Halcyon Days

What Mad Pursuit. A Personal View of Scientific Discovery. FRANCIS CRICK. Basic Books, New York, 1988. xiv, 182 pp., illus., + plates. $16.95. Alfred P. Sloan Foundation Series.

This book is an entry in a series designed "to make the scientific experience and the excitement of discovery accessible to the general reader." It is well written for this purpose.

The title *What Mad Pursuit* is taken from "Ode on a Grecian Urn" by Keats. Keats put a query sign after the phrase because he was asking a question. The omission is significant, because Crick used the phrase as an imprecation, rather than a question, in the title of a seminar he gave at Cambridge when he was a "beginning graduate student" (p. 50). His implication was that a method being used in crystallography by his colleagues was useless and that they were therefore in a "mad pursuit." In response, the professor (Bragg) "was furious." The incident serves to support a little homily (p. 49): "I have learned that if you have something critical to say about a piece of scientific work, it is better to say it firmly but nicely and to preface it with praise of any good aspects of it. I only wish I had always stuck to this useful rule."

Apparently, when Keats is quoted, the ball starts to roll. The book's dust jacket reminds us that the same poem informs us that beauty and truth are synonymous. Another reviewer (John Cairns in *Nature*) introduced quotations from four different poems by Keats into his appraisal, and he even implies that Crick was once alone and palely loitering by the withered sedges of Cambridge in 1977, which seems rather far-fetched. My guess is that the title was selected to attract readers and has very little to do with the text.

Crick tells us about his "pre-double helix" life. It is evident that as a child and young adult he was well sheltered by an affectionate and supportive family. According to some psychologists, genius rarely develops under such conditions, but is favored by vicissitudes. Permissiveness, in contrast, worked well for Crick. He is gregarious and he spontaneously "likes people."

One charming remembrance is that "After I was born, [my mother] instructed her younger sister, Ethel, to carry me to the top of our house. My mother hoped that this little ceremony would make sure that in later life, I would 'rise to the top' " (p. 7). Also, Crick commented in later years to his wife, Odile, that a childhood photograph of him looked angelic. Whereupon she replied, "Not really. Look at those piercing eyes." Odile, whose photograph is among those following p. 112, does quite well at moderating Francis. (She once asked him if Asn was an abbreviation for "asinine." Laughter.)

The book speaks succinctly, pp. 25–30, on evolution and natural selection, and on p. 5 it is stated that "the most important theme of the book is natural selection." Crick says that Darwin in *The Origin of Species* outlined the essential feature of the "Secret of Life" and that the discoveries of genetics and molecular genetics enabled "the secret to stand before us in all its naked glory." The majority of human beings are not aware of it (p. 26), and "in Western society a rather vocal minority are actively hostile to evolutionary ideas." I would add that the world headquarters of that minority is only a few miles away from La Jolla, where Crick now resides. This is the Institute for Creation Research, whose head is a hydraulic engineer, Henry Morris, who proclaims that "evolution is the anti-God conspiracy of Satan himself." Morris's quarrel should be with base-pairing rather than with Satan, in view of the relationship between DNA and evolution.

Returning to his own career, Crick devotes most of the text (a hundred pages) to describing the early history of molecular biology, and the book concludes with some ideas about his present interest, neurobiology. Much in these pages concerns what went on in the "halcyon days" of the RNA Tie Club—a club founded in 1954 by the cosmologist George Gamow with 20 members, one for each amino acid. These were the days of research and theorizing between the discovery of the DNA structure in 1953 and the completion of the genetic code in 1966, which point, says Crick, "marked the end of classical molecular biology." Crick found himself "with most of my ambitions satisfied," so that it was "time to move on to new fields." Actually, he has kept his hand in by writing articles on the helicity of DNA and on "selfish DNA."

Many details of the halcyon days are in Horace Judson's *The Eighth Day of Creation* (as mentioned on p. 31). Crick's account of events between 1953 to 1966 should be studied by all who are interested in science and in how scientists explore a new field that suddenly opens. It is especially rewarding to read Crick, because of his vivid, crisp, and lively prose, sparkling with wit and spiced with jokes and anecdotes.

Gamow, at Woods Hole in 1954, found that he was giving a "whiskey, twisty RNA party" (p. 95). This was a hoax, and one of the perpetrators was James Watson. Numerous people accepted the invitation, and the party was a great success. I recall that 12 years later, Watson organized with equal success a convivial 50th birthday party for Crick at the Cold Spring Harbor Symposium.

In 1958, Crick published a wide-ranging article, "On protein synthesis," in volume 12 of *Symposia of the Society for Experimental Biology*, a tour de force with much impact that still makes excellent reading. Indeed, many of the ideas in it also appear in *What Mad Pursuit*. The article starts by listing the "magic 20" amino acids that participate in protein biosynthesis. Prior to this, there had been no consensus. Some people included hydroxyproline, others excluded asparagine and glutamine or included both cystine and cysteine. The article proclaimed the central dogma that "the transfer of information from nucleic acid to nucleic acid or from nucleic acid to protein may be possible, but transfer from protein to protein or from protein to nucleic acid is impossible," as diagrammed in the book, p. 168. Crick notes (p. 109) that many years later Monod told him that he (Crick) "did not appear to understand the correct use of the word dogma, which is a belief that cannot be doubted. . . . I used the word in the way I myself thought about it, not as the rest of the world does." Next, Crick made a bold proposal: the adaptor hypothesis, which predicted the existence of small RNA molecules, each of which attached itself to a specific amino acid and brought it to its place by codon-anticodon pairing. Shortly afterwards, soluble RNA was discovered and was found to have this function. These early ideas placed Crick in a commanding position in molecular biology.

Pages 99 to 101 describe the comma-free code that was proposed in 1957 by Crick, Griffith, and Orgel. It was completely theoretical. The comma-free code was a triplet code that could be read in only one reading frame. Overlapping triplets did not code for amino acids and were defined as "nonsense." For example, if XYZ is a serine codon, YZX and ZXY are nonsense. By the same token, XXX codons are nonsense, because if XXX adjoins XXX, the reading frame can't tell where to start. The point was to reduce the 64 codons to a total of 20, one for each amino acid (although I can't see why three codons per amino acid wouldn't have been more likely). Objections soon arose. The comma-free code had no evolutionary flexibility among organisms with varying guanine and cytosine content of DNA. Another objection, which was not mentioned, is that 70% of possible single nucleotide substitutions produced by point mutations will give rise to nonsense codons, so evolution would be virtually impossible. In the universal code, only 4.2% of possible point mutations produce stop codons. The comma-free code met a swift death when Nirenberg and Matthaei found that polyuracil coded for phenylalanine so that apparently the translation process could start anywhere. Later, of course, ribosome binding sites and start signals were discovered.

Crick obtained great satisfaction from his experiments in establishing the triplet nature of the code by using addition and deletion mutants of T4 bacteriophage as described on pp. 122–142. One (or two) additions would put the reading frame out of phase. If one (or two) deletions were made a short distance further along, the reading frame would start again. This was beautiful work, but it did not provide a surprise. By contrast, the wobble theory, proposed by Crick in 1966, was entirely unexpected, and was based on striking deductions from a handful of data obtained through model-building. It says, for example, that guanine in first anticodon positions pairs with both uracil and cytosine in third codon positions. Therefore, all pairs of codons ending in uracil or cytosine are synonymous; each of the 16 pairs of codons ending in a pyrimidine should code for a single amino acid, which prediction was promptly confirmed by biochemical studies with synthetic polynucleotides. All anticodons that have been discovered confirm the wobble rules.

Readers are given quite a lot of good advice. Crick says, "Most of the book is fairly easy. Don't give up hope just because a few paragraphs seem a little hard to follow." On p. 142, discussing theorists, "It is amateurs who have one big bright beautiful idea that they can never abandon. Professionals know that they have to produce theory after theory before they are likely to hit the jackpot." And "Theorists almost always become too fond of their own ideas. It is difficult to believe that one's cherished theory, which really works rather nicely in some respects, may be completely false."

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Chromatin Research Surveyed

Chromatin. KENSAL E. VAN HOLDE. Springer-Verlag, New York, 1988. xii, 497 pp., illus. $98. Springer Series in Molecular Biology.

Though the study of chromatin began in 1871 with the work of Miescher on "nuclein," in the past 15 to 20 years investigations of the complex of DNA, histones, and other proteins that make up the genetic material of eukaryotic cells have proliferated at an incredible rate. Milestones marking this development include the first chromatin Gordon Conference in 1972, the Cold Spring Harbor meeting in 1977, and now van Holde's monograph. Though reviews of progress in areas of chromatin research appear at least yearly, this book is the first comprehensive overview of this important field.

In the preface, the author compares his effort, which began eight years ago, to that of Sisyphus. Indeed, the task van Holde took on was gigantic and could have been unending—the book includes about 2000 references, and this list is quite selective—but he wisely set an end to it. The result, though not totally current, is a major contribution for the expanding scientific community that needs to have a background in chromatin.

Chromatin begins with two historical chapters, the first tracing early studies that defined DNA as the genetic element and described its association with structural proteins in the cell nucleus, and the second documenting efforts in the 1970s that led to the paradigm of nucleosomal organization of chromatin. The author then provides three chapters that succinctly but appropriately describe features of DNA, histone, and nonhistone chromatin protein composition and structure. This section of the book is invaluable to a chromatin scientist, a critical compilation of a lot of information for application to research.

With composition established, the second half of the book addresses chromatin structure and function. As the author notes, the time is ripe for some meaningful conclusions about the former topic, but premature for such analysis of the latter. Van Holde, one of the major contributors to the development of ideas about histone–DNA interactions, first deals with nucleosome structure. He recounts how, having a biochemically defined substrate for study, chemists were able to glean much information about the detailed organization of the nucleoprotein complex, culminating in the crystal structure of the core particle, that "precarious marriage of basically incompatible partners," DNA and the histone octamer. The second chapter on structure addresses organization from the chromatin fiber to metaphase chromosomes—again it is critical and illuminates controversies in this area of investigation and the current uncertainties in interpretation of data.

The final two chapters of the volume address the more difficult subject of chromatin function in transcription and replication. As van Holde acknowledges, these are areas where developments are occurring with great rapidity and, as he predicted in the preface, the chapters are already somewhat out of date. He has elected to review a limited subset of transcriptionally active or competent gene structures and reviewed them in detail (an approach I applaud, as opposed to an encyclopedic but shallow compilation of all studied systems). His chapter on replication addresses a complex subject that is of great interest; unfortunately, it has fallen from favor largely because the questions are so difficult and the answers often ambiguous. This chapter is one of the best examinations of replication of chromatin I have read.

What are the weaknesses in the book? Unfortunately, there are not infrequent mechanical errors. References are current only through 1985, with some from 1986 and only a few from 1987. The volume is not meant to be equivalent to a journal minireview—rather, it provides a foundation for assessing the current literature.

What is the major strength of *Chromatin*? The author has provided a critical evaluation of a mass of data that have never before been reviewed in such detail. Admittedly personal, his ideas are well thought out and usually solid. He is willing to take a stand on some controversial issues while admitting he might be shown wrong in the future. He consistently points out limitations in interpretation of data and eschews overly speculative thinking.

Finally, who should read this volume? Not surprisingly, almost anyone who is involved in research directly or peripherally related to its topic. It will be a marvelous springboard for a graduate-level course in eukaryotic protein-DNA interactions. All those interested in *trans*-acting factors, who run mobility shift gels or do footprints, should read it to discover features of the in vivo milieu in which DNA really exists. Those of us who have been around through the nearly two decades of modern chromatin research should read it to relive the excitement and to take heart in still working at the admittedly more difficult current questions involved in relating composition, structure, and function in the eukaryotic genome.

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