Reflections on the Historiography of Molecular Biology

HORACE FREELAND JUDSON

SURELY the time has come to stop applying the word revolution to the rise of new scientific research programmes. Our century has seen many upheavals in scientific ideas—so many and so varied that the notion of scientific revolution has been stretched out of shape and can no longer be made to cover the processes of change characteristic of most sciences these past hundred years. By general consent, two great research programmes arising in this century stand out from the others. The first, of course, was the one in physics that began at the turn of the century with quantum theory and relativity and ran through the working out, by about 1930, of quantum mechanics in its relativistic form. The transformation in physics appears to be thoroughly documented. Memoirs and biographies of the physicists have been written. Interviews with survivors have been recorded and transcribed. The history has been told at every level of detail and difficulty. The second great programme is the one in biology that had its origins in the mid-1930s and that by 1970 had reached, if not a conclusion, a kind of cadence—a pause to regroup. This is the transformation that created molecular biology and latter-day biochemistry. The writing of its history has only recently started and is beset with problems.

Accounting for the rise of molecular biology began with brief, partial, fugitive essays by participants. Biographies have been written of two of the less understood figures in the science, who died even as the field was ripening, Oswald Avery and Rosalind Franklin; other scientists have written their memoirs. Various collections of historical reminiscences and personal tributes have been issued. Three histories have been published. The histories are The Path to the Double Helix, by Robert Olby; 1 A Century of DNA, by Franklin H. Portugal and Jack S. Cohen; 2 and my own The Eighth Day of Creation. 3 The biographies and memoirs include The Double Helix, by James D. Watson; 4 Rosalind Franklin and DNA, by Anne Sayre; 5 The Professor, the Institute, and DNA, a life

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of Oswald T. Avery, by René J. Dubos; and *Heraclitean Fire: Sketches from a Life Before Nature*, by Erwin Chargaff. I propose to discuss here Dubos’ biography, Chargaff’s memoir, and the histories by Olby and by Portugal and Cohen, and to comment briefly on other work including the more important individual historical papers and collections of them. Throughout, my central concern is to establish the fundamental character of the change in thinking—of the transformation of the nature of acceptable answers—that marked the rise of molecular biology. It is my view that the history of biology offers an overdue corrective to certain long-fashionable ideas based almost entirely on classic examples from the history of physics.

*The Standard View and Its Deficiencies*

From the earlier accounts of the rise of molecular biology, particularly those written by participants, has emerged what may be taken as the usual view, the standard view—to put no fancier a name to it—of the origins of this science. The standard view has several elements.

For one thing, new people moved into biology, and most famously the physicists. The invasion of the physicists was celebrated in an admirable essay, “Emigré Physicists and the Biological Revolution”, by Donald Fleming, published in 1969. Fleming’s essay was occasioned, in part, by the scandal that accompanied publication, the year before, of Watson’s *The Double Helix*. It also drew with imagination and panache on various reminiscences found in a collection, *Phage and the Origins of Molecular Biology*, which had been published, two years before that, as a sixtieth-birthday tribute to Max Delbrück, who has been the most influential of the physicists turned biologist. The Delbrück collection is the earliest but still by far the most interesting of such volumes engendered by this science, and Professor Fleming pointed out why: the editors demanded and mostly got contributions that were focused, personal, and coolly depreciatory much in the style that was Delbrück’s own. From these and Watson’s book, Fleming elaborated a brisk and witty narrative which traced the intellectual origins of one of the chief schools in the formation of molecular biology—the circle of biologists around Delbrück in the late 1940s and early 1950s, who worked with the genetics of the simplest of creatures, the viruses, called bacteriophage, that prey on bacteria. Fleming showed how Delbrück, a young quantum physicist in Göttingen in the early 1930s, was influenced by Niels Bohr to try to find in biology...
new scientific laws or principles that would be complementary to, and irreducible to, the laws of chemistry and physics. Bohr’s and Delbrück’s was an antireductionist programme. Delbrück’s earliest biological thinking was about the physical nature of the gene. He wrote a paper about that, in collaboration with a geneticist and a specialist in the mutations caused by X rays. The paper was published in 1935. Its important effect was to stimulate the Austrian physicist Erwin Schrödinger, when in exile in Dublin during the war, to write a tiny book entitled *What Is Life?*. Schrödinger’s book, in turn, in the years immediately after the war, attracted a large number of younger scientists to the idea that the mystery of life could be explained, and soon, in terms of physics and chemistry. Watson has written that his ambitions, and his attraction to the Delbrück circle, were in large part set by *What Is Life?*. As an adolescent scientist he grew up in the phage group. Given this chain of inspiring influences, Fleming’s ironical denouement is that the structure of the chemical stuff of the gene, deoxyribonucleic acid, when Watson and Francis Crick got it in 1953, amounted to a triumph of reductionism.

Many more physical scientists came into the nascent molecular biology. (Fleming mentions some, omits others.) Leo Szilard, one of the inventors of the atomic bomb, switched to biology and put himself under Delbrück’s tutelage after the war, and by the late 1950s had some interesting arguments to offer about the nature of the processes, within the cell, that regulate the expression of genes. Francis Crick was a physicist by training. So was Maurice Wilkins, who shared the Nobel prize in physiology or medicine in 1962 with Crick and Watson because he and others in his laboratory—chiefly Rosalind Franklin, who was dead before the prize was awarded—had got the physical data, the X-ray crystallographic data, on which the Watson and Crick structure was based. Franklin herself had trained as a physical chemist and crystallographer. George Gamow was another quantum physicist who came through biology in the 1950s—on a highly eccentric orbit, but with some original, stimulating, if oversimplified, ideas about the genetic code. Linus Pauling was a physical chemist and X-ray crystallographer who considered the structures of the large biological molecules, including proteins and nucleic acids, to be an inevitable extension of his domain. Of an older generation, Sir Lawrence Bragg, the founder of X-ray crystallography, and Cavendish professor of experimental physics in the University of Cambridge from 1938 through 1953, sponsored Max Perutz’s beginnings with protein crystallography at the Cavendish before the war and remained closely concerned with the work for thirty years, almost until his death. Desmond Bernal, another

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crystallographer of the Bragg school, was the man who first discovered how to get good diffraction patterns from crystals of proteins—an instance of the primacy of technique, for that was in 1934, at the Cavendish. By Crick’s estimate, at least, Bernal was the scientist with the grandest vision of the potential of the technique for dispelling the mysteries of living things. Bernal, in the two years before Bragg’s arrival at the Cavendish, introduced Perutz to the methods and hermetic glamour of X-ray crystallography. Perutz himself was not a biologist but an organic chemist. Then during the war Bernal became an adviser to Admiral Lord Louis Mountbatten, in South-East Asia, where he had as an assistant a young chemist named John Kendrew, to whom he also revealed the fascination of X-ray analysis. In 1946, Kendrew came to Perutz as a graduate student, and in 1950 they were joined by Crick, who had been in Cambridge for two years at another laboratory. They formed the unit that Watson joined on a post-doctoral fellowship in autumn 1951.

With the new men came new agendas. Among these, the most highly articulated was that of Delbrück and his school, the phage group. The phage group worked with a self-consciously fastidious rigour; they restricted themselves to the simplest biological systems; they distrusted biochemists and earlier microbiologists; the younger of them marked the group off from others in a manner frankly snobbish. In Watson and Gunther Stent the phage group has had skilful, insistent public advocates: they have attracted attention to a disproportionate degree.

Another agenda, that of Pauling and some of his many colleagues and students in the United States, and the related enterprises of Bernal and of Bragg among the crystallographers in England, was to investigate the structures of the large biological molecules—of proteins, in the first place, in the late 1930s—with the explicit idea that molecular structure should illuminate physiological function. A more general urge—widely felt in the mid-1930s and voiced by Warren Weaver, who was director of the natural sciences division of the Rockefeller Foundation—was to put physical chemistry to work “to uncover many secrets concerning the ultimate units of the living cell”. Weaver produced the name “molecular biology” and, without having to go into much detail beyond that name, provided money for the work of, among others, Delbrück, Pauling, and Perutz. To these must be added some deliberate attempts in Europe to bring together English and Continental geneticists, cytologists, and crystallographers. A number of small meetings were held, often financed by the Rockefeller

Foundation, most notably one at Klampenborg, near Copenhagen, during the first week in April of 1938; these were recalled in 1969 by one of the participants, C. H. Waddington. In the spring of 1938, Waddington had been finishing *An Introduction to Modern Genetics*, which became, in part, a manifesto for the ideas of the Klampenborg meeting. (The book got some bad reviews as a result.) And at about that same time, J. B. S. Haldane, a colleague of Waddington’s, laid down with astonishing prescience and exactitude an outline of the programme of what he did not yet call molecular biology. Then, after the Second World War, another new group of men formed, this time native to microbiology, around André Lwoff at the Institut Pasteur in Paris.

The new men and their programmes were in touch with one another, particularly and most continually at the California Institute of Technology, where Pauling was, and where Delbrück settled in 1947. Within a few years, the phage group and Lwoff’s unit at the Institut Pasteur were exchanging younger scientists so regularly that in effect they interpenetrated. One reason, obviously, was that these two programmes were fundamentally similar in using genetic manipulation of micro-organisms to isolate elementary biological events for scrutiny—and this despite the caste differences that some of Delbrück’s young enthusiasts felt between themselves who worked with phage and the others who worked with bacteria. But the great merger, of course, was that precipitated by Watson’s moving to the Cavendish Laboratory, to learn crystallography, and finding Crick there.

These elements, the most obvious in the growth of molecular biology, have suggested several attractive ways to state what happened, simply yet more formally. For instance, sciences are sometimes thought to form ladders: by one convention, mathematics, mathematical physics, physics, physical chemistry, chemistry, organic chemistry and biochemistry, cellu-

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14 Cited and quoted fully in Pollock, M. R., “The Discovery of DNA: An Ironic Tale of Chance, Prejudice, and Insight”, Third Griffith Memorial Lecture, *Journal of General Microbiology*, LXIII, 1 (1970), pp. 1–20. Pollock’s paper, though it accepts without question the standard view of the rise of molecular biology, goes somewhat more deeply into its antecedents than any other historical essay as early as his, and does so from a viewpoint that falls usefully aslant that of the members and propagandists of the phage group and, more generally, that of most American biochemists. Pollock has, for example, read Chargaff’s papers more extensively and carefully than most commentators have to this day. Haldane’s programme appeared in Haldane, J. B. S., “The Biochemistry of the Individual”, in Needham, J. and Green, D. E. (eds.), *Perspectives in Biochemistry* (Cambridge: Cambridge University Press, 1937). For an instance of Haldane’s foresight which was published in 1941 and which Pollock does not mention, see my *The Eighth Day of Creation*, p. 189.
lar physiology, and so on to ecology. (What such ladders represent, though, is unclear. Is a step upward a decrease in abstraction? An increase in complexity?) In such terms, molecular biology is taken to be the conquest of biochemistry by what has been called its "antidiscipline"—the science lower in the hierarchy, physics or physical chemistry. This simple dialectic is made more plausible by the very name "molecular" biology, by the fact that physicists moved into the science—and by the attacks of some from older disciplines who decry molecular biology as reductionism. Yet a moment's inspection shows this diagram to be too simple. Consider the physicists and the phage group, for instance. Not only did their programmes and personnel overlap with those of the microbiologists around Lwoff, but, even before discovery of the structure of DNA, the work of both groups was merging with that of the highly individual bacterial geneticists Joshua Lederberg and William Hayes. In what way was the contribution of the physicists to all that, uniquely physical?

More general and more useful is John Kendrew's version of the standard view. Kendrew proposed, first in 1965, that molecular biology was the confluence of two currents, which he labelled "information and conformation". Kendrew's play with words, while memorable, depends on a misleading flash of hindsight. Information theory was a programme of the 1940s and after, by which one would expect mathematicians and physicists to have influenced the course of molecular biology—for example, in solving the genetic code, which is to say, the relationship of the instructions in the genes for building the organism to the biochemical machinery for carrying the instructions out. Yet, in point of fact, information theory played no part. Its chief use has been post hoc, as a way to talk about

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16 Kendrew, John C., "Information and Conformation in Biology", in Rich, A. and Davidson, N. (eds.), Structural Chemistry and Molecular Biology (San Francisco: Freeman, 1968), pp. 187-197, which article is identified as "Based on the Herbert Spencer Lecture delivered at Oxford University, 1965."

17 The only important exception may have been an intervention by Leo Szilard, which took place late in 1957, in the development of the repressor scheme for control of enzyme biosynthesis. At that time, in Paris, Arthur Pardee was in the midst of a series of experiments whose interpretation he, Monod, and Jacob were debating (and which led, eventually, to the theory of the repressor) when Szilard came to visit for several days. Szilard, familiar with information theory, had been interested for several years in the problems of enzyme repression and induction and had proposed to colleagues that the two phenomena might be intimately related, as instances of feedback. Immediately before coming to Paris, he had given a seminar in Berlin on the subjects of enzyme repression and antibody formation. Monod on several occasions after Szilard's death asserted that his visit had been crucial in leading the group in Paris to their eventual formulation—but no independent evidence for the assertion survives, and, in particular, neither Pardee nor Jacob, when questioned carefully on the point, recalled Szilard making a specific contribution. I discussed the surprising ineffectualness of information theory in the formation of molecular biology briefly in The Eighth Day of Creation, pp. 242-246, and described Szilard's role in the problem of repression on pp. 407-411. I concluded there that the
discoveries and models that were reached without appeal to its principles. Kendrew used "information" in this retrospective way. He meant by information the moiety of molecular biology rooted in genetics, particularly of micro-organisms and including the genetical elucidation of biochemical pathways and controls, as by Monod and Jacob, as well as the formulation of the problem of the biological code; he meant by conformation the moiety springing from studies of the structures of the large biological molecules, as by Pauling and by the British crystallographers, culminating in the elucidations of the relations of structure to function in DNA and proteins. These currents in the early years of molecular biology can be more accurately labelled the one-dimensional (the genetic and sequential) and the three-dimensional (the stereochemical or structural). Put that way, the distinction moves beyond the limits of the standard view well towards the crux of the matter.

New men, new agendas, the confluence of neighbouring disciplines—but beyond these, the central and controlling element in the standard view of the early history of molecular biology is the change that took place in the identification of the chemical substance of the genes: the move away from the conviction, held by almost all biologists at the end of the 1930s, that genes were made of protein. In the mid-1940s, this conviction was called into question by the researches of the bacteriologist Oswald Avery and colleagues, at the Rockefeller Institute, and then of others; by the early 1950s, it was becoming widely accepted that genes are made of nucleic acid. The revision of the characterisation of the genetic substance, with the discoveries and arguments that made the revision persuasive, have been widely supposed to comprise the change that was most fundamental to the growth of biology in the latter half of the century. That this revision was the enabling, liberating one has usually been assumed without examination—certainly in the works I consider here. Chargaff identifies Avery's research as the inspiration for his own most important work. The revision is the implicit justification of Portugal and Cohen's writing a history focused on a single biochemical substance. Olby awards the revision the highest honour that fashionable jargon allows: it was, he says, a transformation of paradigms. "An important aim of this book has been to expose to view the great historical significance of the replacement of the Protein Version of the Central Dogma by the DNA Version of the Central Dogma," Olby writes in his last chapter;

particular mechanism of repression Szilard appears to have had in mind in the winter of 1957-58 had no effect whatever on the model that Pardee, Jacob, and Monod were developing, though Szilard doubtless forced them more quickly to a general realisation that the phenomena of enzyme repression and induction could parsimoniously be considered two aspects of some single mechanism. The text of Szilard's Berlin talk has not been published, however, so I was obliged to reconstruct his particular mechanism from other, later publications of his. Szilard's widow, Dr. Gertrud Weiss Szilard, has recently found the text of that talk among his papers, and has kindly sent me a copy. It confirms my conclusions. I shall examine the role of information theory in the growth of molecular biology in more detail in a technical paper now in preparation.
and he continues, "In this transformation of paradigms the discovery of the structure of DNA played a crucial role." 18

The standard view of the origins of molecular biology is incomplete and misleading. The questions here are nested: that is, a series of misconceptions of widening scope presses in the same direction and traces to the same root error. (A symptomatic instance is Olby’s gross misapplication of the term “Central Dogma.”) To begin with, Crick and Watson, like the Delbrück school and like the group around Lwoff, Monod, and Jacob, thought of themselves as wresting the direction of biological thinking at its most basic level away from the biochemists. In this narrow application, as motive or animus, there is that much truth to the dialect of antidisciplines.) The reclassification of the substance of the genes from proteins to nucleic acids, by the early 1950s, has hardly been hidden from view. On the contrary, the switch has been given such prominent attention, and starting well before Olby wrote, that it has obscured the deeper and more general change that was taking place simultaneously. This was nothing less than a change in the ruling preconceptions of biochemistry itself. Despite the prejudices of the founding fathers of molecular biology, this, the most fundamental change, was set in motion by the work of biochemists—in particular by Frederick Sanger and by Chargaff. The fact is that when Crick met Watson (and when Jacob began his ten-year collaboration with Monod) the transformation in ruling preconceptions was already all but complete. The idea transformed was that of biological specificity. The model of DNA—the double helix—that Crick and Watson built, 18 months after Watson came to Cambridge, was not instrumental to the change. Yet it gave legitimacy to the new understanding of biological specificity, in a physical form of compelling explanatory power.

A minimum of technical detail will facilitate precise discussion. Biochemicals occur in two sorts of sizes, having molecules that are either fairly small or very large, with few that are intermediate. This is because the large molecules are made up of long chains of small subunits. The large molecules are of four kinds, namely, lipids, or fats; polysaccharides, comprising sugars made up into starches; proteins; and nucleic acids. In the 1930s, the genetic material was thought to be protein because protein molecules were known to be exquisitely specific in their biological action, even though nobody knew just how they acted. The variety of proteins is bewildering. Many hormones—insulin, for example—are protein molecules. Respiratory carriers, like haemoglobin, are protein molecules. Antibodies are protein molecules. Enzymes, the catalysts of every cellular process, are protein molecules. And the biochemical action of all these substances is highly specific. Genes, too, whatever they were in substance, were highly specific. They seemed in effect to be catalysts. Autocatalytic, they directed the making of more of them-

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18 Olby, R., *Path to the Double Helix*, p. 434; see also p. xxii.
selves. Heterocatalytic, they prompted the making of the rest of the organism. Only proteins were known to be anything like so versatile as genes must be.

The belief that genes must be protein, and the reciprocal conviction that any other substance which seemed to possess such specificity must be contaminated by traces of protein, was commandingly reinforced by one of the greatest scientific reversals in the history of biochemistry—the proof that enzymes are, indeed, proteins, and the humiliation of Richard Willstätter. In Munich, in the early 1920s, Willstätter—who was perhaps the foremost organic chemist of the day, and a specialist in enzymes—had claimed that he had obtained enzymatic, catalytic action with preparations that were purified and free of protein. On his evidence, it came to be widely accepted that the biological specificity of solutions containing certain known enzymes was not attributable to protein. But then in 1926 James Sumner crystallised the enzyme urease, and showed that it was protein. In 1930, John Howard Northrop and his associates developed precise techniques for correlating enzymatic activity with the quantity of protein present, and showed conclusively that Willstätter’s experiments had been contaminated by traces of protein. Everybody in biochemistry in the 1930s and 1940s knew of the Willstätter scandal.

Then in 1935 Wendell Stanley announced the crystallisation of the virus that causes the mosaic disease of tobacco—and that was sensational news. Stanley believed that tobacco-mosaic virus was pure protein, though after a while it was found that about 6 per cent. of the virus is the other kind of nucleic acid, ribonucleic acid, or RNA. And biologists knew that in every organism higher than viruses, bacteria, and the simple blue-green algae the chromosomes themselves, where the genes were known to reside, are made of protein and DNA intimately bound together. As for bacteria, they were not thought to have chromosomes at all.

In 1938, not much detail was known about the structures of protein molecules, except that they were made up of amino acids, these being small subunits that occurred in twenty-odd different varieties. The belief was widespread that the amino acids were assembled in chains; but even though the idea that proteins were chains had been present since the beginnings of biochemistry, consensus was recent and other structural ideas had not been abandoned altogether by their supporters.

In the 1930s, nucleic acids seemed as uninteresting as polysaccharides. That is, their chemical structures were believed to be unvarying and repetitive. DNA, in particular, was known to come in long strands—though how very long the strands typically are was not known. The strands were built up from four structurally similar components, called nucleotides. Each nucleotide carried one of four possible side groups called, collectively, bases. The bases were of two kinds—the single-ringed pyrimidines (thymine and cytosine) and the double-ringed purines (adenine and
The nucleotides were supposed to make up DNA by being strung together in sets of four with all the bases equally represented in unvarying repetition. This exceedingly elementary idea was called the tetranucleotide hypothesis. It had been propounded by Phoebus Levene, at the Rockefeller Institute, an organic chemist of the highest reputation. The idea that DNA might have two or three strands related in some essential way had never been breathed. Acceptance of the tetranucleotide hypothesis was general, if not fervent. As one consequence, everybody took it for granted that the bases were present in equal quantities in DNA—even though, in fact, with the chemical techniques then available accurate measurement of the proportions of the bases in samples of DNA was impossible. As another consequence, DNA in unvarying regularity could not possibly specify diversity. The belief was held tenaciously that the DNA in the chromosomes could only be some sort of structural stiffening, the wooden stretcher behind the Rembrandt, since the genetic material would have to be protein.

Avery and the Notion of Premature Discovery

In the shift from the protein gene to the nucleic-acid gene, between the late 1930s and early 1950s, the most interesting and poignant figure was the bacteriologist Avery. The essential facts of Avery’s life in science have been available, if scattered, in several memoirs by colleagues of his; Dubos also worked with him at the Rockefeller Institute, and has written a useful, pious, reticent brief life. Avery was a physician by training, and by habit was retiring and scrupulous. He spent all his long research life—from before the First World War until after the Second—investigating the pneumococcus, with the idea that eventually it would be possible to immunise human beings against pneumonia. (Incidentally, this is an aim which was washed away, in the late 1940s, by the power and availability of penicillin, but which is reviving now because of the spread of bacterial resistance to antibiotics: Avery’s work will yet yield direct therapeutic results.) Avery—as Chargaff, among others, has pointed out—made not one but two great discoveries. The first came in the early 1920s, when he demonstrated that pneumococci fall into distinct, true-breeding types—separate varieties within species, we would now say. This was the first evidence for fixed varieties in bacteria: if that seems astonishing today, remember that in 1923 the rediscovery of Mendelian genetics was two decades old, the association of Mendelian genes with microscopically visible chromosomes yet more recent—and that bacteria did not appear to have chromosomes. Avery began a long process by which micro-organisms were brought out of a misty biological borderland and made part of Mendel’s

realm. Five years later, a rival, Frederick Griffith, in London, discovered that pneumococci of one fixed type, in the presence of material from a second type, could be transformed to the second type—permanently, heritably. Griffith produced the first transformations by injecting mice with two preparations: with live bacteria of a non-virulent type and simultaneously with killed bacteria of a virulent type. The mice died, and from their hearts' blood were recovered live, virulent pneumococci of the type that had been injected killed. Soon, in Avery's laboratory, the transformation was accomplished without the mice, just in a culture. Then Lionel Alloway, in Avery's laboratory, did the trick without using the carcasses of killed bacteria, but just by adding to a live culture of the first type of pneumococcus an extract, free of whole cells, from pneumococci of the second type—and getting out live bacteria of that second type. In years of work and uncertainty, Avery and his colleagues obtained the material that caused the transformation in progressively purer form, and grew progressively more certain of its surprising identity. By 1943, he was ready to announce, cautiously, that the transforming principle appeared to be DNA, and nothing else. How DNA could do this was baffling. It changed heredity. That spring, Avery speculated—in the course of a long private letter to his brother, Roy Avery, who was at Vanderbilt University—that he had isolated the substance of the gene. The speculation was suppressed in the paper that he published a year later with his colleagues Colin M. MacLeod and Maclyn McCarty—the paper now regarded as a classic and the turning point in the recognition that the genetic substance is nucleic acid rather than protein.

Dubos' biography of Avery is illuminated by intimate acquaintance with the institutional setting and year-to-year progress of the work, and by an evident love of the man. The biography is the best we are likely to be given, but it is a disappointment. To begin with, the book is built up of three parallel but separated narratives. The first is a brief history of the Rockefeller Institute for Medical Research from its founding, in 1901, to its redesignation as the Rockefeller University, in 1955. Dubos acknowledges in his introduction that he wrote this largely from recollection and his own records, consulting little from the large archives of the institute's history that are now open: in effect if not intent he has here made a minor contribution to those archives—but has not written a penetrating epitome of an institution for research complete with its politics and problems. The second narrative is of Avery's life as if isolated from the content of his work—although the work was, in Avery's case far more than most, the centre of the life. A single chapter that recounts "Avery's Personal Life" is followed by another, "Avery's Life in the Laboratory", which attempts to convey, chiefly by anecdote, the man's style in doing and directing research—and yet, once more, as though even this can be isolated from the detailed content of the work in which the
style is expressed. Then, at last, halfway through the text, the third narrative begins, that of Avery's 35 years of research. Dubos floats back and forth, forever obliged to recapitulate. The seasoning of direct and uncritical praise, conventionally expressed, is strong; the demonstration of greatness has been replaced by its assertion.

By giving us the institution and the personal life and the scientific work, Dubos evades the problems of their interaction that we most want to understand. In Avery's case, the most basic problem is: why did identification of the transforming principle take so long? Thus, what was there about the practices and expectations of the institution, and about the beliefs, judgements, and critical attitudes of other scientists there, that made the pace so slow and the conclusions so cautious? For example, it was at the Rockefeller Institute that Northrop and his colleagues carried out the work, in the early 1930s, which definitively established that enzymes are proteins and that Willstätter's results were due to undetected traces of protein in the experimental preparations. Dubos mentions Northrop only twice, fleetingly and in connections far removed from the Willstätter case; he does not mention Willstätter or related work at all. And yet, in a telephone conversation in April 1978, when I asked Dubos about the effect of that on Avery, he replied, "It was on everybody's mind!"

The discoveries of Northrop (and of Stanley) were celebrated, and entirely to the credit of the Rockefeller Institute: Dubos hardly hints that the place, and some of his and Avery's associates, may have had deficiencies that also held Avery back. Thus, Dubos acknowledges in a paragraph that Alfred E. Mirsky, who was working in biochemical genetics at the Rockefeller Institute, suggested after publication of Avery's classic paper that the preparations of DNA had not been conclusively shown to be free of protein. But he nowhere conveys the bitterness, from motives of scientific and perhaps even personal bias, with which Mirsky pressed his objections—both within the institute and outside, and often behind the backs of Avery and his group. In sum, Mirsky campaigned against Avery's results, and with considerable effect in the medium term. When I asked Dubos, he acknowledged that he had deliberately understated Mirsky's attacks.

Even more interesting would be an indication for the time before 1943 of the extent to which Avery's work may have been slowed by explicit opposition and criticism and by such factors that one might imagine as, for example, the relative standing of Avery's unit within the administrative and scientific hierarchy at the institute. Portugal and Cohen recognise at least that a problem exists. They write:

It should also be noted that Griffith's original description of pneumococcal transformation was published in 1928 and that Alloway described the preparation of the pure cell-free transforming substance in 1933; but its identity was

20 Conversation with René Dubos, by telephone to his office at the Rockefeller University, 24 April, 1978.
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not determined by Avery and his coworkers until 1944.... In fact, Avery published nothing from 1934 to 1941 and nothing on transformation from 1933 until 1944.

They continue, "Much has been made of the delay between the publication of the Avery work in 1944" and its acceptance and confirmation by the early 1950s, "yet no mention has been made of the longer delay in following up the studies on the chemical nature of the transforming agent by Alloway, either in Avery's laboratory or elsewhere." Portugal and Cohen offer no explanations.

Dubos gives answers that are no answers. He blames technical difficulties, principally Alloway's early techniques for extracting the transforming substances, which produced preparations of erratic and unpredictable performance. He asserts that once Colin MacLeod joined Avery in 1935 the technical problems were solved and "progress was extremely rapid", though the evidence he cites is a section in the unpublished annual scientific report of the institute for 1940-41. He then says that when MacLeod left in the summer of 1941 and McCarty replaced him, isolation of the transforming substance was accomplished "within an incredibly short time". But the problem of the delay cannot be conjured away.

Similarly, but now in the narrative section Dubos labels "personal", he explains that in the early 1930s Avery suffered from Graves' disease, because of which "he then frequently experienced moods of depression and irritation that he did not always manage to conceal, despite valiant efforts". The problem persisted for years. Avery had a thyroidectomy in 1933 or 1934, which, Dubos implies, relieved the psychological symptoms. But he makes no connection whatever between that malady, its psychological manifestations, and its possible sequelae, on the one hand, and on the other the progress of research in Avery's laboratory. More generally, Avery's apparent severely neurotic traits are not frankly discussed as they may have borne on the work. Piety, discretion about a friend, and reverence for an institution impose obvious limitations: one cannot dust off a reputation if one is afraid it will shatter when picked up.

Dubos reprints in an appendix the relevant portion of the text of the letter Avery wrote to his brother in 1943. This is the most complete and accurate transcription yet published, but it contains a large number of trivial, irritating errors.

The finding that DNA could carry gene-like specificity is the great discovery for which Avery is now remembered. At the time, Avery's publication of the discovery was received with reserve—not with acclaim for the overthrow of the protein gene but, rather, with what can best be described as puzzled consideration. As a result, a piece of folklore has grown up in the scientific community. Avery was ignored, so the folk-

22 Dubos, R., The Professor... and DNA, pp. 140-142, 66.
lore asserts. The Delbrück circle was too snobbish to pay attention. H. V. Wyatt, an English biologist, distilled the folklore and perpetuated it in a brief paper in 1972, in which he summarised the results of a search in the biological literature for citations of the work by Avery and his associates. The notion of using "citation networks" as evidence in studies in the history and sociology of science was fairly new when Wyatt wrote. He looked, first, at the circulation of the journal—*The Journal of Experimental Medicine*, published by the Rockefeller Institute—in which the classic paper by Avery, MacLeod, and McCarty appeared. Thus, Wyatt reported:

It was a famous and respected journal bought usually by medical rather than science libraries, but at that time most geneticists worked in science departments. In 1944, there were thirty-six copies of the journal in libraries in Britain and of these at least twenty and probably more than twenty-six were in medical or veterinary libraries. In libraries in the United States itself there were about 125 copies. Of these at least forty-five were in medical libraries, probably seven in the libraries of pharmaceutical firms and seventy in university libraries. Some of those in university libraries were probably housed in separate medical buildings.

Wyatt then examined the title, the summary, and the conclusion of the paper itself and found in them "few if any key words that would have led to recognition at the time". The summary, for example, in his judgement was "not very provocative—there was no mention of gene, mutation, or any terms to link the findings to general genetic ideas". Abstracts of the paper, in abstracting journals, also ignored the genetic implications. From such evidence Wyatt decided, "Whatever Avery thought of his work, he intended it to be found, seen, and read by those interested in pneumococci, not genetics."

Already one wants to demur: the fact is that with very few exceptions, throughout Avery's career from the time he joined the Rockefeller Institute, he published his work in the institute's *Journal of Experimental Medicine*; and his laboratory colleagues routinely, if with more frequent exceptions, did so too. (An excellent feature of Dubos' book is a chronological bibliography not only of Avery's publications, but, year by year, of his co-workers' as well, whether or not Avery was among the listed authors.)

Wyatt acknowledges, in his next sentence, "Nevertheless the news spread fast." That is, various people did become aware of the work; and he mentions individuals and occasions, like the annual symposia at the Cold Spring Harbor Laboratory, on Long Island, much frequented in the summers by Delbrück and members of the phage group. Despite the velocity of the news, though, "Even at the 1953 symposium where Watson and Crick presented a paper on DNA there was little mention of Avery

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and his associates." More generally, for the period from 1944 through the mid-1950s, Wyatt examined literature likely to be read or papers at meetings likely to be attended by four groups that had need to appreciate Avery’s work—biochemists, geneticists, the phage group, and microbiologists. He found, in fact, just what one might expect: some people discussed Avery’s work, some cited it where relevant, others did not. The conclusion? “Thus, by 1952, there were small numbers of influential people who had accepted the idea that DNA might carry genetic information.”

The objections are obvious. First, the strong implication of Wyatt’s article is that Avery’s work, through his own timidity and through the inattention of various scientific communities, was ignored; yet Wyatt’s evidence does not bear that out. Second, published references to Avery’s work are far more frequent in the crucial years than Wyatt found, as Dubos and especially Hotchkiss have since proved. Third, although Wyatt acknowledged the existence of “commuting [sic] scientists who visit and correspond with each other”, and even drew a social diagram, he made little real allowance for the importance of informal communication; yet, for the phage group especially, that sort of communication was crucial—as even the countless anecdotes in Phage and the Origins of Molecular Biology only begin to hint. For these reasons, Wyatt’s paper is not a demonstration that Avery was ignored but, rather, a demonstration of the fatuity of citation analysis applied to a great turning point in the history of ideas. Most fundamentally, such analysis is irrelevant: some scientific findings and papers, and pre-eminently Avery’s, are of a kind to which immediate acceptance and frequent citation in ensuing research reports are not appropriate. Avery raised deep questions to the level where clear analysis began to be possible: he got the response the work called for.

Wyatt’s paper would not in itself be worth detailed rebuttal, except that the tenor of its conclusions has been widely accepted, at least until the last year or two. Stent has even decided that Avery’s discovery is an example of what he calls “prematurity” in science: that is, stated baldly, that a discovery will not be noticed and believed if it is made before a context has grown up that will support it. Stent has offered two examples of premature discoveries—Mendel’s and Avery’s. The notion has attracted attention and is worth examination.

Wyatt and Stent have provoked several scientists to defend Avery’s scientific standing. All concede that Avery was, indeed, cautious in his conclusions. By today’s standards—or today’s absence of standards, when Nobel laureates call press conferences to announce dubious discoveries in genetic engineering—Avery seems almost pathologically scrupulous. But it is not true that Avery was ignored. Portugal and Cohen address the

24 Stent, G., “Prematurity and Uniqueness...”
problem of the reception of Avery’s work, but do so briefly and ambiguously, seeming to affirm and simultaneously to deny that recognition was delayed. Dubos does better. He stammers oddly at the start:

Avery... was virtually ignored by the theoreticians of genetics, precisely because he made no effort to communicate with them or, more exactly, to communicate to them what he had discovered by working at the bench instead of speculating about the secret of life.25

The petulance is unfortunate. As Dubos well knows, the phage group did experiments. As he may not have realised fully, the group’s leaders were attentive to Avery’s work even before it was published. One instance of this attention is dramatic. Delbrück was at Vanderbilt during the war years, teaching physics while at the bench in biology, and he knew Avery’s brother, Roy, there. The day that Roy Avery received the letter that discussed the findings, he showed it to Delbrück—a fact that Dubos does not mention, although it was Delbrück who brought the letter to light when, wanting to quote it in a memorial address after Oswald Avery’s death, he persuaded Roy to search his papers and find it. But well before 1944 Delbrück had visited Avery and discussed the work. Luria had first learned of the transformation phenomenon on reading the 1941 edition of Theodosius Dobzhansky’s Genetics and the Origin of Species; his own laboratory was then at the Columbia-Presbyterian Medical Center, across Manhattan from the Rockefeller Institute, and he visited Avery right away and repeatedly, getting to know him perhaps best of those in the phage group and developing an intense admiration for him.26 Dubos’ omission is unfortunate and surprising, for he was roused by Stent’s notion that Avery’s discoveries were premature—and, in particular, by Stent’s assertion that “in its day, Avery’s discovery had virtually no effect on the general discourse of genetics.” Dubos ticks off citations that demonstrate that between 1943 and 1948 Avery’s work was indeed attended to and understood by leaders in genetics worldwide. In the United States, these included Dobzhansky, Sewall Wright, George Beadle, and others. In England there was Macfarlane Burnet; Sir Henry Dale, president of The Royal Society, in his presidential address in 1946 cited Avery for the Copley medal and said that transformation of pneumococcal types should be given “the status of a genetic variation; and the substance inducing it—the gene in solution, one is tempted to call it—appears to be nucleic acid of the desoxyribose type.” In France, at the conclusion of a symposium in 1948, Lwoff observed of the work of Avery’s laboratory that “at the present time we know of two varieties of specific nucleic acid of type III pneumococcus. They have been compared to allelomorphic genes.”27

26 Full details and quotations in my The Eighth Day of Creation, pp. 57–63.
27 Dubos, R., The Professor... and DNA, pp. 156–157, 148.
All other attempts to document the reception of Avery's work are superseded, however, by an historical review that Hotchkiss presented at a conference held by The New York Academy of Sciences late in the spring of 1978. He cites and quotes scores of responses to the work in Avery's laboratory and to the great paper and its successors. Attention to the findings was widespread; understanding of their possible genetical implications was clear; confirmation and extension of the work were just as clearly necessary. “In contrast with Stent’s conclusion, it was early generalizations and not the discoveries themselves that were premature.” Hotchkiss finds the integration of Avery's results into the fabric of science to be, in fact, typical:

As I have mentioned, but not stressed, the same broad pattern of discovery, consolidation, and reorientation is woven in and out of the whole connected history, not only in the DNA-transformation part. . . . I have a lively sense that in the DNA revolution at least, the slow process consisted in imagining and designing the new kinds of experiments that could give force and generality to those ideas.

Premature discoveries may well occur in science. Mendel's may have been one. Another often proposed, although not by Stent, is Archibald Garrod's realisation that the product of the formal, unit gene of classical genetics is an enzyme. In the opening years of the century, soon after the rediscovery of Mendelism, Garrod, an English physician, showed that certain rare, inherited human disorders—albinism was one that he identified, and another was alkaptonuria, in which the patient's urine turns terrifyingly but harmlessly black—are caused by the absence of specific enzymes. In 1908, Garrod called such disorders by the term we still use, inborn errors of metabolism. But the relation of gene to enzyme did not assume its pivotal place until the emergence of biochemical genetics in the late 1930s. The most clear-cut instance of premature discovery, though, comes in the history of penicillin. In the 80 years before the day in 1928 when Alexander Fleming noticed that a culture dish of staphylococci was contaminated by a patch of mould that seemed to have caused all nearby bacteria to burst, the antagonism of moulds of the Penicillium family to various bacteria had been noticed repeatedly and not followed up: by Joseph Lister in 1871, by the microscopist John Tyndall in 1875, by Louis Pasteur and Jules Joubert in 1877. The discovery and thorough proof of the action of Penicillium against bacteria, and its potential for medicine, were made in 1896—by Ernest Augustin Clement Duchesne, a student at the Medical Academy of the French army, in Lyons, who was doing the research for his dissertation for the medical

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degree. Duchesne’s dissertation was published in 1897, but was unnoticed for 50 years.

Thus, on the face of it, Stent’s idea of premature discovery merits a more general exploration, which, in fact, it has not yet received. I suspect that many but perhaps not all instances that could be nominated would turn out, on close examination of the context and immediate response, not to meet Stent’s or any other useful criterion for prematurity. For example, the lineage of thought and experiment between Garrod and the biochemical geneticists of the mid-1930s and afterward has not, so far as I know, been carefully elucidated. Furthermore, instances that survived scrutiny would no doubt fall into several categories, depending on the dominant reason for their prematurity. Technological difficulties may have made testing or exploitation of a discovery impossible: such is surely the case with the recorded observations of the antibiotic effects of moulds before Fleming. Bad luck—like good luck—cannot always be disallowed: Duchesne was genuinely unknown and unconnected.29

Be that as it may, Hotchkiss has shown conclusively that Avery’s work was known, understood, and well regarded. The reception at its most thoughtful entailed a radical suspension of judgement—an equivalent of what poetics terms the suspension of disbelief. This suspension was explained by Max Delbrück, in a conversation in 1972. “Everybody who looked at it, and who thought about it, was confronted with this paradox, that on the one hand you seemed to obtain a specific effect with DNA, and on the other hand at that time it was believed that DNA was a stupid substance, a tetranucleotide which couldn’t do anything specific,” Delbrück said. He went on:

So, one of those premises had to be wrong. Either DNA was not a stupid molecule, or—the thing that did the transformation was not the DNA. . . . So this was very clearly the dilemma, and at that time it was not a matter of right thinking or of profundity or of anything except that you had to find out. Which was right. And Hotchkiss was the one who then joined the Avery group, and in several years of very careful work established that indeed it was the DNA.

So then the dilemma became—can DNA carry specificity, or are we really not dealing with specificity at all but with a third possibility, some very special case where all the specificity is already there but just needs a stupid kind of molecule to switch it from one kind of production to another. Today we would say that the information is already in the genes; we might say now that you “de-repress” a gene. At that time we might have said, for example, you can switch a tree from non-flowering to flowering, and if you do it by manipulating the daylight-and-dark cycle then you are not putting in a molecule with information but just throwing a physiological switch. Everybody who was interested in these basic questions discussed this. . . . And even after people began to believe it might be DNA, that wasn’t really so fundamentally a new story, because it just meant that genetic specificity was carried by some goddamn other macromolecule, instead of proteins.

Both proteins and nucleic acids were hopelessly inadequately characterized, in those days.20

Once more, we approach the crux of the matter. The man who began the correct characterisation of DNA was Erwin Chargaff.

The Tragedy of Chargaff

The memoirs of the biochemist Chargaff plunge the commentator who knows the facts into an unhappy conflict of pieties. Erwin Chargaff has been, above all, a man of honour who has refused to let himself become inured to the times' decay. He has protested in countless short pieces addressed to his peers in science or on occasion to a wider audience—and in the past has done so with a fine and witty rage. We must cherish him for that. Chargaff is a man of classical education, which he has kept sharp and shining. He is a master of many languages (reading, by his count, in 15) and a master of language—a mordant stylist and a scathing polemicist. We can admire all this. Chargaff trained as a chemist in Vienna after the First World War, and earned his living at biochemistry for 50 years, 40 of them at Columbia University, eventually becoming chairman of the department there; yet he likes to say that he strayed into science, that biochemistry was but an avocation, that he has always been an outsider at the inside. In the late 1940s, Chargaff made certain simple discoveries about the chemical composition of DNA. His discoveries were crucial to the rise of molecular biology. He has been honoured for those discoveries—though with the parsimonious justice of a ten-per-cent. tip. Yet at the time he made the discoveries he did not fully understand their consequences, and to this day he does not properly value the work he did. This compound failure of judgement—predictive, retrospective—has poisoned his relation to the world of science for a quarter of a century. Now he is old. He has published his apology for his life. It is intermittently fascinating, sometimes beautiful, but, in the end, a treason to himself. Chargaff has demeaned his gift: where he used to be funny and nasty, here the humour has left him. That lapse one might pass in silence. But he is also trying to revise history.

Chargaff, on encountering Avery's paper of 1944, was decisively moved to take up research into DNA, with the hope of characterising the stuff adequately. Methods for separating and accurately measuring tiny quantities of complex and closely similar biological substances, such as the different nucleotides, were only then becoming available. Adapting the methods to DNA took Chargaff several years. By 1949, he and his colleagues had analysed the DNAs of a variety of different organisms. They found the four different bases appearing in DNA in proportions

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20 Interview with Max Delbrück, Cold Spring Harbor Laboratory, New York, 9 July, 1972. For context and more of his comments, see my The Eighth Day of Creation, pp. 58–61.
that, although constant in a given species, varied widely from one species
to another, only in a few species approaching equal representation of the
two. "The results serve to disprove the tetranucleotide hypothesis,"
Chargaff wrote in 1949 in a review paper published the following year.
Then he added—he now informs us, only when the paper stood in
proof—a brief observation about a curious possible regularity that he
noticed, after all, in the proportions of the bases:

It is, however, noteworthy—whether this is more than accidental, cannot yet
be said—that in all desoxypentose nucleic acids [DNAs] examined thus far
the molar [that is, molecule-to-molecule] ratios of total purines to total pyri-
midines, and also of adenine to thymine and of guanine to cytosine, were not
far from 1.31

A young biochemist of exceptional talent said to me a couple of years
ago that Chargaff has found the beauty of science to lie in the mystery
of its problems, even to the point where he could not bear to see them
solved. "That's one of the most remarkable characteristics of most
scientists," I was told. "At some level, eventually, they fondle their
problems." 32

The dominant mood of Chargaff's memoir is nostalgia. The passings
he laments include "the last glow of a calm, sunlit period . . . , the dying
years of the Austrian monarchy", into which he was born in 1905; his
mother, in images out of his childhood, seen "floating behind a screen
of tears", who was "deported into nothingness from Vienna in 1943";
the distinct second-person-singular pronoun in English, "victim to a
grammatical egalitarianism that has corroded the poetic core of the
language". Almost above all, however, Chargaff regrets the disappear-
ance of science and in particular chemistry "of the old observance"—
that is, small-scale, inexpensive, reflective, and, indeed, reverently non-
reductionist before the mysteries of life. Chargaff cuts his nostalgia with
contemptuous hatreds. He excoriates the totality of those American
institutions whose gigantism, competitiveness, faceless hypocrisy, and
ethical insensitivity have led, among other things, to the monstrous mis-
use of science in atomic weapons and, he thinks, in genetic engineering.
Detesting most things he cares to mention about the country that took
him in, he secretes a special sac of venom for the place with which he
was mostly closely associated: Columbia University treated him shabbily
at the time of his retirement, refusing to endorse new grant appli-
cations, changing the locks on his old laboratory, stranding him with a
pension of 30 per cent. of his salary. But worst of all he scorns the
science he unintentionally helped to found—molecular biology. And

31 Chargaff, Erwin, "Chemical Specificity of Nucleic Acids and Mechanism of their
32 Interview with Roger Kornberg at Stanford University, 11 August, 1978; full quota-
tion and context in my The Eighth Day of Creation, pp. 495–496.
where his other hatreds, arresting enough in detail and in phrasing, do not these days seem so original, here lie the pathetic self-betrayals of his book.

The central episode in Chargaff's memoir, by all evidence a psychological pivot of his life—the place where wit now fails him and where he is conjuring the past to be different—was his meeting, in Cambridge, in the last week of May 1952, two younger scientists interested in DNA: Francis Crick and James Watson. The two were then virtually unknown. Chargaff, on the other hand, appeared in the ascendant. Columbia made him a full professor that year; he was invited to lecture that summer at the Weizmann Institute, in Israel, and in several European cities, and was to read a paper about DNA at the Second International Congress of Biochemistry, meeting in Paris; he had hopes of escaping Columbia and the United States to a chair in Switzerland, though this came to naught. Crick had never heard of Chargaff before his colleague Kendrew arranged their meeting; Watson has written that he had previously read of Chargaff's work. Chargaff knew more about the chemistry of DNA than either Watson or Crick did then, and he told them of his findings. Nine months later, Watson and Crick solved the structure of the DNA molecule. The double helix turned out to have immense significance in explaining how genes function—and to have Chargaff's one-to-one ratios built in. The two strands of the structure, their backbones curling up the outside, barber-pole fashion, had their bases projecting inwards—and the whole thing was held together by chemical bonds between the bases, in which adenine on one strand always paired with thymine on the other, and guanine always paired with cytosine. Thus, Watson and Crick's structure of DNA immediately solved the mystery of how the gene makes identical copies of itself: the two strands separate, and each one forms a new, complementary second strand on itself, the nucleotides of the new strand taking position according to the pairing rules, A to T or T to A, and G to C or C to G.

In 1972, in the course of a conversation, I asked Chargaff whether he had perceived the consequences of his discovery of the one-to-one ratios of adenine to thymine and guanine to cytosine. "Yes and no," he answered then. "No, I did not construct a double helix." Priority is the only form of property in intellectual discoveries (as Sir Peter Medawar has pointed out), so it is silly to suppose that scientists ought not be concerned with questions of priority. Now, Chargaff describes his encounter with Crick and Watson in May of 1952 in three pages placed at the exact middle of his memoir. "The first impression was indeed far from favorable," he writes, and goes on:

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33 Interview with Erwin Chargaff, Columbia-Presbyterian Medical Center, 15 February, 1972; letter, Chargaff to me, 25 September, 1976; full quotation and context in The Eighth Day of Creation, pp. 142-143.
I seem to have missed the shiver of recognition of a historical moment: a change in the rhythm of the heartbeats of biology.... The impression: one [Crick], thirty-five years old; the looks of a fading racing tout, something out of Hogarth ("The Rake's Progress"); Cruikshank, Daumier; an incessant falsetto, with occasional nuggets glittering in the turbid stream of prattle. The other [Watson], quite undeveloped at twenty-three, a grin, more sly than sheepish; saying little, nothing of consequence.

But then Chargaff writes:

I told them all I knew. If they had heard before about the pairing rules, they concealed it. But as they did not seem to know much about anything, I was not unduly surprised. I mentioned our early attempts to explain the complementarity relationships by the assumption that, in the nucleic acid chain, adenylc was always next to thymidylic acid and cytidylic next to guanylic acid [these are the names of the nucleotides carrying the various bases].... I believe that the double-stranded model of DNA came about as a consequence of our conversation.

And he goes on:

When, in 1953, Watson and Crick published their first note on the double helix, they did not acknowledge my help and cited only a short paper of ours which had appeared in 1952 shortly before theirs, but not, as would have been natural, my 1950 or 1951 reviews.44

Indeed, though Chargaff does not say so in his memoir, some months after Watson and Crick's paper he wrote a letter chiding Crick for not having cited his work adequately. Discovery of the structure of DNA touched off a widespread search for the means by which the genetic information is read off the DNA and translated to specify the building of the organism—that is, the search for the genetic code and for the biochemistry by which the cell makes proteins. Chargaff, though he does not say this, either, in his memoir, at first tried to take part in the elucidation of the genetic code. By the mid-1950s, though, Crick was to a great degree dominating the direction and style of this effort—an arbiter and an elegantia that Chargaff found intolerable. By 1958, Chargaff was denouncing molecular biology and its practitioners for arrogance, ignorance, reductionism, and self-serving sensationalism. In 1962, the Nobel prize in physiology or medicine was awarded to Watson and Crick, together with Maurice Wilkins.

Whatever the basis and justification, item by item, of Chargaff's dislikes in present-day science and among its practitioners and institutions, it is the case that for a decade at least his attacks, at their most amusing and their most telling—and even in dead earnest on such a possibly important issue as the regulation of experiments that modify inheritance by moving fragments of DNA from one organism to another—have been discounted by many of his peers as impelled by enmity and disappointment. Enmity? At one time, Chargaff could write of molecular biologists,

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44 Chargaff, Erwin, Heraclitean Fire, pp. 101–103; earlier phrases quoted are at pp. 8, 9, 13 and 19.
"That in our day such pygmies throw such giant shadows only shows how late in the day it has become"—an oblique personal reference and a nice inversion of the established conceit that has scientists seeing farther because perched on the shoulders of their giant predecessors. Now he gives us "the looks of a fading racing tout"—and the reader must wince with embarrassment. Disappointment? Chargaff's claim for credit is now broader and more insistent than before. He thus invites scrutiny. "Such things are only susceptible of a later judgement: Quando ludex est venturus/Cuncta stricte discussurus," he writes; but we need not postpone scrutiny so long, for several things can be said with assurance about how Chargaff understood his discoveries at the time he met Watson and Crick, and about the use they made of them.

Chargaff now writes, as we just saw, that he told Watson and Crick in 1952 "about the pairing rules" and "the complementarity relationships". Eight pages earlier in his memoir, writing of the experiments of 1948 and 1949 and the paper of 1950 based on them, he speaks of "the regularities that I then used to call the complementarity relationships and that are now known as base-pairing". However, in that review of 1950 (I quoted the full relevant passage above), Chargaff wrote, "The molar ratios"—molecule to molecule—"of adenine to thymine and of guanine to cytosine, were not far from 1." In a review Chargaff published in 1951, he gave more evidence but said again, "The ratios of adenine to thymine and of guanine to cytosine were near 1." That observation, in slightly varying language, in fact became his standard. Once, in a paper of 1951 about the DNA of salmon sperm, he speculated about the reason, then turned away:

Not only the ratio of purines to pyridines but also that of adenine to thymine and of guanine to cytosine equals 1. As the number of examples of such regularity increases, the question will become pertinent whether it is merely accidental or whether it is an expression of certain structural principles that are shared by many desoxypentose nucleic acids, despite far reaching differences in their individual composition and the absence of a recognisable periodicity in their nucleotide sequence. It is believed that the time has not yet come to attempt an answer.

38 Chargaff, Erwin, Lipshitz, Rakoma, Green, Charlotte and Hodes, M.E., "The Composition of the Desoxyribonucleic Acid of Salmon Sperm", *Journal of Biological
And once, at about the same time, he faced the problem of the structural significance of the base ratios straight on—and came to a conclusion that now seems astonishing. In a major review that he published in 1951 but that he did not choose to reprint, 20 years later, in his collected major papers, he wrote:

If one postulated an ideal case in which a deoxypentose nucleic acid exhibited ratios of adenine to guanine and of thymine to cytosine that were both 1.4 and ratios of adenine to thymine, of guanine to cytosine, and of purines to pyrimidines, all equaling one, a simple construction could, for instance, assume that a subunit consisting of 24 nucleotides contained 7 dinucleotides, in which adenylic acid was linked to thymidylic acid, and 5 dinucleotides, in which guanylic and cytidylic acids were united, all these distributed in a certain pattern. The experimental results have, however, disproved this simplified assumption.

The trouble was that Chargaff considered DNA only as single-stranded, never seriously wondering whether the molecules could be a duplex.

Indeed, nowhere in any paper that Chargaff published before Watson and Crick announced their structure does he refer to the one-to-one ratios as "complementary" or exhibiting "complementarity", or as "base-pairing" or as being "pairing rules". Chargaff’s correspondence for that period is deposited at the Survey of Sources for the History of Biochemistry and Molecular Biology, at the American Philosophical Society Library, in Philadelphia. Though the correspondence itself is still closed, in 1977 the survey issued a thorough analysis and index of the Chargaff papers. The analysis describes Chargaff’s letters to Crick, after the DNA structure, as "confined... to a scolding for Crick's failure to cite Chargaff's base-ratio principle in relation to the specific base pairing stereochemical interpretation advanced by Watson and Crick".

Surely, that catches the point: base-pairing and complementarity are notions that express the structural, three-dimensional conclusion that Chargaff never reached. In particular, they are terms that apply naturally to a two-stranded structure, with chemical bonds between paired bases and a method of replication, of the general sort that Watson and Crick proposed. Watson and Crick got there by model-building, the power of which they learned from Linus Pauling.

Fortunately, we are able to determine more closely what Chargaff actually had in mind about the structure of DNA when he first met Watson and Crick. By then, Chargaff’s laboratory had turned still fur-
ther away from any conception of the structure of DNA to which the
notion of complementarity could be applied, or that could have sug-
ggested a physical, local, "base-pairing" consequence to the one-to-one
ratios. At the Congress of Biochemistry in Paris that July, Chargaff read
a paper which reviewed the published work and mentioned the base
ratios in the same language as before. But Chargaff's name was on
another paper presented in Paris, as co-author with a young colleague
at Columbia, Christoff Tamm. An abstract of this was published in the
proceedings of the congress, and the full results of the work were put
into a longer paper by Chargaff, Tamm, and two others, and sent off to
the *Journal of Biological Chemistry* that December. Chargaff and his
associates were taking tentative first steps in a problem of heroic diffi-
culty—to find a way to read out the specific sequence of nucleotides,
the genetic message, in DNA. They had begun by controlled chemical
degradation of DNA, using a mild acid that stripped the purines (ade-
nine and guanine) off the strands, leaving the backbones with the pyri-
midine bases (thymine and cytosine) still attached. This substance they
then treated in further ways that told them whether pyrimidines were
significantly bunched. Tamm said in Paris, and the group's paper re-
peated, "The structure of DNA that emerges from these experiments
is that of a chain in which tracts of pyrimidine nucleotides alternate
with stretches in which purine nucleotides predominate." 41 Thus, the
one-to-one ratios did not apply at each location along the molecule:
Chargaff had abandoned any literal, local pairing of bases, and any
meaning for his base ratios except a general, statistical one. If he told
Watson and Crick all he knew, he misled them.

Of course, the resolution emerges automatically from the Watson-
Crick model, for *that* DNA had two strands—which Chargaff's chemical
treatments were disrupting. And yet he now writes, "I believe that the
double-stranded model of DNA came about as a consequence of our
conversation." Fortunately, we have authoritative, independent evidence
of what Watson and Crick had on their minds in the five or six months
before they got the structure out. In the autumn of 1952, Jerry Donohue,
a physical chemist and crystallographer trained at the California Insti-
tute of Technology under Linus Pauling, came to the Cavendish Labor-
atory for a post-doctoral year. Donohue is no particular partisan of
their's. He is a scientist of prickly individuality and an almost belligerent

41 Tamm, Christoff and Chargaff, Erwin, "Observations on the Distribution Density of
Individual Nucleotides within a Desoxyribonucleic Acid Chain" (abstract), in *Résumés
205. Chargaff does not list the paper in his lifetime bibliography in *Heraclitean Fire*, pp.
229–252. Tamm did not address the question whether the DNA molecule was made of
more than one chain. The later paper is Tamm, Christoff, Shapiro, Hermann S., Lipshitz,
Rakoma and Chargaff, Erwin, "Distribution Density of Nucleotides within a Desoxyribo-
nucleic Acid Chain"; *Journal of Biological Chemistry*, CXXIII, 2 (August 1953), pp. 673–688,
the quotation at p. 685; the base ratios are restated, in Chargaff's usual language, at p. 685.
insistence on accuracy of detail. At a critical moment in February, 1953, Donohue corrected Watson and Crick about the structure of individual bases, which they had got wrong because much of the published literature showed them wrong. Donohue's correction enabled Watson and Crick to fit the bases into the double helix. Later in the 1950s, Donohue raised the point that other structures of DNA might also be compatible with the crystallographic evidence, implying that Watson and Crick's canvassing of possible structures had been hasty and incomplete; Donohue and Gunther Stent even proposed an alternative model. Donohue had a running argument with Crick about that, which ended only in 1970 with Crick's challenging him, in a letter in Science, to "build such a model and publish the coordinates". In 1978, Donohue wrote a review of Chargaff's memoir for Nature. He found the memoir, on reflection and overall, "delightfully enthralling". But about Chargaff's belief that the double-stranded model of DNA came about as a result of the conversation with Watson and Crick in May of 1952, Donohue said this:

Now, there are only a very few people who are in a position to know whether or not this belief of his is true. I am one of them. I categorically state that it simply is not true. Shortly afterward, when I came on the scene, at such times as they were thinking about DNA, they worried more about the density, the pitch of the helix; pairing, if it came up, was "like with like", not complementarity. They were not, in fact, even using the correct chemical structures of the bases. When the final model of DNA was discovered—more or less by accident—it wasn't Chargaff's rules that made the model, but the model that made the rules.

Just so: a model may be a kind of theory, and Watson and Crick's model of DNA, with the physical pairing of the bases that they discovered, transformed what had been an unexplained anomaly, the base ratios, into one of the crucial structural facts about the gene. (The celebrated parallel is the anomalous perihelion of Mercury. It had been certain since 1845 that the orbit of Mercury was walking around the sun so that its perihelion, or point of closest approach to the sun, was advancing more than Newtonian dynamics could in any way predict, by the tiny amount of 43 seconds of arc per century. But in 1916, when Einstein put forward the general theory of relativity, the physicist Karl Schwarzschild fitted the orbit of Mercury into Einstein's equations—and found that the 43 seconds of arc were exactly accounted for. An unexplained observational anomaly was dramatically elevated into a necessary consequence.)

Chargaff's brooding on his bitterness has so fixated his attention that he has failed to understand the true magnitude of what he did accom-
plish. He, along with most other participants and observers, has been misled by the standard view of molecular biology—by its attention to the change that occurred from the conviction, in the late 1930s, that genetic information was carried by protein to the knowledge that it is carried by DNA. That change did take place, as we have amply reviewed, but consideration of it has obscured the more fundamental transformation that was going on at that same time in the way that the large molecules of the cell—nucleic acids and proteins alike—were understood. To repeat: the fundamental transformation in biology from the 1930s through the 1950s was the working out of the idea of specificity.

Chemical Specificity and Biological Specificity

Biological specificity as it was understood by, say, 1960 had a number of forerunners. In the modern view, three considerations subsume all the rest. The first is linearity: the long-chain biological molecules, both proteins and nucleic acids, are specific in sequence. The second is structure: the large biological molecules owe their functional specificity to specific three-dimensional configurations. The third consideration is that linear specificity determines three-dimensional specificity. That is, the sequence of bases on a particular DNA chain is altogether sufficient as the list that the machinery of the cell translates into a corresponding sequence of amino acids to make up a protein chain that folds itself—without further instruction—into its functional configuration.

In the late 1930s, biologists certainly spoke of specificity. Yet specificity, as a ruling way of thinking about biochemical events, was lacking that entire set of meanings—those distinct dimensions—it had acquired by 1960. In particular, though the action of enzymes (and genes) had to be in some sense specific, when biochemists of the 1930s turned to their substances, their compositions, their chemical makeup, they thought of them in general, non-specific ways. And they thought about nucleic acids and proteins, as substances, in strictly comparable ways—the chief difference being that nucleic acids, supposed to be less interesting, were thought about less elaborately.

Nucleic acids were thought to be monotonous strings of tetranucleotides. Proteins, though built of assortments of more than a score of different kinds of amino acids, were similarly believed to be multiples of fundamental units many times repeated. For example, Theodor Svedberg, inventor of the ultracentrifuge, was convinced that he had discerned with the aid of that instrument that proteins were made of multiples of units of 17,000 molecular weight. In 1937, Max Bergmann and Carl Niemann, at the Rockefeller Institute, claimed that they had

44 For a late statement of this conviction, see Svedberg, T., “Opening Address: A Discussion on the Protein Molecule, 17 November, 1938”, Proceedings of the Royal Society, A (1939), pp. 40-56; and for the sort of acceptance that such ideas had, see the papers and discussions following.
found a general chemical law that ruled the total number of amino acids in a given protein and the proportionate number of each kind of amino acid in that total. They thought this law was the result of rules governing the uniform spacing of each kind of amino acid along the polypeptide chain. And, they said, from "the superposition of many different individual frequencies" of perfectly spaced amino acids arose the "law which determines the total number" of them in the molecule—usually, they said, "288 units or a whole number multiple thereof".

The tetranucleotide hypothesis was generally accepted; the Bergmann-Niemann formulas could hardly have been regarded by many biochemists as conclusive. In either case, however, these ideas represented the traditional direction in which explanations of the chemical structures of these substances were to be sought. Neither for nucleic acids nor for proteins had any plausible alternative been suggested.

Explanations of the biochemical behaviour of proteins sound a similar discord, to present-day ears, between specific functioning and non-specific chemistry. Proteins were held to exchange amino acids with their neighbours in "dynamic equilibrium". They were thought to be made in reversible chemical reactions catalysed by the same enzymes that digested them, while the production of the enzyme molecules themselves was thought to be stimulated by "mass action" promoting the stabilisation of chemical equilibria—principles drawn directly from classical chemistry.

Again, in 1940 Linus Pauling introduced a "theory of the structure and process of formation of antibodies" in which the extreme specificity of an antibody to its antigen was added in a folding-to-fit that took place, as a distinct step, after the protein had been synthesised. Once more, specificity of action had to be obtained from a substance not specific in its original makeup.

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45 Bergmann, Max and Niemann, Carl, "Newer Biological Aspects of Protein Chemistry", *Science*, LXXXVI, 2,226 (27 August, 1937), p. 188.


48 Pauling, Linus, "A Theory of the Structure and Process of Formation of Antibodies", *Journal of the American Chemical Society*, LXII, 10 (5 October, 1940), pp. 2,643-2,657. Pauling followed this up with experiments that, he claimed, "succeeded in endowing normal serum globulin with the properties of a specific antibody"; Pauling, Linus and
The work of two biochemists proved decisive in changing the way people thought about specificity. The man who forced the change was Frederick Sanger, at the University of Cambridge. In a decade's work, beginning in the mid-1940s, Sanger determined the amino-acid sequences of the two chains of bovine insulin, and proved that the sequences were unique, meaning that every molecule of insulin in every cow is exactly like every other and yet with no general periodicities. Even as he worked, the news slowly spread and its implications sank in. Crick, in Cambridge, knew of Sanger's findings step by step. The implications were strong by 1949, when Sanger went to the symposium at Cold Spring Harbor, the summertime headquarters of Delbrück and his associates. The meeting that year was devoted to proteins. Sanger was able to announce that insulin apparently had only two types of chains, and to identify the amino acids in the first four positions at each end of one chain and those in the first five positions at one end of the other chain — 13 specified out of 51. In a paper sent in just before he came to Cold Spring Harbor, he was able to say that "there appears to be no principle that defines the nature of the residue occupying [a particular] position in different proteins". The case was unarguable less than 18 months later, when he was able to list the entire sequence of 30 amino acids in the longer of the two chains. Proteins were entirely and uniquely specified. With that vanished the possibility of a general law, a physical or chemical rule, for their assembly. "With that, you absolutely needed a genetic code," Monod once said to me.

The same transformation of understanding, at exactly the same time, was overtaking nucleic acids. The precision of this parallel is the elementary, essential fact lost to the standard view of the rise of molecular biology. The part that Sanger played for proteins was played for nucleic acids, in a minor key, by Chargaff. To be sure, Chargaff never learned how to read the detailed sequences of the bases, the genetic message, on a strand of DNA. That had to wait a quarter-century until Sanger got around to it, too (and won thereby his second Nobel prize). But Chargaff's demolition of the tetranucleotide hypothesis by 1949 and 1950 released the possibility, and made it highly likely, that nucleic acids were, in fact, specific in sequence, like proteins. Chargaff set nucleic


50 Interview with J. L. Monod, 1 December, 1975. See also The Eighth Day of Creation, pp. 386–387, 211.
acids free to be genes. He saw some of these implications then, and alluded to them in papers before Watson and Crick announced the structure of DNA. Yet 25 years later Chargaff appears as though blinded by the standard view of the rise of molecular biology, numbed by bitterness over his failure to find consequences of his work that he had not seriously looked for; and so he is unable to value properly what he did achieve. The result is terribly sad.

The structure of DNA made specificity comprehensible—and it did this both for nucleic acids and for proteins. “Nobody, absolutely nobody, until the day of the Watson-Crick structure, had thought that the specificity might be carried in this exceedingly simple way, by a sequence, by a code,” Delbrück said. “This was the greatest surprise for everyone.”

Specificity in the modern sense had precursors; in the several more or less obviously related research programmes whose eventual confluence gave rise to molecular biology, ideas of specificity had widely different standing and character.

In microbiology, though the term was used, its relevance in anything like the modern sense awaited resolution of the long, piecemeal shift of opinion, from the early 1920s to the early 1950s, about what sort of creatures prokaryotic organisms (that is, those that are single-celled and without defined cell nuclei) really were. Alternatives were not clearly set against each other across the entire field while this shift was going on. One sees now that the question kept coming back to whether prokaryotes were comparable to higher organisms in the most fundamental respects, and in particular whether their life processes were determined by genes. The dominant opposing idea, in various guises, was that micro-organisms were switched, modified, or adapted in response to their immediate environment. “The last stronghold of Lamarckism”, Luria called bacteriology in the 1940s. Avery began the shift with his demonstration, in 1923, that different types of pneumococci are of distinct varieties that breed true. Indeed, Chargaff was right to say, as once he did in eulogy, that Avery made two discoveries that ought to have claimed the attention of the Nobel selectors. Then in the 1930s, while the phenomenon of bacterial transformation was being pursued at the Rockefeller Institute, Lwoff at the Institut Pasteur showed that micro-organisms had nutritional requirements—for vitamins, say—like those of multi-celled creatures. At the same time, in London, the bacteriologist Paul Fildeis and colleagues were making parallel findings about other bacteria and other vitamins. The discovery flabbergasted many older biochemists and bacteriologists. Micro-organisms were established as creatures ruled like all others by biochemical specificities.

Interview with M. Delbrück, 9 July, 1972. See also The Eighth Day of Creation, pp. 58–61.
The realisation made possible an important technical advance, for micro-organisms, with their quick-step generations and their simply measured, simply blocked metabolic performance, rapidly became the principal tool of biochemical genetics. This transition has been recounted in a volume of reminiscences and testimonials, part in French and part in English, that Jacques Monod and Ernest Borek organised in honour of André Lwoff and titled *Les Microbes et la vie: Of Microbes and Life*. Despite Lwoff's excellent and original science and his generous humanity—he is, for example, one of the rare people who is deliberately and successfully funny in scientific papers—the book, like most of its kind, is variable in quality and only occasionally reaches the level for the most part sustained in the comparable volume that was dedicated to Delbrück by the phage group. For one thing, many of the contributions are brief—to the point of discourtesy, since they can hardly deal seriously even with a single subtopic. None the less, for the detail and reception of Lwoff's early work several of the sketches have value, and notably those of Fildes and of Roger Stanier. (For the work in Lwoff's unit after the war, several others are useful, notably Jacob's and Georges Cohen's.)²² Beyond such particulars, Lwoff's assertion of the biochemical unity (obviously not the identity) of living things was crucial conceptually to the gathering confluence. In 1938, Fritz Lipmann, starting with a bacterium that clots milk, began to work out the transport of energy to five specific events in the cell’s manufacturing processes. In 1940, George Beadle and Edward Tatum, using a mould that grows on bread, first put to effective work Garrod’s realisation that what a gene does is specify an enzyme. In 1943, Luria and Delbrück devised a statistical demonstration that bacteria acquire resistance, in particular to attack by phage, not by adaptation but by genetic mutation; the demonstration is called the fluctuation test. Nine months later, independently in German-occupied Paris, Monod and Alice Audureau demonstrated that bacteria acquire the capacity to make so-called adaptive enzymes by genetic mutation. With that, bacteria were brought at last into Mendel’s realm. It remained for Joshua Lederberg, by his announcement, in 1946, that bacteria mate, to set off the tumultuous exploitation of classical genetics in bacterial systems.

Mendelian genetics itself, of course, had always been built upon a concept of stringent specificity, and of an abstract kind. From very early days, the genetic specificity—the map—was understood to form a strictly linear array. That the line of genes had no branches was known decades before polypeptides or DNA were shown to be unbranched.

Thomas Hunt Morgan, in his Nobel prize lecture, delivered in the summer of 1934, asserted:

At the level at which the genetic experiments lie, it does not make the slightest difference whether the gene is a hypothetical unit, or whether the gene is a material particle. In either case the unit is associated with a specific [i.e., particular] chromosome, and can be localised there by purely genetic analysis. None the less, genetics was already coming down from that abstractness. It was turned biochemical by the experiments of two students of Morgan's, Boris Ephrussi and George Beadle, on the enzymes that determine eye colour in flies. These, in turn, soon set Beadle to working with Edward Tatum on the demonstration with moulds that what a gene does is specify an enzyme.

In physical chemistry, by contrast, specificity was not abstract and not linear, but concretely physical and three-dimensional. Some of the most powerful strategies of molecular biology are rooted in Pauling's rules—explicitly formulated in 1929—for the close packing of atoms and the local balancing of electrical charges in the structures of molecules; in the precision with which, following Pauling, the lengths and angles of chemical bonds can be known; in the realisation of the importance of hydrogen bonds for the structures of large biological molecules. Such ideas underlay Pauling's invention of molecular-model building. They were apparent in principle and understood to matter to biology by a few people at the end of the 1930s. They were seen in steadily sharpened detail and brought home to many in the late 1940s and early 1950s. In important respects, the model of the structure of DNA was Francis Crick's homage to Linus Pauling.

Crystallography, allied closely to physical chemistry in the developments that led toward molecular biology, was also permeated with ideas of structural specificity, yet of a somewhat different character. The crystallographers, particularly those who were struggling to get out three-dimensional structures of protein molecules, were the least surprised by Sanger's results. They had long understood that substances which were to form crystals at all had to be built from units that were essentially alike—right down to the molecular level. Otherwise they would not pack. This requirement had been clear well before the invention of X-ray crystallography, by Lawrence Bragg, in 1912. And the requirement had been known to apply to some proteins—for, although the first crystals of an enzyme were not produced until 1926, haemoglobin was crystallised at least as early as 1840, and its protein nature established soon thereafter. 54

53 Morgan, Thomas Hunt, "The Relation of Genetics to Physiology and Medicine", Nobel prize lecture delivered 4 June, 1934, in Nobel Foundation, Nobel Lectures... Physiology or Medicine, 1922-1941 (Amsterdam: Elsevier, 1965), pp. 315-316.
54 The earliest reference to crystals of haemoglobin appears to be by Hünfeld, F. L., Der Chemismus in der thierischen Organisation (Leipzig: F. A. Brockhaus, 1840), pp. 158-163. A machine copy of the relevant pages was kindly obtained for me by Dr. Jürgen
Thus, in 1909 appeared an extraordinary book, *The Crystallography of Hemoglobins*, by Edward Tyson Reichert, a physiologist at the University of Pennsylvania, and Amos Peaslee Brown, a mineralogist there. Reichert had conceived the ambition to plot the evolutionary relationships among species of animals by calculating the divergencies among their protein molecules. His essential idea was merely 70 years ahead of the technology: only with the advent of Sanger's methods for sequencing polypeptides could students of evolution begin to measure the similarities among proteins, and only with Sanger's means of sequencing nucleotides in DNA could such measurements of genetic similarity begin to be accurate. But Reichert understood the enormous scope for diversity if protein molecules were large yet truly specific; he settled on crystal forms—and recruited his colleague Brown—as the means to get at degrees of difference, and on haemoglobin as the easily crystallised protein universal among animals. Their book surveyed the nineteenth-century literature of haemoglobin; catalogued crystals of the stuff from 101 different vertebrate species—Philadelphia had a good zoo—complete with drawings and measurements of the crystal forms; and ended with 600 large, clear, well-printed photo-micrographs of haemoglobin crystals.

The fact that crystals grow only from identical molecules laid down in repeated arrays became incontrovertibly applicable to proteins in 1934, when Bernal, working with Dorothy Crowfoot and crystals of pepsin, showed how to get X-ray-diffraction patterns from protein crystals, and saw from the first successful photographs that "it can be inferred that the arrangement of atoms inside the protein molecule is also of a perfectly definite kind". Five years later, giving a Friday Evening Discourse at the Royal Institution, Bernal—showing some of Perutz's X-ray-diffraction photographs of crystals of haemoglobin—said that the patterns yielded by proteins were "of exceptional perfection"; they "indicated that not only were the molecules of the proteins substantially identical in shape and size, but that they had identical and regular internal structures reaching right down to atomic dimensions". Such results were not necessarily incompatible with notions of general chemical laws and periodicities determining the structures of proteins; yet, in Bernal's mind, the X-ray and other evidence was casting doubt on such schemes as Svedberg's for proteins built of multiples of 17,000 molecular weight, while reducing "the figure of 288 amino-acid residues in a 35,000 molecular weight class protein", as proposed by Bergmann and Niemann, to no more than "an inspired guess".55

Rimpaup of the University of Göttingen. The indispensable guide to the early history of research in haemoglobin is the splendid monograph by Edsall, John T., "Blood and Hemoglobin: The Evolution of Knowledge of Functional Adaptation in a Biochemical System", *Journal of the History of Biology*, V, 2 (Fall 1972), pp. 205-257; Edsall does not, however, cite Hünfeld.

55 Bernal, J. D. and Crowfoot, D., "X-ray Photographs of Crystalline Pepsin", 
Meanwhile, in Prague, the biochemist Felix Haurowitz, working with crystals of haemoglobin, had made a startling observation. In the first week of April 1938, Haurowitz took from a cupboard a sealed bottle of a solution of purified haemoglobin of horse that he had set to grow crystals. He used a pipette to move a few drops of slushy liquid to a microscope slide, then put a glass cover slip over them and put the slide under the microscope. He had expected to see light-coloured needle crystals of haemoglobin in its oxygenated form. Instead, the slide carried bluish-red, flat, large hexagonal tablets of deoxyhaemoglobin. (Later, he decided that the bottle had been contaminated by bacteria that used up the oxygen.) As he looked at the crystals, a wave of change moved across the field of view. Beginning at one side, progressing across the middle, the hexagonal tablets disappeared, dissolving back into the liquid. Then beginning again at the same side, new crystals formed and quickly grew—the lighter red needles of oxyhaemoglobin. Air had penetrated from one edge of the cover slip. In every other way, the conditions from which the two forms of crystals had emerged were, of course, literally identical. Inescapably, the binding of oxygen changed the structure of each molecule of haemoglobin from one form to another, enough to change the crystal lattice totally. Haurowitz had caught molecular specificity in action. He reported the observations in a paper published in Germany that summer, with a picture, taken through the microscope, of the crystals transforming. Though the political turmoil of those months may have limited the attention paid to Haurowitz’s paper in Britain and the United States, Haurowitz was, in fact, married to a cousin of Perutz and had been the first to suggest to Perutz that he study haemoglobin. Perutz found that Haurowitz’s description and photograph brought the problem of the relation of structure to function in haemoglobin so vividly alive that 30 years later he told me Haurowitz had shown him the transformation through the microscope on a visit to Prague in September 1937 which was, in fact, seven months before Haurowitz made the observation. Biochemical specificity in the present-day sense was never a surprise to the crystallographers.

Sequence Hypothesis and Central Dogma

In September 1957, in London, at the yearly symposium of the Society for Experimental Biology, Francis Crick gave a talk. The subject of the
symposium that year was "the biological replication of macromolecules". The symposium lasted two days and presented 16 papers. Among them, the organisers allowed one about "the biosynthesis of oligo- and polysaccharides". Every one of the 15 other papers had to do with nucleic acids or with proteins or with the relations between them. In September 1957, the essential experiments to test the Watson and Crick structure of DNA had not been carried out—or, rather, the most decisive of those experiments, that by Matthew Meselson and Franklin Stahl to look for the method of DNA replication predicted by the model, was just being performed and was months from publication. Watson and Crick had, of course, gone on to other problems. Watson had tried several things, but chiefly to determine the structure of the other kind of nucleic acid, ribonucleic acid. This endeavour had proved fruitless. Crick had taken up a more general problem, which was how the information in the genes, on the DNA, is in fact and mechanistic detail expressed in the building of the organism. In the first place, the expression of the instructions meant the synthesis of many and various kinds of protein molecules. Crick’s endeavour had not conspicuously begun to make progress, either, by September 1957.

None the less, Crick gave his talk the bold title "On Protein Synthesis". With energy and assurance, he organised the state of knowledge of molecular biology as it then stood by means of a series of observations about other people’s experiments on the relation of genes to the organism—observations, that is, about the relation of DNA to proteins. He said, for example:

I shall also argue that the main function of the genetic material is to control (not necessarily directly) the synthesis of proteins. There is a little direct evidence to support this, but to my mind the psychological drive behind this hypothesis is at the moment independent of such evidence. Once the central and unique role of proteins is admitted there seems little point in genes doing anything else.

He discussed possible mechanisms; he predicted, among other things:

Biologists should realise that before long we shall have a subject which might be called "protein taxonomy"—the study of the amino acid sequences of the proteins of an organism and the comparison of them between species. It can be argued that these sequences are the most delicate expression possible of the phenotype of an organism and that vast amounts of evolutionary information may be hidden away within them.

He introduced two general principles, calling them by the curious names of "the sequence hypothesis" and "the central dogma".

**The Sequence Hypothesis**... In its simplest form it assumes that the specificity of a piece of nucleic acid is expressed solely by the sequence of its bases, and that this sequence is a (simple) code for the amino acid sequence of a particular protein.

This hypothesis appears to be rather widely held. Its virtue is that it unites
several remarkable pairs of generalisations: the central biochemical importance of proteins and the dominating biological role of genes, and in particular of their nucleic acid; the linearity of protein molecules (considered covalently) and the genetic linearity within the functional gene...; the simplicity of the composition of protein molecules and the simplicity of the nucleic acids....

The Central Dogma. This states that once "information" has passed into protein it cannot get out again. In more detail, 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. Information means here the precise determination of sequence, either of bases in the nucleic acid or of amino acid residues in the protein.

This is by no means universally held...but many workers now think along these lines. As far as I know it has not been explicitly stated before.57

Crick's paper of September 1957, and in particular the two principles, established the simple, formal scheme upon which is built the new way of thinking about the processes of the cell that characterises contemporary biology. The fundamental logic of molecular and cell biology has more to it, of course, than the sequence hypothesis and the central dogma, including essential elements that were not envisaged by anyone in September of 1957. Another ten years were to be required before even a schematic outline of the problem of gene expression—including mechanisms of transcription and translation of the genetic message, the details of the genetic code, and the patterns of interaction by which expression of the genes is switched and regulated—was firmly in place, and that only for prokaryotes. Crick's paper "On Protein Synthesis" was more than a summary of research and problems: it was a manifesto. Crick regarded it as such. None the less, the rest of that logic turned out to conform to Crick's two principles.

The sequence hypothesis and the central dogma proclaimed the research programme that was rising then and dominates today. But in another respect, they mark a convenient terminus: the point at which the underlying ideas were first clearly defined for the wider audience of biologists.

Thus, by the late 1950s nucleic acids and proteins were being thought of, as functional biochemical substances, in strictly comparable ways—as they had been 20 years earlier, except that now they were ruled by a conception of biological specificity at the structural molecular level that then had been unknown. The nature of acceptable explanations in biochemistry had been transformed. Any historical treatment must fail which does not consider not only the working out of the correct relations of nucleic acids to proteins but, behind those, the strictly parallel movement in understanding of how the biochemistry of both classes of substances was to be apprehended.

A Single-Stranded History

Such a failing vitiates Portugal and Cohen's *A Century of DNA*. At first glance, the book has attractive and useful features. The writing is pleasant, though flaccid. The history of early chemical investigations of nucleic acids, beginning with Friedrich Miescher's discovery of "nuclein"—DNA—in 1869, offers details that have not been brought together into a single narrative before. For the recent period, the authors interviewed 13 scientists, and excerpts from two or three of these conversations are fitfully illuminating. Interesting, for example, are comments of Sven Furberg, the Norwegian crystallographer who worked in Bernal's laboratory, in London, from 1947 to 1949, where he was the first to establish the correct three-dimensional configuration of the individual nucleotide in DNA, and who went on to build up a plausible single-stranded helical structure for DNA which, though he did not publish it until 1952, became known before that, at least to Franklin and Wilkins.

The book does not press hard; it repeatedly misses connections. To begin with, the interviewing fails—by an order of magnitude—to be widespread and intensive enough to provide the multiple views of individual events or developments that are the unique power and the validation of the oral method, when used in conjunction with published and unpublished documents. To take just one example, no reader could be sure from this account that, as was the case, Franklin and Wilkins had early access to Furberg's model. Intensive multiple interviewing is uniquely valuable, obviously, in eliciting the relationship of personal factors to research results. The history of the discovery of the structure of DNA is full of these factors, and even if it were desirable to avoid them, Watson's book has made that impossible. Wilkins and Franklin were incompatible; the biophysics unit at King's College, London, where they worked, was crippled by shortcomings of leadership; the longstanding friendship of Wilkins for Crick, and Watson's skill at insinuating himself into Wilkins's confidence, resulted among other things in the Cambridge pair becoming the beneficiaries of the mess in London.

Portugal and Cohen acknowledge the problem, then conspicuously fail to resolve it. For one thing, of the principals and well-placed bystanders they did not interview Watson, nor Crick, nor Perutz, nor Bragg, nor any of Franklin's various colleagues and graduate students, nor anybody else at King's College but only Wilkins—though, to be sure, they have not relied unduly on what he may have told them.

For chapters at a time, *A Century of DNA* reads like a bloated review article—not a year but a hundred years of "progress in nucleic-acid research". When the authors jog along in this mode, they are at their best. They do well, though in fuzzy focus, with Miescher's work and his surprisingly subtle views of his work. They do notably well with
the discoveries, in ensuing decades, of the components of nucleic acids. By contrast, their discussion of the early history of genetics is perfunctory; but good accounts of this are not in short supply. The treatment of the development of the tetranucleotide hypothesis, though the narrative is disjointed, appears sound—but, in fact, misses a crucial point that Hotchkiss has recently pointed out.

Hotchkiss's examination of the literature shows the tetranucleotide hypothesis to have been almost data-free. The hypothesis was first put forward about 1910, but the classical statement, the source universally cited, was a monograph by P. A. Levene and L. W. Bass in 1931. There, a table presents the "theoretical and experimental percentages of purines and pyrimidines in thymonucleic acid"—that is, DNA. One column gives the values predicted by the tetranucleotide hypothesis. Another lists the values found in Levene's laboratory 33 years earlier. The found values approximate the theoretical ones only roughly; in particular, Hotchkiss points out, some 17 per cent. of the mass is unaccounted for. Considering the difficulties of the chemical methods then available, this in itself "should not be surprising", Hotchkiss says. "But it should tell us that we need not take the values too seriously"—and Hotchkiss asserts that he, Chargaff, and several others working with nucleic acids in the 1940s "all stated that we didn't feel obliged to take the tetranucleotide calculations seriously. But others did, persons not perhaps acquainted with these perilous calculations, and the assumptions they rest upon."

The assertion of the early presence of doubt about the tetranucleotide hypothesis is itself interesting. But Hotchkiss then turns to another column in Levene's table of 1931—a column that reports values "found" by H. Steudel, from a paper of 1906. When Hotchkiss looked up that paper, he discovered that Levene had taken from it figures that Steudel had himself calculated from theory, "derived for an arbitrary tetranucleotide", and not those he had found at the bench. "Thus what seems like double support for the tetranucleotide hypothesis collapses into one set of analyses (Levene's) and a redundant quotation from another worker who made the same idealised drastic assumption." Hotchkiss's observation is spectacularly ironical. Now, Portugal and Cohen cite these same papers but obviously they did not scrutinise them. The difference between writing a review article and writing a critical history turns out to be considerable.

The latter portion of the book exhibits most glaringly the insuperable difficulty of telling the history of research into nucleic acids without constant correlation with the problem of protein synthesis. The last chapter but one treats of "the genetic code". It is irredeemably muddled. The problem of the code was to find out how the instructions

carried on the DNA, in a sequence made up from the four different sorts of nucleotides—forming as it were an alphabet, hence the "code"—is translated into a polypeptide chain, in a sequence made up from the 20 different kinds of amino acids. This was the problem of protein biosynthesis put in molecular terms. The problem was essentially biochemical, but it had an important if rudimentary theoretical aspect. For instance, two-nucleotide code words could express only 16 different amino acids, three-nucleotide words could express as many as 64: were there redundancies, or nonsense words, or was the code overlapping, or did some stereochemical, structural feature of the double helix narrow the possible combinations from 64 to 20? Did the message include punctuation, such as starting or termination signals? Again, was the translation done directly off the DNA or were there intermediates—some sort of biochemical devices for translation? Again, what exactly was the connection between the code and the control of gene expression—that is, between the mechanisms of protein biosynthesis and the regulation of that synthesis? Yet again, where does the energy for protein synthesis come from? As it turned out, these questions were intertwined; solution of each required elucidation of the whole network of biochemical processes. As it also turned out, there are intermediates between DNA and proteins—and these are, chiefly, several different classes of RNA, including what are now called transfer RNA, messenger RNA, and the ribosomes, which are complex structures of RNA and proteins. The history of the experimental side of the solution of the code, then, is all about the disentangling of the biochemical sequence and in particular of the different classes of RNA.

Portugal and Cohen have written an account that must leave the reader who is not intimately familiar with the science entirely confused about which of these classes of RNA is which and does what—and about the ways in which each step of discovery, along each of at least three principal lines, pursued in at least seven major laboratories, influenced each other successively over a span of more than ten years. They leave out crucial discoveries and experiments, omit important workers. The worst omission is of Paul Zamecnik and his team; another is of Paul Berg; another is of Arthur Pardee; Sydney Brenner, deeply implicated in many stages, is mentioned once, momentarily in a quotation from Crick without further identification or role. They invert the order in which discoveries were made. The worst inversion is the sketch of certain developments that culminated in the idea of messenger RNA—a sketch which also leaves out the superb and essential experiments that identified the stuff and demonstrated its function. Inexplicably, this sketch precedes the account of the development of the idea of transfer RNA—though transfer RNA is conceptually simpler, though the period when the crucial work was done on transfer RNA lay slightly earlier
and though transfer RNA had to be established in principle before messenger RNA could be elucidated. As one ludicrous result of this particular disorganisation, Portugal and Cohen quote a paper of 1961 about messenger RNA, then mention a relatively unimportant confirming experiment originally published in French in 1962, then double back to Crick's brilliantly imaginative and indispensable "adaptor hypothesis"—the theoretical proposal he made first in 1955 (though they trace it no earlier than 1957) that prefigured the discovery of transfer RNA. Portugal and Cohen do this doubling-back and change of topic without one date on the page to indicate the turn. And at each side of the hairpin they label the RNAs—first messenger, then transfer—as the "template". One must wonder whether the authors themselves understood the science as a process—or, indeed, at all. Compare this, for example, with the excellent, historically organised opening chapters of Martynas Yčas's technical monograph, *The Biological Code*.59

On another matter, how is it possible for a book that purports to be a history of DNA and its biochemistry to omit, altogether, the monumental work of Arthur Kornberg which explained how DNA is replicated in the cell?

**The Misappropriation of Rosalind Franklin**

Getting the connections and interrelations correct is peculiarly difficult in writing the history of modern science because, to begin with the obvious, modern science is such a densely woven fabric both intellectually and socially. The difficulty is most acute in writing biographies of scientists, and goes far to explain why so few good ones have been published. Where a scientist dominated his field the connections make themselves naturally: the biography of Einstein is the history of physics in the first third of this century. Where a scientist writes memoirs or an autobiography, at least the web centred on himself can be regrown from inside rather than reconstructed from outside. Indeed, good scientific memoirs are often, in large part, reflections on the particular experience of the social processes of intellectual history: Max Born's *My Life*, or Stanislaw Ulam's *Adventures of a Mathematician*, for example, owe what real interest they offer chiefly to this quality; Werner Heisenberg's *Physics and Beyond* articulates the experience of the social processes of discovery as a formal scheme of dialogues, part remembered, part idealised, among the makers of the emerging quantum mechanics. Watson's *The Double Helix*, in its twitchy way, is galvanised by the experience of the social processes of discovery, and therein, however coarse, lies much of the reason for the book's success; Chargaff's *Heraclitean Fire* is all but empty of the interactions of discovery, and, how-

ever fine in other ways, from this lack the book takes on an eerie tone—a man talking to himself in a whispering gallery.

Rosalind Franklin did not write an autobiography. All we have are a brief, appropriately sentimental, non-scientific memorial, privately circulated by her mother, and, by a friend, Anne Sayre, a shrill biographical sketch. Sayre is professionally a fiction writer, with several stories published. Her husband is a crystallographer, and through this connection they met Franklin in Paris, where she worked from 1947 to 1950 in a laboratory of the French government, on the crystallography of coal, graphite, and suchlike amorphous substances. In January 1951, Franklin moved to the biophysics laboratory headed by John Randall at King's College London. Sayre and she occasionally corresponded as friends during the next years, though they did not meet again until after Franklin had moved to Bernal's laboratory, at Birkbeck College, in the spring of 1953, and had turned from DNA to tobacco-mosaic virus. Franklin died of cancer in the spring of 1958, aged thirty-seven. Watson's caricature of her in *The Double Helix*, ten years later, was conspicuously cruel and relentlessly depreciated her scientific talent and achievement. Sayre was outraged. Her book attempts to correct Watson's injustices.

Unfortunately, Sayre's research was shallow and led her into many errors and distortions. Watson's book so transfixed her with loathing that she neglected the larger history of the subject, attacking her opponent frontally rather than outflanking him. Worst, her book, published in 1975, took a facile women's-liberationist tone that already seems antiquated and is, in any case, anachronistic in relation to the situation and events at King's College London nearly a quarter-century earlier. One extraordinary mistake will illustrate all these defects. Sayre asserts that King's College was a man's world, excluding women socially and scientifically. She offers almost no particulars; the most significant piece of evidence she does advance is a crude error. "At the time there was one other woman scientist on the laboratory staff besides Rosalind," Sayre writes. But this is wrong. A report that Randall prepared for the Medical Research Council in December 1952 listed, on its first page, the professional staff of the Biophysics Research Unit. It contains 31 names, ranging from Randall himself down to research fellows, and holders of scholarships and studentships. Eight of these were women: Dr. H. B. Fell, now Dame Honor Fell, "Senior Biological Adviser"; Dr. E. J. Hanson, who was, in fact, the unit's senior full-time biologist and an authority on muscle; Dr. A. V. W. Martin, now Dr. Angela Martin Brown; Dr. M. B. M'Ewen; Miss M. I. Pratt, a tutorial student,

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now Dr. Margaret Pratt North; Franklin herself, a Turner and Newall fellow; Miss P. Cowan, a Nuffield research fellow, now Dr. Pauline Cowan Harrison; Miss J. Towers, holder of a Carnegie scholarship. Women, in other words, worked as professional scientists at every level and held about a quarter of the posts. Not listed was Mary Fraser, who had left the laboratory earlier in the autumn of 1952, and Sylvia Fitton Jackson, who was one of the laboratory technicians—but an unusual technician, for she had already completed and published research at the laboratory and soon afterwards, with Randall’s backing, went to Cambridge, where, with no previous degrees, she took a Ph.D. Of these ten women, two have died, Franklin and Jean Hanson. Of the eight living, I have talked with five and corresponded with several of them and with two others; the eighth, Miss Towers, I have been unable to trace. The seven agreed in the opinion that as science in England was then practised, women at their laboratory were represented in good strength and were well treated both professionally and socially. Dr. Jackson’s case is striking evidence. Several reasons were offered. The biophysics unit at King’s was not a crusty, established institution but a postwar creation. Few distinctions of seniority or length of service had had time to grow up; the staff was relatively young, homogeneous, and new at the work. I must add that though I did not ask any of the seven about Franklin’s relations with the rest of the staff, every one of them made a point of telling me that she had found Franklin stiff to get along with and isolated from the rest of the laboratory apparently by her own choice. Now, the fact is that Sayre refers to the content of Randall’s report at a key passage later in her book. But she either failed to see the report, or failed to pursue the clues provided by the list of staff. For whatever reason, she did not get in touch with any of Franklin’s women colleagues—an omission they found astonishing when her book appeared.

Back to the science: Randall’s report must enter into any account of the discovery of the structure of DNA because it contained, among much else about work going on in his laboratory, a brief account by Franklin and her assistant, Raymond Gosling, of their results with DNA—and when this came to Crick’s attention, in Cambridge early in 1953, it allowed him to deduce an important fact about the structure. Sayre lets the reader suppose that Crick learned the diameter of the structure, 20 angstroms, or its density, which suggested that it contained two chains and not three. Neither of these facts was new, however; both had been familiar to Watson and Crick for nine months or more. Crick learned from the report something subtler and even more important—that the crystalline form of DNA that Franklin was working with had what crystallographers call the space group C2. The significance was immediately obvious to Crick, because the substance he was working
on in his own research, the oxyhaemoglobin of horse, had the same space
group. And therefore he recognised a technical fact, that the structure
of DNA ought almost certainly to consist of two chains that ran in
opposite directions. Franklin had not understood this; nor had Wilkins;
and it was essential to the final structure. Sayre ignores the matter.

Franklin was a scientist for whom no special feminist plea need be
entered: by the time of her death her great skill and considerable origin-
ality were becoming widely recognised, and a distinguished career was
open to her. Her life, had it not been cut short, would stand as a vigor-
ous counter-example to the vulgar subtext of Sayre's book.

An Editorial and Scholarly Débâcle

Robert Olby's *The Path to the Double Helix* is the only attempt yet
published, besides my own, to write a comprehensive account of the
origins of molecular biology. The book stops short with the discovery
of the structure of DNA in 1953. My own goes on to the chief discoveries
that ensued, until about 1970; on the other hand, Olby traces certain
of the antecedents back further and in more detail than I do. The
centres of gravity of the two books are thus somewhat different. Olby's
book appeared in 1974. Four years earlier, he published a brief sketch
that was threaded on Francis Crick's career and that carried part of
the story further than 1953.62 I must say at once that I found the earlier
sketch invaluable and parts of the book useful in my own research.
Olby interviewed many scientists, including several whom by death or
geography I was prevented from reaching. In two instances, he kindly
allowed me to listen to the tape-recordings of interviews and to make
my own transcripts of them. Olby has aspired to be definitive; he has
been, at least, dauntingly painstaking, reading widely, conscientiously
trying to master the arcana of crystallography and microbial bio-
chemistry.

His digging has produced passages—chiefly in the early part of the
book—of considerable interest and value. He offers a tantalising dis-
cussion of Garrod's work and its reception by the pioneers of Mendelism
in the first decade of the century, and traces the thread of recognition
of Garrod and of biochemical genetics that was maintained by J. B. S.
Haldane and by several investigators, and notably Rose Scott-Moncrieff,
working out the relationship between the genetics of plants and their
pigmentation. The account falls short of excellence only because Olby does
not rephrase and press the question of Garrod's "prematurity" by asking
why, since the point of Garrod's discoveries remained influential in this one

62 Olby, Robert, "Francis Crick, DNA, and the Central Dogma", *Daedalus, XCIX*, 4
(Fall, 1970), pp. 938-987. That issue of *Daedalus* was devoted to *The Making of Modern
Science: Biographical Studies*, and contains three more pieces of some relevance to the
882-908; Stent, Gunther, S., "DNA", *ibid.*, pp. 909-937; and Pauling, Linus, "Fifty Years
of Progress in Structure Chemistry and Molecular Biology", *ibid.*, pp. 988-1,014.
line of research into the physiology of gene action, it was ignored elsewhere. Again, Olby presents a detailed and engaging narrative of the career of William Astbury, who established the X-ray crystallography of fibrous substances like the protein of wool, at the University of Leeds, beginning in 1928, and who also worked with DNA and speculated influentially and early about the relation of protein to DNA. And Olby’s bibliography is, in some areas, indispensable. However, his book is also infuriating—by far the sloppiest scholarly publication, at every level from concept to proof-reading, that I have ever seen.

At the most elementary level, the failure is not solely the author’s fault: his book has been scandalously ill edited, and he has every reason to be angry with Macmillan. (The American publishers bought what Macmillan had printed.) Proof-reading and copy-editing are normally beneath the reviewer’s notice, but they cannot be ignored here. Names of major scientific figures are frequently misspelt: out of dozens of examples, Joshua Lederberg is spelled “Ledeburg” in the index and on page 435, Oswald Avery is spelled “Ostwald” on page 469, C. H. Carlisle’s name is spelled two different ways in three lines of page 375, D. O. Jordan’s is spelled two ways in successive lines of page 364. Bibliographic entries get dates, volume numbers, pages wrong; material is cited in the text which then appears nowhere in notes or bibliography. Dates wander like names: as one example among many, Chargaff’s encounter with Crick and Watson is dated as occurring in 1953 and then three lines later, correctly, as 1952. Usage reveals startling ignorance: “The University of Columbia”, “The University of Vanderbilt”, or calling a term paper of Watson’s student days a “terminal essay” —errors like these, trivial in isolation, are ubiquitous. And they are cumulative, betraying the publisher’s contempt for the book, sapping the reader’s confidence in the accuracy of any detail he has not checked himself.

Gradually, through the confusion on the surface, the reader begins to detect other errors, more serious. Dates are too often askew. To begin with a minor, early example: T. H. Morgan got his Nobel prize in 1933, but did not give his prize lecture until June of 1934. Olby is at least aware that in those days Nobel laureates did not necessarily go to Stockholm for the anniversary of Nobel’s death, the second week in December, as they do today; he quotes Morgan’s lecture as being in June—but in 1933, and he repeats that year twice in the text and again in the bibliography. He next cites a paper by T. S. Painter from Science in 1933, which includes a diagram of the bands in a chromosome of Drosophila. Then he writes: “In his Nobel lecture in 1933, before Painter’s work was published, Morgan showed a slide of the famous salivary gland chromosomes of Drosophila...” which, he thinks, influenced three Swedish scientists in the audience. In establishing priority of ideas, an error like this can reverse the true flow.

68 Olby, R., Path to the Double Helix, pp. 103–105.
A graver instance occurs in the discussion of Pauling’s growing interest in the structure of DNA, which culminated in his construction, with Robert Corey, late in 1952, of a three-stranded model of the stuff and their publication of their erroneous structure early in 1953. In the course of a single page, Olby discusses several events involving Pauling in June 1952—a note withdrawing an error, which Pauling and a colleague published in June, a letter from Watson that Delbrück showed Pauling in June. Olby then writes that Pauling knew from Watson’s letter “that Wilkins had obtained ‘extremely excellent X-ray diffraction photographs’”. And Olby goes on:

Indeed he [Pauling] would very likely have been able to see the King’s pictures that summer had the U.S. government not taken away his passport, thus preventing him from attending the one-day Royal Society protein meeting in London. His colleague, Robert Corey, did come and was shown DNA pictures by Rosalind Franklin. Corey reported back to Pauling that the King’s group had got good pictures, but when Pauling wrote to Wilkins asking for details, the latter replied that he had not yet reached the stage when he wished to release them.64

A lot is wrong with that. The Watson letter was dated May 20, and Delbrück wrote a letter dated June 4 which said he and Pauling had gone over Watson’s letter in detail, so that Pauling would have read it late in May or very early in June. The United States government did not take away Pauling’s passport, but refused to issue him one; this took place not in the summer of 1952 but at the end of April, and that summer, indeed, the State Department reversed itself and issued Pauling a passport. The Royal Society meeting on proteins took place not in the summer but on Thursday, 1 May. (Nine pages earlier, in a context of events of the spring that does not mention Pauling or Corey, Olby says in passing that “Crick and Watson attended the one-day protein conference which the Royal Society held on the 1st May.”) Olby does not say that the conference had been called to discuss the alpha helix and that Pauling was announced as its chief attraction; nor does he say that Franklin attended. Furthermore, Wilkins’s “excellent” diffraction patterns had been obtained two years earlier. No date can be placed on Pauling’s writing to Wilkins requesting to see pictures, since no letter apparently survives and neither man, by the early 1970s, was certain of the timing. A question of high interest, though Olby does not reach it, is on which day early in May Corey saw Franklin, and which pictures she showed him—since it was over the weekend immediately after the Royal Society meeting on 1 May that Franklin took the X-ray photograph that yielded essential clues to the structure when Wilkins showed it to Watson nine months later.

Even with patience and much cross-reference, the unaided reader can only disentangle part of this. The facts about Pauling’s passport, for example, must be dug out of The New York Times for 12 May and 16

64 Ibid., p.378.
July, 1952, and the open dating of Pauling’s request to Wilkins depends on conversations with the two men.65

This sort of tiresome muddle turns up again and again. Olby attempts to describe Watson’s undergraduate career, at the University of Chicago: Chicago University took him for a Bachelor’s course in science when he was only 15 years of age (as part of an experimental policy of early intake from their Laboratory School). Chicago gave him the integrated kind of courses in biological sciences that have since become fashionable. But Watson was not “switched on” by them. His boyhood zest for ornithology remained dominant. ... But from the moment he read Schrödinger’s book What is Life? he “became polarised towards finding out the secret of the gene”.... One may doubt how strong this polarisation was at the time—it did not prevent him from enrolling in a summer school for advanced ornithology and systematic botany at the University of Michigan in 1947.66

In fact, Watson entered the University of Chicago not from the Laboratory School but from the Chicago public educational system. He was indeed 15, but that was not extraordinary: the College of the University of Chicago then and for years thereafter routinely took students at 16, two years short of secondary school graduation. These students came from all over the country. They were not, however, allowed to specialise in science, but were all obliged to pass the same four-year sequence of courses, literature through science to mathematics and philosophy. Far from fashionable, the course in biology was unlike any taught anywhere today. And though Watson did take that summer course in ornithology at Michigan, that was in 1946, a year before his graduation, rather than in the summer between Chicago and his graduate work at Indiana University.

The book’s unreliability is worst—and most clearly the author’s—when he prints previously unpublished documents. Consider the following case.

One of the most fascinating aspects of the history of the discovery of the structure of DNA is the determination of what Rosalind Franklin was attempting step by step, of how close she came to getting the structure independently, and of what held her back. An essential piece of evidence is a set of notes she made in preparation for a colloquium that took place at King’s College London, the evening of 21 November, 1951. Watson attended that colloquium, and the information she presented spurred him and Crick to a first, disastrously mistaken, attempt to build a structure. Her notes are preserved in the files of Dr. Aaron Klug, who was a doctoral student and colleague of hers after she moved to Birkbeck, and who is now at the Medical Research Council Laboratory of Molecular Biology, in Cambridge. Olby consulted these notes with Klug’s permission and extensive help; so did I. Few others have read them closely. Olby publishes what purports to be “an edited version of her notes”67. The

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65 For the history, see my The Eighth Day of Creation, pp. 131–136, 138, 144–146.
67 Ibid., pp. 349–350.
notes do not, in fact, need editing. They are entirely clear if presented exactly as she wrote them. All Olby did was fill in elided words and expand occasional abbreviations. In the process, he dropped things—important things. Franklin wrote three pages about experimental data, which Olby summarised. She then wrote three pages and two half-pages of discussion. Here is the first of those, not in Olby’s transcript but in my own literal one, preserving her line and paragraph breaks.

*Interpretation*

*General hypotheses*

*Chain groups*

Structure is v nearly hexagonal in section \( \perp \) [perpendicular to] fibre axis. Molecular chains presumably run \( \parallel \) [parallel to] fibre axis. Suggests that structure is only slightly distorted cylindrical units in nearly hexagonal close packing.

*Evidence for spiral structure*

1. Straight chains, untwisted, highly improbable—unbalanced forces
2. Absence of reflections on meridian in X-talline form suggests spiral structure, in which electron density projected onto fibre axis is nearly uniform
3. Strong 27Å period. This is much too marked to result merely from diff. betw diff nucleotides, & must mean nucleotides in equivalent positions occur only at intervals of 27Å. Suggests 27Å is length of turn of spiral

Near-hexagonal packing suggests that there is only one helix (containing possibly \( > 1 \) chain) per lattice point.

Density measurements (24 residues/27Å) suggest \( > 1 \) chain

In those last two lines, Olby omits the “greater than”—putting neither the conventional symbol she used nor the equivalent words. The difference, of course, is crucial to her position on an issue that was crucial to the structure: where she believed the helix was likely to be double or more, Olby represents her as believing exactly the opposite.

The next of Olby’s omissions deprives us of another sort of clue to Franklin’s thoughts. On the next page, writing of the relationship between two forms of DNA X-ray patterns that she had discovered at different degrees of humidity of the fibre being photographed, she noted—and the note is crowded in between two paragraphs as though she added it on re-reading:

... isolated helix has not got same structure as in Xtal—Xtal form involves some strain of helix, cf Pauling

Olby prints that without the last two words. He thus deprives us of the important indication that Franklin was thinking, even then, about molecular structures in the manner of Linus Pauling with the alpha helix. The missing two words introduce not only a fact about her reading but a qualification we do not get anywhere else to the attitude against the
building of molecular models, in the Pauling manner, which Watson, Wilkins, and Crick have ascribed to her.

Olby makes two more gross errors in his partial transcript of Franklin’s lecture notes, both of which make her look less sophisticated than the notes really suggest, although neither affects the heart of the argument.

Olby also prints excerpts from Franklin’s laboratory notebooks which have never been published before. These, too, contain omissions which matter to our understanding of Franklin’s reasoning. Once, for instance, he leaves out a sentence which suggests she was staring at a clue that would have shown her how to fit two helical strands into a structure. But Olby neither mentions this nor allows us to see for ourselves; he does not print ellipsis points or any other indication that something is missing.

I have been forced to the conclusion that at the simplest level of fact almost nothing in *The Path to the Double Helix* can be accepted without independent verification. Most culpable are those errors, like these in transcripts of unpublished material, which the reader cannot check. But the problem is pervasive: errors are so frequent that they poison confidence.

Suppose, for a moment, that all such errors were cleaned up, as an editor should have directed they be, and as they might be in a second edition. Would the resulting book—call it Olby₂—help us see the origins of molecular biology clearly?

Once again, but this time at the level of style, organisation, relevance, and coherence, Olby simply did not receive the editorial help his project deserved. If the present book is taken as a rough first draft of Olby₂, an editor would have to point out to the author that he displays grave difficulty in constructing a connected, sequential narrative line. Events and observations which happened at one time—within days of each other, in some cases—and which are intellectually closely connected are often separated by many pages. An example is the two glancing references to the “Royal Society protein meeting” on 1 May, 1952, which, if brought together, would at once have reorganised a section 20-odd pages long to put the narrative into simple sequence and to set what Franklin was doing in contrast to what Pauling was working on. Olby’s attendant errors and confusions would have been exposed automatically.

Further examples are too frequent and tedious to catalogue. They all hang from an organisational problem on the scale of the entire last half of the book. Olby commits himself from the beginning to a division of the research by academic disciplines—macromolecular chemistry, protein crystallography, nucleic acid research, classical and biochemical genetics, and so on—and, as a gloss or shading within this breakdown by standard fields, an approach by way of lines of attack. This works reasonably well in the first two sections of the five that comprise the book: after all, in the period before the mid-1930s the specialities were distinct, and, at the

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same time, Olby's earlier writing is somewhat more polished and careful. At the centre of the book, the third section treats bacterial transformation and, in particular, the work of Avery. Here, though, the rigid compartments must be abandoned. Because Olby is unable to do that, he says nothing about the work of Delbrück, Luria, and the phage group until much later. His discussion of the reception of Avery's discovery is therefore truncated and never completed. Olby mentions Delbrück's and Luria's contacts with Avery, but in four sentences only, and only in relation to their influence on Watson's possible understanding of the importance of DNA by summer 1948—and he talks about this at all only a hundred pages after his discussion of the reception of Avery's work. Instead, he turns to Chargaff and the base composition of DNA. That line he takes forward past the discovery of the structure of DNA, before doubling back in the next section to pick up Delbrück and the phage group in the mid-1930s, and then doubling back yet again, to the 1920s, to pick up the career of Bernal and the development of protein crystallography. And though the strength of the book, in its early chapters, was its tracing of certain scientific antecedents, in this central portion Olby never says, for example, what Lwoff was doing with bacterial metabolism at the Institut Pasteur in the 1930s, which was complementary to Avery's work; thus, among other things, a reference to Lwoff's admiration for Avery's research has no intellectual mooring.

Olby never describes Monod's research in the mid-1940s, and even ignores Delbrück and Luria's fluctuation test of the same period (a gross omission), though these demonstrated that bacteria reproduce in a fashion controlled by genes; thus, among other things, Olby leaves out an entire aspect of the significance of Avery's discoveries that was made clear by Watson to Crick. Olby never mentions Lederberg's demonstration that bacteria mate, though Lederberg has said that this work (like Chargaff's) was inspired by Avery's results, while in turn it led to work that the bacteriologist William Hayes was doing in London in 1952 when Watson met him and collaborated on a paper; thus, among other things, the two brief references to Hayes float inexplicably. The first and longer of these reads, in full:

Watson hurried over his breakfast, then returned to his College to write a covering letter to send off with the MS which he and Bill Hayes had recently written on the genetics of K12. This manuscript had been the chief purpose of Watson's recent visit to London when he also took the Pauling manuscript on a structure for DNA to King's. 69

These two sentences appear twelve pages and several weeks past the account of the visit to London and King's College; nowhere are Hayes or K12 further identified. (K12 is a strain of the bacterium Escherichia coli.)

The structure of the last part of the book and the denouement are

69 Ibid., p. 408.
bizarre. A chapter treats “DNA as a Single- or Multiple-Strand Helix”, and yet again doubles back, to June 1945, before carrying into Franklin’s work. The next discusses “DNA as a Triple Helix”, and begins with the first, erroneous structure proposed by Watson and Crick late in 1951, then Franklin’s attempts to analyse her X-ray data, in spring and summer 1952, though this never envisaged a triple helix, then Pauling’s erroneous model, which moves up to early 1953. The next treats “DNA as a Double Helix”, and doubles back to the spring of 1952 and the meeting of Watson and Crick with Chargaff, before proceeding—jumpily, either avoiding or recapitulating episodes already mentioned—to the solution. There the book stops dead. Though the Watson-Crick model was, when published, an hypothesis with attractive biological consequences, it had not a scrap of biological support. None the less, Olby omits any discussion of the work in several laboratories over the next several years, that confirmed the structure and verified its consequences.

In short, the mess of Olby’s book is more pervasive and deep-seated than his slovenly scholarship. The omissions from the history and the confusions of the organisation are so severe that paragraphs, pages, entire episodes are incomprehensible to the reader who does not already know a lot of the science and something of the intellectual and personal relations that led to discovery.

Behind all that, Olby has no perception of the underlying nature of the transformation that took place in fundamental biochemical understanding between the late 1930s and the late 1950s. His ideas of such transformation are borrowed, and garbled in the borrowing. The first thing he borrows is the theme of Donald Fleming’s article “Émigré Physicists and the Biological Revolution”, from the book The Intellectual Migration. Thus, Olby gives the fourth of his sections the title “Intellectual Migrations”. Within that, chapter 15, “Physicists in Biology: The Information School”, is in effect a recapitulation of Professor Fleming’s argument—though with only the most cursory hint of acknowledgement, in a citation that suggests, if anything, that Olby discounts Fleming rather than relying heavily on his ideas, insights, terminology, and sources.* Chapter 16, “Physicists and Chemists in Biology: The Structural School”, treats of the roots of protein crystallography and is more original—but now the borrowing, more fully acknowledged, is from Kendrew’s “information and conformation” as the two strands that came together when Watson met Crick. Yet how Kendrew’s is more than just another pretty phrase—that is, how information and conformation most deeply relate to each other in the structure of DNA and the central dogma—escapes Olby. The borrowings are to no purpose beyond the ornamental—as is the third and most egregious, the tired word “paradigm”, the tired phrase “transformation of paradigm.”

* Ibid., p. 238.
A "paradigm transformation", if it is to bear any weight of meaning at all, must be a major change in the ruling preconceptions of a science, and a change achieved precipitously, catastrophically even, and against considerable reasoned opposition. The ruling preconceptions of biochemistry did indeed change, as I have outlined, between the late 1930s and the early 1950s, by the emergence of the molecular understanding of specificity in the gene and in protein synthesis and function—the one-dimensional and the three-dimensional and their relation. Olby does not perceive this emergence, however. For him, the change was simply that from the idea of genes as protein to the idea of genes as nucleic acid. Thus, he is able to write, repeatedly, of "the protein version of the Central Dogma" being replaced by "the nucleic acid version of the Central Dogma"—which appears an almost wilful blindness. The central dogma is one thing only. It is a particular and precise statement about the relationship of nucleic acid to proteins. It asserts that "once 'information' has passed into protein it cannot get out again". The assertion has great consequence. The central dogma is no more identical with the whole of molecular biology than the equation $e=mc^2$ comprises the theory of relativity. But if there is one statement from the new science that deserves the general currency of that equation of Einstein's, it is this assertion of Crick's. Most immediately and narrowly, the central dogma defined the difference between the functions—between the two kinds of specificity—of nucleic acids and proteins. In making this distinction, the statement was radical and absolute. Most widely, the central dogma was the restatement—radical, absolute—of the reason why characteristics acquired by an organism in its life but not from its genes cannot be inherited by its offspring. "Once 'information' has passed into protein it cannot get out again."

On Transformations in Science

The transformation of preconceptions was explained to me once by a younger, and post-molecular, biochemist, Roger Kornberg, now at Stanford University. Molecular biology made a difference in the sort of explanation that is acceptable. "What matters is, what constitutes a solution to a problem in various people's minds?" Kornberg said, and went on:

And I think there the problem doesn't lie between molecular biology and biochemistry—because it is true that there was a school of molecular biology, that of Delbrück, Luria, and so on, that was mainly concerned with the genetic side and put forward a formalism in the same sense that the biochemists of the thirties were solving their problems in terms of a formalism. But there is a clear distinction—it being that for people who either think in terms of genetics (as opposed to structure), or who think in terms of biochemistry as a sequence of chemical reactions (as opposed to structure), it is true that the problem is solved when they have defined all the components. Or, in the case of genetics,

71 Ibid., at, e.g., pp. xxi, xxii, 96, 432-434.
when they have mapped all the components, and defined their relation to one another.

And it really is true, that with Pauling and the advent of structural chemistry in molecular biology and biochemistry, there has been a change in what some people are willing to accept as a sufficient explanation, from the formalistic side to a kind of mechanical one. In other words, from being able to define all the components and feel that you've solved the problem because you've encompassed it, and are not missing any of the ingredients, to the other side where you say, But the transformation is a mechanically almost inconceivable one. How do you do it with nuts and bolts; how do you do it with squares and blocks and the sort of things that you know molecules are made of? 72

Yet the change in the ruling preconceptions of biology stole into scientists' minds gradually, and never elicited coherent resistance. Historians of science, in trying to account for revolutionary change, have relied upon the history of physics almost exclusively, and in physics have appealed to certain great set-piece battles: the changes associated with the eras of Copernicus, Newton, Einstein, and the quantum. The rise of molecular biology asks for a different model—one to which the received idea of paradigms and their shifts does not apply. Biology has proceeded not by great set-piece battles but by multiple small-scale encounters—guerrilla actions—across a broad landscape. In biology, no large-scale closely interlocking, fully worked out, ruling set of ideas has ever been overthrown. In the way of growth characteristic of this science, variant local states of knowledge and understanding may persist for considerable periods. A new and anomalous discovery—Avery's, Sanger's, Chargaff's—is exploited in a manner at first localised, then spreading and generating new strains and consequential discoveries.

The rise of present-day biochemistry, in fact, offers an alternative description of the ways of great scientific change, and one that most scientists, I think, find closer to their own perceptions of the processes. One aspect of these processes is what one might call the tension of the tentative—the psychological attitude towards new explanations (and old ones), new relations of facts (and old ones), and, of course, to new (and old) items of data in themselves, which holds them all as, to varying degrees, suspect and provisional. Closely related to that tension is the effect by which a new and seemingly significant datum or group of data, arranged into a seemingly appropriate relationship to what is already known in its immediate vicinity, creates strains and readjustments of other relationships that work their way progressively through the body of accepted knowledge—and through the overlapping sets of the scientific community—often with the most surprising consequences at some remove from the original vicinity. (This process has been admirably described by the physicist and philosopher of science John Ziman, in his recent Reliable Knowledge, a book of four-square practicality that seems to me

72 Conversation with Roger Kornberg, 12 September, 1975, Cambridge, quoted more fully and in context in The Eighth Day of Creation, pp. 495–496.
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far more perceptive and better informed about the practices of scientists than any of the celebrated, fashionable discourses on scientific revolutions.) A consequence of these strains and readjustments is the spreading back of new ways of explanation into older disciplines, as their established facts and theories are captured and realigned by the new programme.

Behind such aspects of the practice of science lies the profoundly and necessarily conservative nature of the enterprise—a conservatism that is ignored by loose talk of revolutions, and that stands in open opposition to notions of transformation of paradigms. This conservatism is characterised by the Correspondence Principle—the observation elevated to an epistemological doctrine, first by Niels Bohr, that coherence maintains between the several theories that arise successively in the growth of a mature science. In other words, the interconnectedness of science is itself the most stringent (and productive) restriction on the making of new theory. A new theory, in replacing a successful older one, at the minimum must account for all the results that the old one explained, and at least as successfully. Responsible treatment of the Correspondence Principle and the matters it brings in tow would be the subject of another review: none the less, the pressure to conserve what is known is a powerful one and felt to be justified by every practising scientist, whether he puts the name to it or not. Its working is, I think, exemplified in the origins of molecular biology.

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74 The best discussion of the Correspondence Principle in English is by the Polish philosopher Władysław Krajewski, in Correspondence Principle and Growth of Science (Dordrecht: D. Reidel, 1977). I am grateful to Philip Morrison for first telling me to read this remarkable book.