

DNA Structure: Happy 50th Birthday!

George B. Kauffman*

Department of Chemistry, California State University, Fresno, Fresno, CA 93740-8034, georgek@csufresno.edu

Received May 14, 2003. Accepted May 14, 2003.

Abstract: On the occasion of the 50th anniversary of the publication of Watson and Crick's double-helical structure of deoxyribonucleic acid (DNA), the history of the compound from its discovery in 1869 through the latest cutting-edge developments in forensic science, biotechnology, and genetic engineering as well as its exploitation in the mass media are recounted. Some anniversary events and exhibitions are also mentioned.

Today, April 25, 2003, marks the 50th anniversary of the publication of James Dewey Watson and Francis Harry Compton Crick's double-helical structure of deoxyribonucleic acid (DNA)—a feat hailed as “the culmination of a brilliant piece of detective work—and a discovery that has proven to be the key to molecular biology and modern biotechnology” [1, 2].

On December 10, 1962, the 66th anniversary of Alfred Nobel's death, in Stockholm's *Konserthus* (Concert Hall), Sweden's King Carl Gustav VI Adolf awarded the 1962 Nobel Prize in Physiology or Medicine to Watson [3, 4] (Figure 1) of Harvard University; Crick [5, 6] (Figure 2) of the Institute of Molecular Biology, Cambridge University; and Maurice Hugh Frederick Wilkins [7, 8] (Figure 3) of King's College, University of London “for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material” [9]. In his presentation speech A. Engström of Karolinska Institutet (the Caroline Institute) predicted:

Today no one can really ascertain the consequences of this new exact knowledge of the mechanisms of heredity. We can foresee new possibilities to conquer disease and to gain better knowledge of the interaction of heredity and environment and a greater understanding for the mechanisms of the origin of life. In whatever direction we look we see new vistas. We can, through the discovery by Crick, Watson, and Wilkins, to quote John Kendrew, see “the first glimpses of a new world.”...Your discovery of the molecular structure of deoxyribonucleic acid, the substance of heredity, is of utmost importance for our understanding of one of the most vital biological processes. Practically all the scientific disciplines in the life sciences have felt the great impact of your discovery. The formulation of the double helical structure of the deoxyribonucleic acid with the specific pairing of the organic bases, opens the most spectacular possibilities for the unravelling of the details of the control and transfer of genetic information [10].

Engström's prediction has come true to an unanticipated degree. Indeed, DNA is everywhere—literally. Not only in our very bodies but everywhere we look or turn. DNA is so deeply imbedded in our popular culture that I even have a T-shirt proclaiming it as “The Code of Life” and depicting the double

helix and the structures of its constituent four nucleotide bases (Figure 4).

DNA on TV

Pick up any newspaper any day, and you're certain to find several articles or stories involving DNA, and writers of television programs, our civilization's primary source of entertainment and news, vie with each other in their attempts to be *au courant* in presenting the latest cutting-edge developments. In one of CBS's “CSI: Crime Scene Investigation” episodes a forensic scientist states “Watson and Crick are the granddaddies of DNA. Without their discovery I would have nothing to do all day,” while on its spin-off “CSI: Miami” forensic criminologist Horatio Caine (David Caruso) warns a criminal, “And I can assure you that DNA doesn't lie.” Not only do such crime-related dramas as NBC's “Crossing Jordan” and “Law and Order” involve DNA, but DNA evidence makes its appearance on a host of other programs where we would hardly expect it.

Not to be outdone by broadcast TV, cable television has A&E's “Cold Case Files” series, and on March 9 and 10, 2003 the History Channel aired a series, “Dead Reckoning,” featuring DNA evidence and showing actual forensic investigators working at crime scenes.

In our consumer-oriented culture DNA is used routinely in advertisements of health and nutrition products. I've even seen entire TV infomercials devoted to such products. DNA or Double Helix seems to have been used for everything except for the name of a rock group—or has it? (I'm not really up on such matters).

DNA in the Movies

In the realm of motion picture films we have Director Mick Jackson's British made-for-television movie, “The Race for the Double Helix” (1986), based on Watson's book of the same name and starring Jeff Goldblum as James Watson, Tim Pigott-Smith as Francis Crick, Alan Howard as Maurice Wilkins, and Juliet Stevenson as Rosalind Franklin. Other scientists involved in the story who are portrayed by actors are Erwin Chargaff, Jerry Donahue, Sir Lawrence Bragg, Peter Pauling, Max Perutz, and John Kendrew. More recent and less serious films include, among others, “DNA” (1997), in which an idealistic doctor (Mark Dacascos) mistakenly reveals his radical DNA theories to an unscrupulous scientist (Juergen

* Series Editor contribution



Figure 1. James D. Watson. <http://www.nobel.se/medicine/laureates/1962/watson-bio.html> (Courtesy, the Nobel Foundation).



Figure 2. Francis H. C. Crick <http://www.nobel.se/medicine/laureates/1962/crick-bio.html> (Courtesy, the Nobel Foundation).



Figure 3. Maurice H. F. Wilkins. <http://www.nobel.se/medicine/laureates/1962/wilkins-bio.html> (Courtesy, the Nobel Foundation).

Prochnow), who uses the knowledge in mutant experiments, and “The Nutty Professor II: The Klumps” (2000), in which Eddie Murphy plays eight roles.

DNA before Watson and Crick

In 1869 Friedrich Miescher (1844–1895) [11–13], a young Swiss chemist working in the renowned biochemist Felix Hoppe-Seyler’s (1825–1895) laboratory at the Universität Tübingen made his first and most important discovery [14, 15].

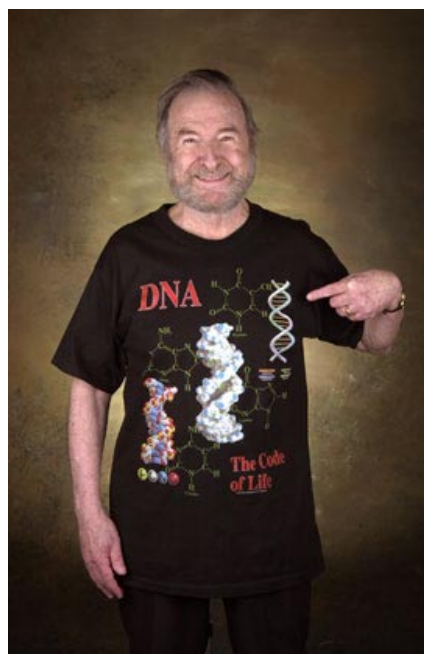


Figure 4. George B. Kauffman pointing to the double helix on a DNA T-shirt (photograph by Randy Vaughn-Dotta).

He isolated from the pepsin digestion of pus (white blood cells) a new class of phosphate-rich compounds (nucleohistone), which he named “nucleins” and which he correctly concluded to be as important in metabolic activity as the proteins [16]. In 1874 he isolated a purer form of nuclein from salmon spermatozoa and showed the salt-like combination between its two major constituents—an acid fraction (“pure nuclein,” now known to be DNA) and a basic fraction, which he called “protamine” and considered an alkaloid rather than a protein [17]. Miescher left the determination of the detailed chemical constitution of these compounds to others. His further studies of the formation of large amounts of nuclein by the male salmon during its fasting period was unfortunate in that it encouraged other workers to attempt to demonstrate that nucleic acids are derived from proteins, which in turn furthered the false view that nucleic acids are compounds formed between proteins and phosphoric acid.

During the first decades of the 20th century, researchers found that nucleic acids, like proteins, are polymers [18, 19]. Because the monomeric units of nucleic acids are called nucleotides, these biopolymers are also called polynucleotides. A nucleotide can be hydrolyzed to a nitrogenous base, a five-carbon sugar, and phosphoric acid. The German Albrecht Kossel (1910 Nobel Prize in Physiology or Medicine) [20] and the American Phoebus Aaron Theodor Levene [21] found that nucleic acids contain purines (adenine and guanine), pyrimidines (cytosine, thymine, and uracil) in a repetitive unit containing phosphoric acid and pentose sugars (ribose and deoxyribose). Two types of nucleic acids exist—ribonucleic acid (RNA), with ribose as its pentose; and deoxyribonucleic acid (DNA), with 2-deoxyribose as its pentose. Both types of acids are present in all plants and animals, but there was much confusion about their nature and function. In nucleic acids the nucleotide units are linked to each other by phosphodiester bonds forming macromolecules, which in the case of DNA can have molecular weights in the billions.

Although the chemistry of the nucleic acids was studied by numerous investigators from the time of its discovery, three-quarters of a century elapsed before their biological significance was realized. In 1944, in a classic paper [22], bacteriologists Oswald T. Avery, Colin M. MacLeod, and Maclyn McCarty of the Rockefeller Institute (now Rockefeller University), who, in their study of the phenomenon of transformation in bacteria, identified DNA as the transforming principle [23]. Their identification also revealed the chemical nature of the gene. Many scientists feel strongly that the three should have received the Nobel Prize for their discovery [8, p 755; 24–26]. However, the fact that the genetic material is DNA was not universally accepted until the early 1950s.

In 1949–1950 Austrian refugee scientist Erwin Chargaff and co-workers at Columbia University found that in DNA the ratio of the amounts of adenine (A) to thymine (T) and the ratio of guanine (G) to cytosine (C) are very close to unity [27–29]:

It is, however, noteworthy—whether this is more than accidental cannot yet be said—that in all desoxypentose nucleic acids examined thus far the molar ratios of total purines to total pyrimidines, and also of adenine to thymine and of guanine to cytosine, were not far from 1 [27c].

He also found that the ratio of A+T to G+C was characteristic of a species. In 1952 Hershey and Chase's finding that bacteriophage DNA carried the viral genetic information from generation to generation produced a revolution in research [30].

Linus Pauling's Related Work

Following Avery, MacLeod, and McCarty's discovery that DNA rather than protein was the transforming principle [22], its structure became a topic of great interest and a subject of intense competition among several research groups. The most probable person to have won what became known as the "race for the double helix" was Linus Pauling, the supreme patriarch of structural chemistry.

In 1948 Pauling was on leave from Caltech as a guest professor at Oxford University. While ill in bed with influenza, he sketched a chain of linked amino acids, the basic building blocks of proteins. He folded the paper and discovered the α -helix—a cylindrical, coil-like arrangement of amino acids connected by hydrogen bonds. Although these intramolecular bonds are weak compared to other types of bonds such as covalent bonds, hydrogen bonding is an incredibly significant force in holding biological molecules in their appropriate shapes [31].

The shape of protein molecules is as important as the constituent amino molecules that comprise them. Like a key in a lock, the protein molecules must possess the correct configuration to carry out their appropriate biochemical reactions, such as acting as enzymes. Together with Robert B. Corey, Pauling published a description of the α -helix [32], and the structure was soon verified experimentally. Pauling's application of structural chemistry to proteins initiated a revolution in molecular biology that continues to this day. His "lock and key" theory of enzyme action is at the heart of research into genetic defects and immunology. In his Nobel lecture Watson paid tribute to Pauling, and he cited Pauling and Corey's paper as his first reference:

The main challenge in biology was to understand gene replication and the way in which genes control protein synthesis. It was obvious that these problems could be logically attacked only when the structure of the gene became known. This meant solving the structure of DNA. Then this objective seemed out of reach to the interested geneticists. But in our cold, dark Cavendish lab, we thought the job could be done, quite possibly within a few months. Our optimism was partly based on Linus Pauling's feat in deducing the α -helix, largely by following the rules of theoretical chemistry so persuasively explained in his classical *The Nature of the Chemical Bond* [4, p 785].

Because Pauling, who was to win the Nobel Peace Prize in 1962 in addition to his Nobel Chemistry Prize in 1954, thus becoming the only person to receive two unshared Nobel Prizes in different fields, had been unwilling to name the collaborators in his "Ban the Bomb" campaign, he was refused a passport to attend a crucial symposium on proteins held in England in 1952. Many have speculated that if he had attended it and seen Rosalind Franklin's [33–36] X-ray diffraction photographs, he, rather than Watson and Crick, might have discovered the double-helix structure of DNA, a supposition dealt with in detail in the aforementioned movie "The Race for the Double Helix." The discovery almost certainly would have earned him an unprecedented third Nobel Prize. It is one of those ironies of history that Pauling's erroneous triple-stranded model of the molecule lost out to "an adolescent postdoc [Watson] and an elderly graduate student [Crick]" [37].

In an interview with my wife Laurie and me, Pauling told us:

I can't be sure what might have happened.... I knew Rosalind Franklin, and I might well have seen her and gotten an idea that would have put me on the right track.... I published [the idea] that the gene consists of two mutually complementary strands, each of which can serve as a template for the other one.... Both Watson and Crick heard me talk about that.

My wife made a comment, which I think was pertinent. She said, "If that was such an important problem, why didn't you work harder at it?" And I think I can say, "If I had worked harder, I wouldn't have needed to go to London to see Rosalind Franklin. I might well have discovered the double helix. I really wasn't paying much attention to the problem of the structure of nucleic acid" [38].

Watson and Crick's DNA Research [39–42]

The American member of the duo, James D. Watson, who was born on April 6, 1928 in Chicago, IL, had studied ornithology and received his Ph.D. in zoology at age 22 from Indiana University with a dissertation under the guidance of Salvador E. Luria (1962 Nobel Physiology or Medicine laureate) on the effect of hard X-rays on bacteriophage multiplication [3]. After he met Maurice H. F. Wilkins in 1951 at a symposium in Naples and first saw the X-ray diffraction pattern of crystalline DNA, he changed the direction of his research. Luria arranged for him to begin work under John C. Kendrew (1962 Nobel Chemistry laureate) in early October 1952 at the Cavendish Laboratory of Cambridge University. Watson soon met Francis H. C. Crick, and the pair shared their common interest in solving the DNA structure problem, using the experimental data obtained at King's College, London and the possible stereochemical configurations of polynucleotide chains. Although their first serious attempt made in late fall

1952 was unsatisfactory, their second effort, based on further experimental evidence and a better understanding of the nucleic acid literature and made in early March 1953, resulted in their proposal of the complementary double-helix configuration. Watson has carried out research on molecular biology, the human genome, recombinant DNA, and cancer [43–47]. He was the first Head of the Human Genome Project until he was “fired” [his term] by Bernadine Healy. He is currently director of the Molecular Biology Laboratory at Cold Spring Harbor, NY.

The English member of the famous pair, Francis H. C. Crick, was born on June 8, 1916 at Northampton and received his B.Sc. degree in physics from University College, London in 1937 [5]. His graduate study under Edward Neville da Costa Andrade was interrupted by World War II, and in 1947 he began to study biology, organic chemistry, and crystallography. In 1949 he joined the Medical Research Council (MRC) Unit of Cambridge University headed by Max F. Perutz (1962 Nobel Chemistry laureate), and in 1950 he became a graduate research student for a second time, this time at Caius College, Cambridge. He did not receive his Ph.D. until 1954—a year after his celebrated first paper with Watson—with a thesis titled “X-ray Diffraction: Polypeptides and Proteins.” In 1951, at age 35, he met Watson, then an enthusiastic young man of 23, leading to their double-helix structure proposal and replication scheme of 1953. Crick, a confirmed agnostic, now works on prebiotic chemistry, the origin of life and the soul, and brain research at the Salk Institute for Biological Studies at La Jolla, CA [48, 49].

Although Watson and Crick, despite their differences in age and personalities, worked well together, the same cannot be said of the other pair of actors in this quest for the structure of DNA. At King’s College, London biophysicist Maurice H. F. Wilkins (born at Pongaroa, New Zealand on December 15, 1916; Ph.D., Birmingham University, 1940) and crystallographer Rosalind E. Franklin (born in London on July 25, 1920; Ph.D., Cambridge University, 1945) both worked on DNA, but their relationship was one of mutual dislike. Franklin felt isolated and suffered the double handicaps of being both a woman and Jewish. In England at this time two laboratories were working extensively on the crystalline structures of biological materials—King’s College on DNA and the Cavendish on proteins. Despite an unspoken agreement between the organizations that their two areas would not overlap, Watson and Crick decided that DNA research was more exciting than the protein research on which they were supposedly engaging [35].

Because the conflict between Wilkins and Franklin had escalated to the point that they were hardly speaking to each other (She soon left for Birkbeck College to work for John Desmond Bernal), when Watson and Crick visited King’s College, Wilkins did not hesitate to show Franklin’s unpublished X-ray diffraction photographs of the “B” structure of DNA to the two (The “A” form, which is more crystalline, contains more water than the “B” form, which is the form that occurs in cells). In Watson’s words,

The instant I saw the picture my mouth fell open and my pulse began to race. The pattern was unbelievably simpler than those obtained previously (“A” form). Moreover, the black cross of reflections which dominated the picture could only arise from a helical structure [50, pp 167, 169].

Franklin’s critique of some of Watson and Crick’s earlier work helped in their reformulation of their structure. She also came very close to the double-helical structure, but she failed to recognize the significance of the monoclinic C_2 symmetry in “B” DNA, whereas Crick, who was working for his thesis on hemoglobin, which also possessed C_2 symmetry, recognized that this meant that the nucleic strands are antiparallel so that they could serve as templates for each other. This insight, together with Watson’s knowledge of Chargaff’s base pairing, led to their final success [34]. However, she did not make use of the three-dimensional models popularized by Pauling and by Watson and Crick.

In his personal account of their classic research, *The Double Helix* [50], a book that portrayed the participants in “the race” with all their foibles and idiosyncrasies, Watson created a bestseller [51]. However, he was especially criticized by both scientists and feminists for his misogynistic, unflattering “warts and all” portrayal of Franklin. He characterized her as a bad-tempered bluestocking obstructionist and referred to her as “Rosy,” although not to her face.

On April 22, 2003 the Public Broadcasting System (PBS) broadcast a poignant television program titled “The Secret of Photo 51,” produced by WGBH (Boston) and narrated by Sigourney Weaver as part of its “Nova” series [52], which explored in detail Rosalind Franklin’s largely neglected contribution to Watson and Crick’s structure of DNA. The program’s title referred to Franklin’s X-ray image of DNA that led “to one of the greatest discoveries in science and, some believe, to one of its greatest injustices” [52]. Although most of the living participants in the pioneering DNA work took part in the program, Watson declined Nova’s request for an interview.

According to Brenda Maddox,

When *The Double Helix* was in rough draft, Harvard University Press, which was planning to publish it, asked that all those so candidly mentioned be given a chance to read it, and they did, and Wilkins and Crick, above all, but not only, objected most strongly [52].

Crick wrote to Watson, “Your book is misleading and in bad taste. It does not illuminate the process of scientific discovery; it distorts it” [52]. Wilkins complained that the book was “unfair to almost everyone mentioned except Professor Watson himself” [52], and referring to Franklin, he asked Watson, “Is there any mention in your book that she is dead?” [52]. The implication was that Franklin, whom Brenda Maddox referred to as “that gifted girl who could not defend herself” [52], was unable to refute Watson’s charges.

Harvard University Press withdrew its offer to publish the book, but it was accepted by a commercial publisher.

Watson added a tribute to Franklin in the “Epilogue” to his book:

Since my initial impressions of her, both scientific and personal (as recorded in the early pages of this book), were often wrong, I want to say something here about her achievements. The X-ray work she did at King’s is increasingly regarded as superb. The sorting out of the A and B forms, by itself, would have made her reputation; even better was her 1952 demonstration, using Patterson superposition methods, that the phosphate groups must be on the outside of the DNA molecule.... By then [later, when Watson was teaching back in the United States] all traces of our bickering were forgotten, and we both [Watson and Crick] came to appreciate greatly her personal honesty

and generosity, realizing years too late the struggles that the intelligent woman faces to be accepted by a scientific world which often regards women as mere diversions from serious thinking. Rosalind's exemplary courage and integrity were apparent to all when, knowing she was mortally ill, she did not complain but continued working on a high level until a few weeks before her death [50, pp 225–226].

However, in Maddox's words, "it does nothing to alter, soften the character of the terrible Rosy" [52].

When asked what would be his longest ranging impact, Watson replied:

Probably my books. The discovery of DNA was just waiting to be made. It was not a difficult thing. Any good chemist focused on DNA should have found the structure of DNA. Pauling's failure to find the double helix was a very low probability event. But *The Double Helix* could not have been written by anyone beside myself [25, p 7].

Franklin died of ovarian cancer, possibly caused by her excessive exposure to X-rays, on April 16, 1958 at the age of 37. Because the Nobel Prize is never awarded posthumously, she could not be included in the 1962 prize (Furthermore, the prize is limited to three persons). In the Nobel addresses of the three laureates, only Wilkins acknowledged Franklin's role in the discovery [8, pp 758, 780]. Franklin has finally received some long overdue recognition for her work in the form of plaques placed on the places where she lived and worked and the Royal Society's Rosalind Franklin Award to support women in science (Murphy, M. Chemistry crusader [Susan Gibson] wins the first Rosalind Franklin award. *Chem. & Ind.* **2003**, 8 (April 21), 12).

According to Franklin's last student collaborator, 1982 Nobel Chemistry laureate Aaron Klug:

Watson's book [*The Double Helix*] placed her firmly as a protagonist in the story. It is very clear to me that if she had lived, she might have shared the Nobel Prize with Watson and Crick.... For the feminists, however, she has become a doomed heroine, and they have seized upon her as an icon, which, of course, is not her fault. Rosalind was not a feminist in the ordinary sense, but she was determined to be treated equally just like anybody else [25, pp 313–314].

Watson and Crick's Classic Paper [39–42, 53–55]

On February 28, 1953 at lunchtime Francis Crick "winged into the Eagle [pub] to tell everyone within hearing distance that we had found the secret of life" [50, p 197].

According to Brenda Maddox,

Watson and Crick wanted to publish quickly to get ahead of Linus Pauling in California, but they were held back by the embarrassing fact that all the experimental work that had led to their great leaps of the imagination had been done at a rival institution, at King's, and Rosalind's data hadn't been published. [Lawrence] Bragg of the Cavendish and [John] Randall of King's approached the editors of *Nature* to engineer a solution. They agreed to publish three articles within a single issue [52].

Watson and Crick's short paper [55], which occupies only slightly more than a single page (a mere 898 words exclusive of acknowledgments and references) and includes a single diagram of the DNA molecule drawn by Crick's second wife Odile (née Speed), in the April 25, 1953 issue of *Nature*, is modestly titled "A Structure for Deoxyribose Nucleic Acid"

not "The" structure. The authors did not exclude other possible configurations (Single- and triple-stranded configurations are known, and the double-stranded configuration occurs in three forms—A, B (which Watson and Crick describe), and Z [53].

The authors first criticize Pauling and Corey's three-intertwined chain model [56] on the basis of net charges as well as of interatomic distances that are too small. They then propose a structure for

the salt of DNA with two helical strands each coiled around the same axis...Each chain consists of phosphate diester groups joining β -D-deoxyribofuranose residues with 3', 5' linkages. The two chains (but not their bases) are related by a dyad [the pairing of opposite bases] perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions [they are anti-parallel].... The bases are on the inside of the helix and the phosphates on the outside.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases, [which] are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain.... One of the pair must be a purine and the other a pyrimidine for bonding to occur. If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations [50, Chap. 26]) it is found that only specific pairs of bases can bond together....adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).... If only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.... The ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity [Chargaff's rules [27c] are a consequence of DNA's double-helical structure].... It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact [55].

In one of the greatest scientific understatements of all time the usually impetuous Watson and Crick then uncharacteristically state:

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material [55].

An excellent almost sentence-by-sentence analysis of Watson and Crick's paper has been given by Tom Zinnen [53]. Immediately following Watson and Crick's paper the same issue of *Nature* (April 25, 1953) contains additional experimental evidence in favor of their structure. Wilkins, Stokes, and Wilson [57] analyze the X-ray crystallographic data and propose that the DNA structure exists in biological systems, and Franklin and Ray Gosling [58] conclude that the phosphate backbone lies on the outside of the structure and provide the experimental evidence for the helical structure of nucleic acids. Actually, Franklin and Gosling's paper provided the basis for Watson and Crick's paper. According to Maddox,

its position at the end suggests that Franklin's findings merely confirm Watson and Crick's model instead of providing the essential data used to formulate it [52].

In the May 30, 1953 issue Watson and Crick [59] follow up their speculation on “a possible copying mechanism for the genetic material” by showing how base pairing in the double helix is the means for self-replication of DNA and appears to be the basis for information transfer during protein synthesis. In the July 25, 1953 issue Franklin and Gosling [60] discuss the differences between the A and B structures of the DNA double helix.

RNA

Ribonucleic acid (RNA), a class of long, unbranched nucleic acid macromolecules primarily involved in translating the genetic information carried by DNA into proteins, has played second fiddle to its better-known related molecule. However, it has recently been shown to control key actions within the cell and may play a role in cancer. A class of RNAs, called small RNAs, has been shown to operate many of the cell's controls and can shut down genes or alter their actions. These discoveries, which may cause biologists to change their views of the cell and its evolution, have been cited by *Science* magazine, the prestigious weekly magazine of the American Association for the Advancement of Science, as 2002's “Breakthrough of the Year” [61].

We shall now briefly consider a few of the recent manifold scientific advances made possible by Watson and Crick's discovery, hailed as “arguably the most significant [event] to biology since Charles Darwin published his theory of evolution in 1859” [40]. Because of their great number, these examples are illustrative rather than exhaustive.

Forensic Analysis

In the realm of forensic analysis who can forget Monica Lewinsky's famous—or infamous—blue dress that resulted in the first impeachment of an American president since Andrew Johnson in 1868? In another celebrated and controversial case, begun as long as two centuries ago, third U.S. President Thomas Jefferson was alleged to have fathered children by his slave Sally Hemings. As the physical basis of heredity, DNA analysis, first used in 1996, confirmed on November 5, 1998 that indeed Jefferson was the father of at least one of her children [62]. The technique has also made possible the conviction of criminals who might otherwise escape justice or the freeing of prisoners who had been unjustly incarcerated [63, 64].

In view of the increasing number of prisoners who had been found to be innocent, Illinois Governor George Ryan, in a controversial act, ended his term by commuting 167 death sentences out of a concern that some prisoners on death row had been wrongly convicted. In 1992 defense lawyer Barry Scheck co-founded the Innocence Project, a nonprofit legal clinic at the Yeshiva University Law School, which to date has exonerated 117 prisoners. He maintains that the single greatest cause of unjust convictions is mistaken eyewitness identification, and instead he uses more reliable DNA tests.

Undergraduate biochemical experiments involving the analysis of forensic samples and manipulation of DNA technology have appeared in the literature [65]. Carolina Biological Supply Company advertises CD-ROM sets (“DNA Science: A First Course” and “DNA from the Beginning”) and various DNA laboratory experiment kits about different aspects of DNA in its latest catalogue [66]. Similarly, a DNA

Optical Transform Kit allows teachers and students to simulate the X-ray diffraction experiment that led to the discovery of the structure of DNA. Instead of X-rays and crystals, it uses a hand-held laser pointer (not included) and two-dimensional patterns on a photographic slide to explore how the DNA structure was determined [67].

On February 7, 2003 the Center for Public Integrity obtained and published a complete copy of the Department of Justice's draft “Domestic Security Enhancement Act of 2003”—the so-called “Patriot Act II” legislation—that authorizes a DNA database of broadly defined “suspected terrorists” [68]. On March 11, 2003 the Bush administration announced a plan “to commit \$1 billion to DNA testing in the next five years in a bid to stem a growing backlog of forensic evidence from crime scenes” [69]. According to Attorney General John Ashcroft, it would commit federal funds for DNA testing of convicted felons claiming to be innocent and would expand the kinds of crimes included in a national DNA database.

Refinements of the Polymerase Chain Reaction (PCR), acting as a molecular copying process, and the use of fluorescently-labeled primers have enhanced the technique of forensic DNA analysis by increasing its sensitivity by factors of millions [70]. On February 28, 2003 the New York Medical Examiner's Office announced that it had identified the remains of two of the September 11 hijackers by using DNA profiles supplied by the Federal Bureau of Investigation.

However, the FBI crime laboratory has recently been challenged in scores of cases involving DNA and bullet analysis. One FBI laboratory scientist has been indicted after admitting that she gave false testimony in connecting suspects to bullets by lead analysis, and a laboratory technician has resigned while under investigation for alleged improper testing (failing to compare the evidence with control samples) of at least 103 DNA samples [71]. In an attempt to increase the FBI's ability to investigate bioterrorist crimes, geneticist Bruce Budowie has been placed in charge of a new forensic science laboratory at Quantico, VA, focusing on microbial DNA and threats of bioterrorism [72].

Cloning

Ian Wilmut and Keith Campbell of the Roslin Institute in Edinburgh, Scotland created Dolly, born on July 5, 1996 as the first mammal cloned from an adult cell. She quickly became the world's most famous sheep thanks to the popular and scientific press, which reported her every move in headlines around the globe [73]. On February 14, 2003 the six-year-old ewe was euthanized after being diagnosed with an incurable progressive disease unrelated to her cloning. Her body was donated to Edinburgh's National Museum of Scotland, where she has been put on display [74].

Although scientists have successfully cloned sheep and pigs, the technology is not yet reliable, and most scientists think that attempting to clone humans is difficult, unethical, and risky. However, Brigitte Boisselier, a 46-year-old chemist and CEO of Clonaid, a company founded in 1997, announced that “Eve,” a baby cloned from the DNA of a 31-year-old American woman, was born on December 27, 2002. Boisselier is a member of the Raelians, a religious sect, founded by a former French race car driver and journalist who calls himself Rael. The sect believes that extraterrestrial aliens visited Earth about 250,000 years ago and produced the human race by cloning. The group promised to provide DNA evidence

to substantiate its claims but later withdrew the offer. Clonaid spokeswoman Nadine Gray announced on January 4, 2003 that a second human clone was born to a lesbian couple in The Netherlands on January 3, 2003 [75].

Clonaid's claims are believed to be a hoax to gain publicity [76], and scientists, including Ian Wilmut, who cloned "Dolly," have denounced them as science fiction and called upon the media to cease coverage of the claims until scientific evidence is provided. They have also asked the U.S. National Academy of Sciences (NAS) or the American Association for the Advancement of Science (AAAS) to oversee "essential independent tests on the alleged offspring" and for "all nations to enact responsible legislation to prevent human reproductive cloning" [77]. However, human cloning may be impossible with today's technology. On April 11, 2003 a team of a dozen scientists reported that cloning robs a rhesus monkey embryo of key proteins that permit a cell to divide chromosomes properly [78].

Unfortunately, the public and politicians have confused stem-cell research or cloning for biomedical research with attempts to create a "Frankenstein," and on February 27, 2003 the U.S. House of Representatives passed a bill, adopted by a 241 to 155 vote, to ban all human-cloning experiments, both for reproduction or to create cells to be used to treat disease, but the legislation still faces an uncertain fate in the Senate [79].

Representative Jim Greenwood (R-Pa.), who sponsored an alternative proposal, argued that it is wrong to ban research cloning and stated that millions of Americans with Parkinson's or Alzheimer's disease might benefit from genetic screening and cloning experiments. The NAS has concluded that cloning shows scientific promise, and 40 Nobel laureates support the statement. Somatic cell nuclear transfer (SCNT) research, a promising but controversial alternative approach to research cloning, would regulate the research rather than banning it, and an ethicist considers a permanent or even temporary ban to be "premature, preemptive, and unprecedented" [80]. Hopefully, public discussion of the ethical and scientific issues will continue.

Human Genome Project

In 1990 an international group of scientists launched one of the most ambitious projects in history—the location of the approximately 100,000 genes comprising the human genome—the blueprint of human life. The research, named the Human Genome Project (HGP) and carried out by biologists, physicists, computer experts, engineers, biochemists, and an assortment of scientists and technicians, was expected to locate, classify, and characterize the genetic defects responsible for hereditary diseases like Alzheimer's disease; heart disease; cystic fibrosis; Huntington's disease; breast, colon, and other cancers; muscular dystrophy; diabetes; obesity; and other diseases [81–83].

After years of work the stunning achievement of the sequencing of the human genome was completed by two separate groups, "not a contest but a marriage (perhaps encouraged by shotgun) between public funding and private entrepreneurship" [83a]. The group led by J. Craig Venter of Celera Genomics, a private company, reported its results in a special February 16, 2001 issue of *Science* [84]. Most of the issue was devoted to various aspects of the project, including a pullout timeline and a separate "Annotation of the Human

Genome Assembly." Recently the timeline of key events in the history of the human genome that appeared in this issue has been enhanced; linked to classic research articles, reviews, and news coverage; and made available online [85]. As I predicted in a book review [86], the number of authors on the human genome paper would exceed the 49 authors in the publication listed as that with the most authors (49 persons, R. B. Woodward et al. *J. Am. Chem. Soc.* **1981**, *103*, 3210–3213) in the book under review (Quadbeck-Seeger, H.-J.; Faust, R.; Knaus, G.; Siemeling, U., Eds. *World Records in Chemistry*; Russey, W. E., transl.; Wiley-VCH: Weinheim, New York, 1999). The second set of articles, produced by the group led by Francis S. Collins of the Human Genome Project (HGP), a publicly funded consortium of laboratories, appeared in the February 15, 2002 issue of *Nature* [87].

In an introductory editorial in *Science* the articles were hailed as "a powerful tool for unlocking the secrets of our genetic heritage and for finding our place among the other participants in the adventure of life." The editorial stated, "The sequencing of the human genome represents, not an ending, but the beginning of a new approach to biology," and it concluded,

The human genome has been called the Book of Life. Rather, it is a library, in which, with rules that encourage exploration and reward creativity, we can find many of the books that will help define us and our place in the great tapestry of life [88].

On April 14, 2003 an international consortium of scientists announced the completion of the final version of the human genome map, "the most accurate edition to date of life's genetic blueprint and the last milestone for one of the modern era's grandest scientific endeavors" [83a]. Researchers worldwide have free access to the DNA data from the final version of the map, which is considered 99.99 percent accurate. An *Encyclopedia of the Human Genome* is scheduled for publication in June 2003 [89].

Two Spanish microbiologists, Aurora Sánchez-Sousa and Fernando Banquero, and French composer Richard Krüll have even begun a project called "Genome Music," similar to Johann Sebastian Bach's music based on the four letters of his last name [90]. The three have turned the complete nucleotide sequences of several microbe genes into compositions based on DNA bases, which were performed during Madrid's "Week of Science" (November, 2002) and are available on CD.

Miscellaneous Genomic Developments

After humans, the mouse was the second mammal to have its DNA deciphered, and the results should help in the quest for the causes and potential treatments for AIDS, cancer, schizophrenia, heart disease, and other ailments. In several articles published in the December 5, 2002 issue of *Nature* researchers reported that 99 percent of the approximately 30,000 human and mouse genes are similar and about 80 percent of mouse genes are almost identical to their counterparts in humans [91].

In addition to the role of human embryonic stem (ES) cells in transplantation therapy, they have a potentially more important use as a basic research tool for understanding the development and function of human tissues. Bone morphogenetic protein 4 (BMP4) has been shown to induce the differentiation of human ES cells to trophoblast, thus providing

a new understanding of some of the earliest differentiation events of human post-implantation development [92]. The same group also was able, for the first time, to splice out individual genes from human embryonic stem cells and substitute different genes in their place, an important step toward the biomedical goal of rebuilding or regenerating parts of the human body by transplanting either ES cells or tissues grown from ES cells into patients [93].

DNA has been synthesized by the catalytic action of a DNA polymerase on a template of threosuccinic acid (TNA), which contains the sugar threose instead of deoxyribose in its backbone. The goal of this work is to find a DNA polymerase that can catalyze the synthesis with simpler nucleic acids [94]. Life expectancy in elderly people has been linked to the length of the telomeres, special structures at the end of the chromosomes in their DNA; the shorter the telomeres, the earlier the person died [95].

Almost all organisms use only 20 amino acids to synthesize proteins, the nitrogen-containing molecules required for all life processes. However, on January 4, 2003 Peter Schultz and co-workers reported that they had engineered the genes of a living organism—the common bacterium *Escherichia coli*—to incorporate a 21st amino acid (*p*-aminophenylalanine) into its proteins, making it the first synthetic life form with a chemistry unlike anything found in nature. The bacterium not only incorporates the 21st amino acid, but it also manufactures the compound by itself [96].

Genetically modified (GM) crops, animals, and foods have been opposed by various groups, especially in Europe [97]. In 2002 the California Fish and Game Commission rejected a proposal to make California the first state to prohibit fish farmers from introducing genetically altered fish, dubbed “frankenfish” by opponents, which grow faster and fatter, into public waterways. On February 7, 2003 the commission adopted rules that would allow production of these genetically engineered fish [98].

For more than three decades researchers have been seeking to develop a noninvasive test for cancer. On March 14, 2003 Hengmi Cui and his group reported a DNA-based blood test that may serve to predict the risk of developing colon cancer [99].

Some studies and novels such as Jean M. Auel's *The Clan of the Cave Bear* have postulated that extensive interbreeding took place between modern humans and Neanderthals, the longest known and best understood of fossil humans. Recent studies of mitochondrial DNA from Neanderthal fossils suggest that modern humans and the Neanderthals had a common ancestor about 500,000 years ago. However, the studies do not support the idea that interbreeding occurred after modern humans evolved in Africa and invaded Neanderthal habitats beginning about 45,000 years ago so that when Neanderthals died out, their genes did also [100].

Obese persons who claim that a weak gene rather than their poor willpower is responsible for their condition may take solace from a recent study. On March 20, 2003 a Swiss-German-American team reported that the melanocortin 4 receptor gene, which manufactures a protein by that name that helps stimulate appetite in the brain's hunger-regulating hypothalamus may be mutated in some persons. The mutated gene makes too little protein so that the body feels too much hunger [101].

Over the weekend of April 11–13, 2003 Canadian scientists announced that they had established the genetic sequence of a

completely new type of coronavirus believed to be the cause of SARS (severe acute respiratory syndrome), the deadly flu-like illness that had infected 3,169 persons and killed 144 persons up to that time [102]. According to Julie Gerberding, Director of the Centers for Disease Control and Prevention in Atlanta, GA, “Sequencing the virus is a major scientific achievement unprecedented in the history of science” [102]. The gene sequencing is expected to create accurate diagnostic tests and to increase the chance that a drug or vaccine will be found to defeat the virus [103].

On April 16, 2003 Francis S. Collins and co-workers reported the cause of Hutchinson-Gilford progeria syndrome, a very rare (one baby per 4 to 8 million worldwide) and fatal disorder that turns children into old persons. The disorder is caused by a mutation on a single gene called lamin A or LMNA in the human genome that contains some three billion DNA units. The work may lead to a treatment for the illness and may also increase our knowledge of normal aging [104].

All of the above breakthroughs in forensics, medicine, and genetics as well as a number of Nobel prize-winning discoveries would have been impossible without Watson and Crick's epoch-making discovery. Indeed, “it is the biological equivalent of Rutherford's model of the atom in the physical sciences” [105].

Anniversary Activities and Exhibits

In connection with the 100th anniversary of the awarding of the first Nobel Prizes, a Nobel Centennial Symposium, “Beyond Genes,” with introductory comments by James D. Watson and lectures by 19 internationally prominent researchers was held on December 6–8, 2001 at Karolinska Institutet in Stockholm, and on-demand videos are available on the Nobel e-Museum web site [106].

The Cold Spring Harbor Laboratory, NY held a 5-day conference, “The Biology of DNA,” featuring such pioneers as Watson, Francis S. Collins, Walter Gilbert, Thomas Cech, and Sydney Brenner placing the discovery in context, on February 26 through March 2, 2003. The laboratory's web site shows webcasts of the sessions [107], and between sessions an Exploratorium film crew broadcast interviews with many of the conference participants [108].

A number of scientists including more than ten Nobel laureates were interviewed on the origins of DNA research and its present and future consequences, and the video and animation sequences are available on the Internet [109]. Six exhibitions making up “The DNA Age” anniversary festival in New York City were reviewed in the Arts section of the March 14, 2003 issue of *The New York Times* [110].

The National Human Genome Research Institute (NHGRI), the National Institutes of Health (NIH), and the Department of Energy (DOE) hosted a scientific symposium, “From Double Helix to Human Sequence—and Beyond,” held on April 14–15, 2003 at the Natcher Conference Center in Bethesda, MD. Watson, Collins, and members of the International Human Genome Sequencing Consortium described the history and science of the HGP. The symposium explored the future of science and medicine brought about by breakthroughs in genomic science. It also unveiled the NHGRI's new scientific plan [111].

On April 22, 2003 original photographs and historical artefacts were exhibited, and Maurice H. F. Wilkins, Raymond Gosling, and Herbert Wilson, members of the original King's

DNA research team, were interviewed at “DNA at King’s—50th Anniversary of the Discovery of the Structure of DNA: A Day of Celebrations” [112]. On April 25, 2003, the 50th anniversary of the publication of Watson and Crick’s paper, three Cambridge University laboratories—the MRC Laboratory of Molecular Biology, the Sanger Institute, and the Cavendish Laboratory—sponsored a conference at Cambridge to commemorate the discovery. Internationally renowned scientists discussed the history behind the discovery, the progress made during the past half-century, and other subjects [105]. On April 28–29, 2003 a “Conference on Molecular Biology in the Twentieth Century at the Royal Institution” will be held at the Royal Institution in London [113].

The XIX International Congress of Genetics to be held at Melbourne, Australia July 6–11, 2003 touts itself as the “Olympics of Genetics.” It will feature 54 symposia and 280 invited international speakers, including eight Nobel laureates (Sydney Brenner, Peter Doherty, Robert Horvitz, H. Gobind Khorana, John Sulston, Susumu Tonegawa, James D. Watson, and Eric Wieschaus) [114].

The Oregon State University Libraries Special Collections has a web site, which features more than 800 original letters, manuscripts, photographs, audio clips, and video excerpts that show the history of DNA in the making. The material is not limited to Pauling’s contributions but includes those of all the major players [37].

A special 50th anniversary collection of reprints, overviews, and reviews celebrating the historical, scientific, and cultural impacts of the discovery of the double helix and providing the context for the discovery and views toward future research in the field is available on the *Nature* web site [115]. All the content is free, and throughout 2003 it will include news, special features, and an archive including all the classic 1953 articles. The American Association for the Advancement of Science also has a web site to celebrate the anniversary [116].

Additional DNA web sites include: “Celebrating 50 Years of DNA” (sponsored by Cold Spring Harbor Laboratory, Columbia University, Rockefeller University, and the Dana Alliance for Brain Initiatives): <http://www.dna50.org/>; “Exhibit: The Genomic Revolution” (designed by the American Museum of Natural History): http://www.amnh.org/exhibitions/genomics_0home/index.html; “The Dolan DNA Learning Center” (featuring “The Gene Almanac and DNA at 50: Finding the Double Helix” by James D. Watson): <http://www.dnalc.org/>; “Molecular Biology Network: Structure of DNA”: <http://rothamsted.bbsrc.ac.uk/notebook/courses/guide/dnast.htm>; “DNA Structure”: <http://www.biochem.uwo.ca/meds/medna/doublehelix.html>; “Base Pairing”: <http://www.biochem.uwo.ca/meds/medna/bp.html>; and “DNA: The Code of Life”: <http://library.thinkquest.org/20465/DNAstruct.html>.

In January, 2003 the British Royal Mint issued a £2 coin depicting the double helix to commemorate the 50th anniversary of Watson and Crick’s seminal discovery [117].

Acknowledgments. I am indebted to University Photographer Randy Vaughn-Dotta of the California State University, Fresno Academic Innovation Center for his excellent photographic work; Reference Librarian Diane Majors of the CSUF Henry Miller Madden Library for locating source material; and Research Corporation of Tucson, Arizona for financial support.

References and Notes

1. James Watson and Francis Crick...Discovery of the DNA Structure. <http://www.mun.ca/biology/scarr/4241/W&C2.htm> (accessed May 2003).
2. Kauffman, G. B. Story of DNA is full of twists and turns. *The Fresno Bee*, April 19, 2003, p B11.
3. Biography. In The Nobel Foundation, *Nobel Lectures including Presentation Speeches and Laureates' Biographies: Physiology or Medicine 1942–1962*; Elsevier Publishing Company: Amsterdam—London—New York, 1964; pp 809–810; <http://www.nobel.se/medicine/laureates/1962/watson-bio.html> (accessed May 2003).
4. Watson, J. D. The Involvement of RNA in the Synthesis of Proteins. In The Nobel Foundation, *Nobel Lectures including Presentation Speeches and Laureates' Biographies: Physiology or Medicine 1942–1962*; Elsevier Publishing Company: Amsterdam—London—New York, 1964; pp 785–808; <http://www.nobel.se/medicine/laureates/1962/watson-lecture.pdf> (accessed May 2003).
5. Biography. In The Nobel Foundation, *Nobel Lectures including Presentation Speeches and Laureates' Biographies: Physiology or Medicine 1942–1962*; Elsevier Publishing Company: Amsterdam—London—New York, 1964; pp 820–821; <http://www.nobel.se/medicine/laureates/1962/crick-bio.html> (accessed May 2003).
6. Crick, F. H. C. On the Genetic Code. In The Nobel Foundation, *Nobel Lectures including Presentation Speeches and Laureates' Biographies: Physiology or Medicine 1942–1962*; Elsevier Publishing Company: Amsterdam—London—New York, 1964; pp 811–819; <http://www.nobel.se/medicine/laureates/1962/crick-lecture.html> (accessed May 2003).
7. Biography. In The Nobel Foundation, *Nobel Lectures including Presentation Speeches and Laureates' Biographies: Physiology or Medicine 1942–1962*; Elsevier Publishing Company: Amsterdam—London—New York, 1964; pp 783–784; <http://www.nobel.se/medicine/laureates/1962/wilkins-bio.html> (accessed May 2003).
8. Wilkins, M. H. F. The Molecular Configuration of Nucleic Acids. In The Nobel Foundation, *Nobel Lectures including Presentation Speeches and Laureates' Biographies: Physiology or Medicine 1942–1962*; Elsevier Publishing Company: Amsterdam—London—New York, 1964; pp 754–782; <http://www.nobel.se/medicine/laureates/1962/wilkins-lecture.pdf> (accessed May 2003).
9. The Nobel Prize in Physiology or Medicine 1962. <http://www.nobel.se/medicine/laureates/1962> (accessed May 2003).
10. Engström, A. Physiology or Medicine 1962. In The Nobel Foundation, *Nobel Lectures including Presentation Speeches and Laureates' Biographies: Physiology or Medicine 1942–1962*; Elsevier Publishing Company: Amsterdam—London—New York, 1964; pp 751–753; <http://www.nobel.se/medicine/laureates/1962/press.html> (accessed May 2003).
11. Olby, R. Johann Friedrich Miescher II. In *Dictionary of Scientific Biography*; Gillispie, C. C., Ed.; Charles Scribner’s Sons: New York, 1974; Vol. 9, pp 380–381.
12. de Meuron-Landot, M. Friedrich Miescher, l’homme qui a découvert les acides nucléiques. *Histoire de la Médecine* **1965**, *15*, 2–25.
13. Greenstein, J. P. Friedrich Miescher, 1844–1895: Founder of Nuclear Chemistry. *Sci. Monthly* **1943**, *57*, 523–532.
14. Mirsky, A. The Discovery of DNA. *Sci. Amer.* **1967**, *218*, 78–88.
15. Ihde, A. J. *The Development of Modern Chemistry*; Harper and Row: New York, 1964; pp 551–552.
16. Miescher, F. Ueber die chemische Zusammensetzung der Eiterzellen. In *Medicinisch-chemische Untersuchungen aus dem Laboratorium für angewandte Chemie zu Tübingen*; Hoppe-Seyler, F., Ed.; A. Hirschwald: Berlin, 1871; Vol. 4, pp 441–460.
17. Miescher, F. Die Spermatozoen einer Wirbelthiere: Ein Beitrag zur Histochemie. *Verhandl. Naturforsch. Gesellschaft in Basel* **1874**, *6*, 138–208.
18. Noller, C. R. *Chemistry of Organic Compounds*; 3rd ed.; W. B. Saunders Company: Philadelphia and London, 1966; pp 701–704.

19. Armstrong, F. B. *Biochemistry*, 3rd ed.; Oxford University Press: New York/Oxford, 1989; pp 9–14; Chap. 12.
20. Kossel, A.; Neumann, A. Ueber das Thymin, ein Spaltungsproduct der Nucleinsäure. *Ber.* **1893**, *26*, 2753–2756; Darstellung und Spaltungsproducte der Nucleinsäure (Adenylsäure). *Ber.* **1894**, *27*, 2215–2222.
21. Levene, P. A.; Bass, L. W. *Nucleic Acids*; Chemical Catalog Company: New York, 1931.
22. Avery, O.; MacLeod, C. M.; McCarty, M. Studies of the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III. *J. Exper. Med.* **1944**, *79*, 137–158; <http://www.nature.com/nature/dna50/macleodmccarty.pdf> (accessed May 2003).
23. McCarty, M. *The Transforming Principle: Discovering That Genes Are Made of DNA*; W. W. Norton & Co.: New York, 1985.
24. Lindsten, J.; Ringertz, N. The Nobel Prize in Physiology or Medicine. In *The Nobel Prize: The First 100 Years*; Levinovitz, A. W.; Ringertz, N., Eds.; Imperial College Press: London; World Scientific Publishing Co.: Singapore; River Edge, NJ, 2001; p 125.
25. Hargittai, I. *Candid Science II: Conversations with Famous Biomedical Scientists*; Hargittai, M., Ed.; Imperial College Press: London, 2002; pp 89, 90, 358, 392.
26. Hargittai, I. *The Road to Stockholm: Nobel Prizes, Science, and Scientists*; Oxford University Press: Oxford/New York, 2002; pp 221, 225–226.
27. (a) Chargaff, E.; Vischer, E.; Doniger, R.; Green, C.; Misani, F. The Composition of Desoxypentose Nucleic Acids of Thymus and Spleen. *J. Biol. Chem.* **1949**, *177*, 405–416; (b) Vischer, E.; Zamenhof, S.; Chargaff, E. Microbial Nucleic Acids: The Desoxypentose Nucleic Acids of Avian Tubercle Bacilli and Yeast. *J. Biol. Chem.* **1949**, *177*, 429–438; (c) Chargaff, E. Chemical Specificity of Nucleic Acids and Mechanism of Their Enzymatic Degradation. *Experientia* **1950**, *6*, 201–209; Chargaff, E. How Genetics Got a Chemical Education. *Ann. New York Acad. Sci.* **1979**, *325*, 345–360; this lecture, edited by Donald R. Forsdyke, is available at <http://crystal.biochem.queensu.ca/forsdyke/bioinfo1.htm> (accessed May 2003).
28. Chargaff, E. *Heraclitean Fire: Sketches from a Life before Nature*; Rockefeller University Press: New York, 1978.
29. Abir-Am, P. From Biochemistry to Molecular Biology: DNA and the Acculturated Journey of the Critic of Science E. Chargaff. *Hist. Phil. Life Sci.* **1980**, *2*, 3–60.
30. Hershey, A. D.; Chase, M. Independent Functions of Viral Protein and Nucleic Acid in Growth of Bacteriophage. *J. Gen. Physiol.* **1952**, *36*, 39–56.
31. Kauffman, G. B.; Mayo, I. A Giant among Chemists, a Giant among Men. *The World & I* **1995**, *10* (1) (January), 208–215.
32. Pauling, L.; Corey, R. B. Atomic Coordinates and Structure Factors for Two Helical Configurations of Polypeptide Chains. *Proc. Nat. Acad. Sci.* **1951**, *37*, 235–240.
33. Sayre, A. *Rosalind Franklin and DNA*; W. W. Norton & Co.: New York, 1975, 2001.
34. Maddox, B. *Rosalind Franklin: The Dark Lady of DNA*; HarperCollins Publishers: New York, 2002; Creager, A. N. H. Crystallizing a Life in Science. *Am. Sci.* **2003**, *91*, 64–66.
35. Harvey, J.; Ogilvie, M. B. Rosalind Elsie Franklin (1920–1958). In *The Biographical Dictionary of Women in Science: Pioneering Lives from Ancient Times to the Mid-20th Century*; Ogilvie, M.; Harvey, J., Eds.; Routledge: New York and London, 2000; Vol. 1, pp 465–466.
36. Elkin, L. O. Rosalind Franklin and the Double Helix. *Physics Today* **2003**, *56* (March), 42; Rosalind Franklin: the woman behind the DNA helix. *Chem. & Ind.* **2003**, *8* (April 21), 13.
37. Linus Pauling and the Race for DNA. <http://osulibrary.orst.edu/specialcollections/coll/pauling/dna/index.html> (accessed May 2003).
38. Kauffman, G. B.; Kauffman, L. M. Linus Pauling: Reflections (based on a personal interview). *Am. Sci.* **1994**, *82*, 522–524; An Interview with Linus Pauling: Contribution to the Symposium: A Tribute to Linus Carl Pauling (1901–1994). *J. Chem. Educ.* **1996**, *73*, 29–32.
39. Wright, R. Time 100: Scientists & Thinkers—Molecular Biologists James Watson & Francis Crick. <http://www.time.com/time/time100/scientist/profile/watsoncrick.html>. For a detailed discussion of Anthony Barrington Brown's famous photograph of Watson, Crick, and their double-helical DNA model, which has become an iconic image of 20th-century science, see de Chadarevian, S. Portrait of a Discovery: Watson, Crick, and the Double Helix. *Isis* **2003**, *94*, 90–105.
40. Perlman, D. Marking First 50 Years of DNA Revolution: Double-helix discovery began era of genetic manipulation. *San Francisco Chronicle*, March 2, 2003; <http://www.sfgate.com/cgi-bin/article.cgi?file=/chronicle/archive/2003/03/02/MN217810.DTL&type=printable> (accessed May 2003).
41. Olby, R. *The Path to the Double Helix*; University of Washington Press: Seattle, WA, 1975.
42. Henry, C. M. The Chemical Side of the Double Helix. *Chem. Eng. News* **2003**, *81* (Mar 10), 49–60; <http://www.cen-online.org> (accessed May 2003).
43. Watson, J. D., Ed. *Molecular Biology of the Gene*; 3rd ed.; W. A. Benjamin: New York, 1976; 4th ed.; Benjamin/Cummings: Menlo Park, CA, 1987. The 5th edition is scheduled for publication in December, 2003.
44. *Origins of Human Cancer*; Watson, J. D., Ed.; Cold Spring Harbor Laboratory, NY, 1977.
45. Watson, J. D. *Recombinant DNA—A Short Course*; Scientific American Books; W. H. Freeman: New York, 1983.
46. Watson, J. D. *Nucleic Acid Research: Future Development*; Academic Press: New York, 1983.
47. Watson, J. D.; Berry, A. *DNA: The Secret of Life*; Alfred A. Knopf: New York, 2003. For a negative review of Watson's overly enthusiastic view of genomics in this book see Lindee, M. S. Watson's World. *Science* **2003**, *300*, 432–434. For a recent biography of Watson and his work see McElheny, V. K. *Watson and DNA: Making a Scientific Revolution*; Perseus: Cambridge, MA, 2003.
48. Crick, F. *Life Itself: Its Origins and Nature*; Simon and Schuster: New York, 1981.
49. Crick, F. *The Astonishing Hypothesis: The Scientific Search for the Soul*; Maxwell Macmillan International: New York, 1994.
50. Watson, J. D. *The Double Helix: A Personal Account of the Discovery of DNA*; Atheneum: New York, 1968; Touchstone: New York, 2001.
51. Watson's recent sequel, *Genes, Girls, and Gamow: After the Double Helix*; Alfred A. Knopf: New York, 2002, has not repeated the success of *The Double Helix*. However, his reputation as a “brash young man” has continued. For example, recently on a British Channel 4 documentary screened in the United Kingdom, the brash septuagenarian “suggested that stupidity is a genetic disease that could be cured...[and] that it would be great to make all girls pretty” (Watson: Stupidity Disease. *Chem. & Ind.* **2003**, *6* (6) (March 17), 6.
52. Secret of Photo 15. <http://www.pbs.org/wgbh/nova/photo51> This web site includes a number of links to an article (“Before Watson and Crick”), an interview (“Defending Franklin's Legacy”), a slide show (“Picturing the Molecules of Life”), interactives (“Anatomy of Photo 51” and “Journey into DNA”), and other resources.
53. Zinnen, T. Watson and Crick Case Study. <http://www.access.excellence.org/AB/BC/casestudy2.html> (accessed May 2003).
54. Introduction to DNA Structure. http://www.blc.arizona.edu/Molecular_Graphics/DNA_Structure/DNA_Tutorial.HTML (accessed May 2003).
55. Watson, J. D.; Crick, F. H. C. A Structure for Deoxyribose Nucleic Acid. *Nature* **1953**, *171*, 737–738; <http://www.nature.com/nature/dna50/watsoncrick.pdf> (accessed May 2003); <http://classes.web.waseda.ac.jp/z-funatsu01/LOCAL/biophysics01.pdf> (accessed May 2003).
56. Pauling, L.; Corey, R. B. Structure of the Nucleic Acids. *Nature* **1953**, *171*, 346; A Proposed Structure for the Nucleic Acids. *Proc. Nat. Acad. Sci.* **1953**, *39*, 84–97.

57. Wilkins, M. H. F.; Stokes, A. R.; Wilson, H. R. Molecular Structure of Deoxyribose Nucleic Acids. *Nature* **1953**, *171*, 738–740; <http://www.nature.com/nature/dna50/wilkins.pdf> (accessed May 2003).
58. Franklin, R.; Gosling, R. G. Molecular Configuration in Sodium Thymonucleate. *Nature* **1953**, *171*, 740–741; <http://www.nature.com/nature/dna50/franklingosling.pdf> (accessed May 2003).
59. Watson, J. D.; Crick, F. H. C. Genetical Implications of the Structure of Deoxyribonucleic Acid. *Nature* **1953**, *171*, 964–967; <http://www.nature.com/nature/dna50/watsoncrick2.pdf> (accessed May 2003).
60. Franklin, R.; Gosling, R. G. Evidence for 2-Chain Helix in Crystalline Structure of Sodium Deoxyribonucleate. *Nature* **1953**, *172*, 156–157; <http://www.nature.com/nature/dna50/franklingosling2.pdf> (accessed May 2003).
61. Couzin, J. Breakthrough of the Year: The Winner: Small RNAs Make Big Splash. *Science* **2002**, *298*, 2296–2297.
62. Lander, E. S.; Ellis, J. J. Founding Father. *Nature* **1998**, *396*, 13. Also see Huskey, R. J. Thomas Jefferson and Sally Hemings. <http://www.people.virginia.edu/~rjh9u/tomsally.html> (accessed May 2003).
63. Salant, J. D. Legal groups seek ways to halt wrong convictions: DNA testing plays key role in clearing the innocent. *The Fresno Bee*, Jan 18, 2003, p A4.
64. Newfield, J. It Could Happen to Any of Us. *Parade*, Feb 23, 2003, pp 4–6; Lavoie, D. DNA Evidence frees 19-year inmate. *The Fresno Bee*, April 4, 2003, p A3; Bragg, R. DNA Clears Louisiana Man on Death Row, Lawyer Says. *The New York Times*, April 22, 2003; <http://www.nytimes.com/2003/04/22/national/22DEAT.html?th=&pa gewanted=print&position=> (accessed May 2003, requires registration).
65. Millard, J.; Pilon, A. M. Identification of Forensic Samples via Mitochondrial DNA in the Undergraduate Laboratory. *J. Chem. Educ.* **2003**, *80*, 444–446.
66. *Carolina Biotechnology 2003*, 2700 York Road, Burlington, NC 27215-3398; <http://www.carolina.com> (accessed May 2003).
67. Order No. 99-001; Slides No. 99-001S, Institute for Chemical Education, University of Wisconsin, Madison, 1101 University Avenue, Madison, WI 53706; email: ICE@chem.wisc.edu; web site: <http://ice.chem.wisc.edu> (accessed May 2003).
68. Media Advisory: Muted Response to Ashcroft's Sneak Attack on Liberties, email from FAIR (Fairness & Accuracy in Reporting), February 12, 2003 (fair@fair.org). Incidentally, USA Patriot Act is an acronym for "Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism."
69. Lichtblau, E. New Federal Plan for DNA Testing. *New York Times*, March 12, 2003.
70. Baker, C. Exhibition Chemistry: Chemiluminescence. *Educ. Chem.* **2003**, *40*, 39.
71. Solomon, J. FBI lab results challenged after problems found. *The Fresno Bee*, April 16, 2003, p A5.
72. Enserink, M. FBI's Top Scientist Takes the Lead in Forensic Biology. *Science* **2003**, *300*, 41, 43.
73. Campbell, K. H. S.; McWhir, J.; Ritchie, W. A.; Wilmut, I. Sheep Cloned by Nuclear Transfer from a Cultured Cell Line. *Nature* **1996**, *380*, 64–66.
74. Dolly Goes to Greener Pastures. *Science* **2003**, *299*, 1163; Goodbye, Dolly. *Chem. Eng. News* **2003**, *81* (Feb 24), 7; Dolly's death not due to cloning, say creators. *Chem. & Ind.* **2003**, *5* (March 3), 5.
75. Sterling, T. Clonaid claims it has produced a second cloned human. *The Fresno Bee*, Jan 5, 2003, p A8.
76. Human Cloning: An Elaborate Hoax According to Scientists. *Chem. & Ind.* **2003**, *2* (January 20), 5; The Rael Thing. *Sci. Amer.* **2003**, *288* (March), 110.
77. Schatten, G.; Prather, R.; Wilmut, I. Claim Is Science Fiction, Not Science. *Science* **2003**, *299*, 17.
78. Vogel, G. Misguided Chromosomes Foil Primate Cloning. *Science* **2003**, *300*, 225, 227; Simerly, C. et al. Molecular Correlates of Primate Nuclear Transfer Failures. *Science* **2003**, *300*, 297; Protein arrangements may make primate cloning impossible. *Chem. & Ind.* **2003**, *8* (April 21), 7.
79. Stolberg, S. G. House bans human cloning; Senate vote uncertain. *The Fresno Bee*, February 28, 2003, p A3; Baum, R. M. Science Versus Ideology. *Chem. Eng. News* **2003**, *81* (18) (May 5), 5.
80. Walters, L. Research Cloning, Ethics, and Public Policy. *Science* **2003**, *299*, 1661.
81. Kauffman, G. B.; Kauffman, L. M. Map of Life: Science, Society, and the Human Genome Project. *J. Coll. Sci. Teaching* **1994**, *24*, 143; Molecular Miracles: Human Gene Therapy and the Future of Modern Medicine. *J. Coll. Sci. Teaching* **1997**, *26* (December 1996/January 1997), 221; Genome: Solving the Code of Life. *J. Coll. Sci. Teaching* **1997**, *26*, 365–366.
82. Hall, S. *Invisible Frontiers: The Race to Synthesize a Human Gene*; Oxford University Press: New York/Oxford, 2002.
83. (a) Jasny, B. R.; Kennedy, D. The Human Genome. *Science* **2001**, *291*, 1153; (b) Henry, C. Human Genome Project Finished. *Chem. Eng. News* **2003**, *81* (16)(April 21), 12; Pennisi, E. Reaching Their Goal Early, Sequencing Labs Celebrate. *Science* **2003**, *300*, 409; Human genome complete well ahead of schedule. *Chem. & Ind.* **2003**, *8* (April 21), 4–5.
84. Venter, J. C. et al. The Sequence of the Human Genome. *Science* **2001**, *291*, 1304–1351. The number of coauthors, listed after Venter's name in alphabetical order from A to Z and filling an entire journal page, was 273—possibly a record in the history of science.
85. Science Functional Genomics: The Human Genome—An Interactive timeline. <http://www.sciencemagazine.org/feature/plus/sfg/human/timeline.shtml> (accessed May 2003).
86. Kauffman, G. B. World Records in Chemistry. *The Chemical Intelligencer* **2000**, *6* (3) (July), 62–63.
87. Lander, E. S. et al. Initial Sequencing and Analysis of the Human Genome. *Nature* **2001**, *409*, 860–921 (101 authors); Bentley, D. R. et al. The Physical Maps for Sequencing Human Chromosomes 1, 6, 9, 10, 13, 20 and X. *Nature* **2001**, *409*, 942–943 (101 authors); Cheung, V. G. et al. Integration of Cytogenic Landmarks into the Draft Sequence of the Human Genome. *Nature* **2001**, *409*, 953–958 (60 authors).
88. Collins, F. S.; Green, E. D.; Guttmacher, A. E.; Guyer, M. S. A Vision of the Future of Genomics Research. *Nature* **2003**, *422*, 835–847.
89. Cooper, D., Ed.-in-Chief. *Nature Encyclopedia of the Human Genome*; 5 volumes; Nature Publishing Group; Macmillan Publishers, Ltd.: London, 2003; <http://www.ehgonline.net> (accessed May 2003).
90. Sing Along With the Genome. *Science* **2002**, *298*, 2325.
91. The Mouse Gene: The Real Deal. *Nature* **2002**, *420*, 456–457; Dennis, C. The Mouse Gene: A Forage in the Junkyard. *Nature* **2002**, *420*, 458–459; Butler, D. Piecing It All Together. *Nature* **2002**, *420*, 460.
92. Xu, R.-H.; Chen, X.; Li, D. S.; Li, R.; Addicks, G. C.; Glennon, C.; Zwaka, T. P.; Thomson, J. A. BMP4 Initiates Human Embryonic Stem Cell Differentiation to Trophoblast. *Nature Biotechnology* **2002**, *20*, 1261–1264.
93. Zwaka, T. P.; Thomson, J. A. Homologous Recombination in Human Embryonic Stem Cells. *Nature Biotechnology* **2003**, *21*, 319–321.
94. Chaput, J. C.; Ichida, J. K.; Szostak, J. W. DNA Polymerase-Mediated DNA Synthesis on a TNA Template. *J. Am. Chem. Soc.* **2003**, *125*, 856–857; Henry, C. DNA synthesized from TNA template. *Chem. Eng. News* **2003**, *81* (2) (Jan 13), 9.
95. Cawthon, R. M.; Smith, K. R.; O'Brien, E.; Sivatchenko, A.; Kerber, R. A. Association between Telomere Length in Blood and Mortality in People Aged 60 Years or Older. *Lancet* **2003**, *361*, 393.
96. Mehl, R. A.; Anderson, J. C.; Santoro, S. W.; Wang, L.; Martin, A. B.; King, D. S.; Horn, D. M.; Schultz, P. Generation of a Bacterium

- with a 21 Amino Acid Genetic Code. *J. Am. Chem. Soc.* **2003**, *125*, 935–939; Service, R. F. Researchers Create First Autonomous Synthetic Life Form. *Science* **2003**, *299*, 640.
97. Strauss, S. H. Genomics, Genetic Engineering, and Domestication of Crops. *Science* **2003**, *300*, 61–62.
98. Thompson, D. Rules adopted for producing bioengineered fish. *Fresno Bee*, February 8, 2003, p B3.
99. Cui, H.; Cruz-Correa, M.; Giardiello, F. M.; Hutcheon, D. F.; Kafonek, D. R.; Brandenburg, S.; Wu, Y.; He, X.; Powe, N. R.; Feinberg, A. P. Loss of IGF2 Imprinting: A Potential Marker of Colorectal Cancer Risk. *Science* **2003**, *299*, 1753–1755; Ransohoff, D. F. Developing Molecular Biomarkers for Cancer. *Science* **2003**, *299*, 1679–1680.
100. Klein, R. G. Whither the Neanderthals? *Science* **2003**, *299*, 1525–1527.
101. Farooqi, I. S.; Keogh, J. M.; Yeo, G. S. H.; Lank, E. J.; Cheetham, T.; O'Rahilly, S. Clinical Spectrum of Obesity and Mutations in the Melanocortin 4 Gene. *New Engl. J. Med.* **2003**, *348*, 1085–1095.
102. Mystery Illness: SARS: Canada cracks SARS code. *The Fresno Bee*, April 14, 2003; p A3; Enserink, M. Calling All Coronavirologists. *Science* **2003**, *300*, 413–414; Zurer, P. SARS Cause Found. *Chem. Eng. News* **2003**, *81* (16) (April 21), 11; Butler, R. A science success story. *Chem. & Ind.* **2003**, *8* (April 21), 11.
103. Mystery Illness: SARS: Much study still lies ahead. *The Fresno Bee*, April 15, 2003.
104. Recer, P. Gene Found for Aging Disease in Children. <http://www.heraldsun.com/healthmed/34-342967.html> (accessed May 2003).
105. DNA: 50 Years of the Double Helix. <http://www2.mrc-lmb.cam.ac.uk/dna2003/conference.html> (accessed May 2003).
106. Nobel Centennial Symposia, 2001, Beyond Genes. <http://www.nobel.se/medicine/symposia/ncs2001-3/about.html> (accessed May 2003).
107. The Biology of DNA Online. <http://www.cshl.org/leadingstrand> (accessed May 2003).
108. Speaking of DNA: Insights into the Process of Scientific Discovery. <http://www.exploratorium.edu/origins> (accessed May 2003).
109. The Making of DNA Interactive. <http://www.dnai.org/index.html> (accessed May 2003).
110. Boxer, S. At Play With DNA. *The New York Times*, March 14, 2003; <http://www.nytimes.com/2003/03/14/arts/design/14BOXE.html?th=&pagewanted=print&position=top> (accessed May 2003, requires registration).
111. April 2003 Scientific Symposium: From Double Helix to Human Sequence—and Beyond. <http://www.genome.gov/page.cfm?pageID=10506368> (accessed May 2003).
112. DNA at King's—50th anniversary of the discovery of the structure of DNA: A day of celebrations. <http://www.kcl.ac.uk/phpnews/wmview.php?ArtID=362> (accessed May 2003); <http://www.kcl.ac.uk/dna> (accessed May 2003).
113. Conference on molecular biology in the twentieth century at the Royal Institution. <http://www.rigb.org/events/DNA.pdf> (accessed May 2003).
114. Genetics Congress. <http://www.geneticscongress2003.com/index.php> (accessed May 2003).
115. Double Helix: 50 Years of DNA. <http://www.nature.com/nature/dna50/index.html> (accessed May 2003).
116. Anniversary of the Discovery of the Structure of DNA. <http://www.aaas.org/news/genome> (accessed May 2003).
117. DNA in your pocket. *Educ. Chem.* **2003**, *40*, 31; Double Helix Coin. *Science* **2003**, *300*, 577.