one of the few groups that were capable of solving such structural problems? Or does the fact that Watson and Crick now surround themselves with numerous biochemists and specialists in many other disciplines in their productive laboratories at Harvard and Cambridge reflect conclusions they themselves have drawn? Olby has not considered such questions, which clearly fall within his province.

Nor has he asked if the process by which the structure of DNA was generated and the derived new paradigm fit the concepts of Kuhn, particularly that relating the performance of "normal science" to the old paradigm and of "extraordinary science" to the inception of the new. Watson and Crick used classical techniques to attempt to solve their puzzle; to borrow a phrase from Kuhn, *they were in difficulty*, not current theory. These workers had been moved to work and to continue working on DNA by the conviction that this substance had been neglected in the old fuzzy "paradigm" of the protein or nucleoprotein nature of the gene, and they hoped their solution would also say something about heredity and gene replication. Nevertheless they had set themselves no more of a problem than had their predecessors and contemporaries interested in protein structure. Solutions to protein structure have stated little or nothing about the mechanism of protein synthesis. In short, in Kuhn's terms Wat-

son and Crick were engaged in normal science, "the activity which practitioners are trained to carry on," as had been Chargaff, Mirsky, and everyone else. It appears that several limited lines of normal science converged in the Cambridge laboratory to help solve the structure. However, the solution did contain elements that permitted its virtually immediate acceptance both as an event of extraordinary science and as the core of a new paradigm. Certainly Avery's discovery of bacterial transformation by DNA was every bit as epoch-making as the discovery of the DNA structure. Would Kuhn and Olby conclude that recognition as well as discovery is required to constitute "extraordinary science"?

I have no doubt that these three sections of Olby's book, introduced by the chapter on "the nature of proteins" in J. S. Fruton's *Molecules and Life* (Wiley-Interscience, 1972), would form the basis for a useful course on the history and organization of science for students of biophysics and biochemistry. After discussions of the important question posed by Olby's case history of the complexities of a path to discovery, one can imagine another, approximately equal period of inquiry into the validation of the ingenious construct of the double helix as the genetic material. The verification of the structure, which is not discussed in this book, has involved such matters as the x-ray analysis of model compounds, proof of the postulated antiparallel separate chains, the clarification of some mechanisms of mutagenesis, the discovery of messenger RNA, and the determination of the genetic code. This process has taken two decades already, and understanding of the structures and mechanisms developed by cells to effect the synthesis of DNA is still far from clear. I suspect that it would be instructive to both students and investigators to attempt to define the nature of the laboratory or the interactions of laboratories necessary to develop extensive knowledge of the biological synthesis of DNA.

The two large intervening sections of the book, those on the nature of hereditary material and on bacterial transformation, need a thorough overhauling or, even better, should have been reserved for a separate study. In contrast with the extensive discussions of the methodology and concepts that were involved in approaching problems of polymer structure, here a reader becomes familiar with the battles of

P. A. Levene and Simon Flexner over administrative matters but does not learn the structure of the bases or see a clear representation of a nucleoside or nucleotide until almost the end of the book. We do not discover the relation of alkaline extraction to the size of the RNA isolated by early workers, nor do we learn when and how RNA joins DNA as a species of macromolecule. Olby delivers such uninformed judgments as a reference to "the hallmark of biochemistry before the 1950's—a limitation to metabolic pathways" and the comment, referring to December 1949, "Now one could use the techniques of biochemistry."

Even worse, Olby finds it necessary to assign blame to such creative workers as Levene, Muller, and Stanley for the lack of progress in defining the genetic role of nucleic acid. Having suggested that Stanley is particularly responsible for the failure to identify nucleic acid as the genetic material of tobacco mosaic virus, he fails to credit him and his laboratory with the discoveries that the RNA of this virus is far larger than a tetranucleotide and eventually that this RNA is infectious in its own right.

Olby has found it convenient to explain the limitations of many investigators as a consequence of their belief in "the protein version of the central dogma." This superficial explanation is only a beginning. Olby indicates neither the strength of convictions derived from traditional learning and habits of practice nor the overwhelming evidence required to shake and shatter the old comfortable habits of thought and to replace these with a new utilizable framework. Why did Mirsky (and others) resist a straightforward interpretation of Avery's experiment, why did the laboratories of Stanley, and of Schramm, and of Bawden, Pirie, Markham, *et al.* fail to test the infectivity of the polymeric RNA of tobacco mosaic virus before 1956, and why did Luria, and even Hershey, hesitate in interpreting the Hershey-Chase experiment correctly? Can all these instances be explained merely as "normal science," which Kuhn has described as "a strenuous and devoted attempt to force nature into the conceptual boxes supplied by professional education"? These questions seem worthy of Erik Erikson, as well as of historians of science. Obviously we must attempt to understand these hindrances to progress, and Olby's practice of awarding demerits to certain scientists appears

quite inappropriate to such an effort.

These sections also close with a discussion of the discovery of the analytical foundations of base pairing, that is, the crucial chromatographic work of Chargaff and Wyatt. Olby then asks why these men, who knew the pairing rules, did not themselves come up with the structure of DNA. Does he really expect that bond angles and helices will fall out of classical analytical data on base composition? Having composed an entire book to tell us why x-ray analysis and model building were essential to determining the structure of DNA, Olby appears to be taunting and deprecating those less glorious scholars who were untrained in those undeniably essential techniques. He would do better to ask why, when Chargaff, Wyatt, or any other biochemist did publish crucial data, their papers did not reach the biophysicists concerned with problems of macromolecular structure. Nor do I doubt that the biophysicists can on occasion find similar reasons for complaint concerning their own data, lost in the wilderness.

In addition to the historical labors, the preparation of a book such as this is a formidable technical task. After submitting a final manuscript, one is usually so busy checking and correcting in the course of various stages of proofreading that it is virtually impossible to read the book again. In the case of this book, there are so many minor errors that it seems impossible that it was proofread at all by the author, an editor, or technically knowledgeable colleagues. I have found at least two dozen misspellings of words and names in the text. Incorrectly spelled names can be found in the bibliography as well, and numerous references are inappropriate to the text. The index is far from thorough, and Delbrück, a major figure in the book, is not listed at all. Among the minor errors in the text, we can find phenylmaltosazone described as a polypeptide derivative and biotin as a hormone, Stanley's group placed in California in 1942, and many others.

To sum up, a considerable quantity of valuable material is collected in this volume. Indeed, the central theme of the book on the advance of our knowledge of the structure of proteins and DNA is well presented and provides an important case history of the difficulties in merging several paths of investigation to form this knowledge. Unfortunately the author has chosen to enlarge the central theme by less

valuable discussions of relevant chemical and biological topics. Some of his interpretations in these sections are unreasonably harsh, personal, and injudicious. The book is marred also by numerous minor errors of presentation and technical substance.

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