5

THE SECRET OF LIFE

It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts.

—SHERLOCK HOLMES IN *A SCANDAL IN BOHEMIA* (1891) BY ARTHUR CONAN DOYLE

THE PROCESS OF SCIENCE is often compared to a detective story, where the solution to some mystery is arrived at by the dogged pursuit of evidence and clever deductions by a scientist (the lead detective). In the case of the mystery of the structure of DNA, and how it helped explain the mechanism of inheritance, the detective story unfolded more like a game of *Clue*.

In the popular board game, first introduced by Parker Brothers in 1949, just before the case of DNA was cracked, the goal is to be the first of several players to solve a murder by correctly identifying which character committed the crime, with what weapon, and in which room of a mansion. Each player assumes the identity of one of the six characters in the game and moves that game piece around the board making "suggestions" of the solution, for example, "I suggest the crime was committed by Colonel Mustard with the candlestick in the library." Players then try to prove the suggestion is false by secretly showing the accuser a clue card that proves the suspect, weapon, or room is not in the special solution envelope. Once a player is confident that they know the solution, they make an "accusation" to win the game.

The game of DNA likewise involved six main players, several false suggestions, a fair amount of sharing—and not sharing—of important clues, and some accusations. The cast of characters involved was every bit as quirky as the fictional Miss Scarlet, Professor Plum, and Mr. Green. They included:

Erwin Chargaff, erudite, intense, often critical of others, professor of biochemistry at Columbia University, College of Physicians and Surgeons, New York;

Linus Pauling, brilliant, outgoing, politically outspoken, and famous professor of chemistry at Caltech (Pasadena) who in 1951 deciphered the major structures formed by proteins;

Maurice Wilkins, a shy and reserved Englishman, who worked as a physicist on the Manhattan Project (the atomic bomb) in the United States, and turned to biology after the war. Wilkins was a member of the biophysics unit at King's College London;

Rosalind Franklin, confident, sometimes impatient with others, and an expert in using X-rays to decipher the structure of molecules. Franklin joined Wilkins' unit at King's College in 1951.

Each of these players would hold vital clues, and might have solved the mystery on their own, or had an even better chance of success by working together. But none of the four worked together. When Pauling and Chargaff first met, Pauling took an instant dislike to Chargaff and avoided him. Wilkins on the other hand did believe that he and Franklin were to work together, but intense personality conflicts drove them apart. The structure was ultimately deciphered by perhaps the unlikeliest detectives, two men with barely any credentials who had even been barred at one point from pursuing the case—Dr. Watson and Mr. Crick:

James Watson, brash, ambitious, who received his PhD in zoology at age 22 in 1950. He went to Europe seeking the training he would need to crack DNA;

Francis Crick, talkative, adept at theory and mathematics, who first studied physics then switched to biology after the war. He was still a graduate student (age 35) at the University of Cambridge in 1951.

One might think that there would be more than six people on the trail of something as important as the structure of DNA (Figure 5.1). But that importance is largely a matter of hindsight. No one could have known just how much the structure itself would reveal about the mechanisms of heredity. Moreover, even several years after Oswald Avery's discovery of the transforming principle (Chapter 4), there were still lingering reservations and uncertainty

FIGURE 5.1 The Players

Central Press/Getty Images, Express/Getty Images; Bettmann Archive/Getty Images; Donaldson Collection/Michael Ochs Archives/Getty Images; Horst Tappe/Getty Images; New York Public Library/Science Source.

about DNA being the chemical basis of heredity. Chargaff was convinced—indeed, he was so persuaded by Avery's studies that he shifted his laboratory from working on fat and proteins to working on DNA. But Pauling was not so sure. He thought that proteins with their great diversity of structures and functions should somehow be involved in heredity. Furthermore, most scientists who were keenly interested in genes and heredity did not have the training or expertise to tackle structural biochemistry.

Watson himself was in this latter group.

GETTING INTO THE GAME

No one was more convinced of the importance of DNA than Watson. He was certain that a Nobel Prize awaited whoever could crack the structure. But Watson knew little chemistry. He had avoided the subject as an undergraduate at the University of Chicago (1943–1947), where he was much more interested in birds and dreamed of someday becoming the curator of ornithology at the American Museum of Natural History in New York. He did learn, however, about Avery's work in a genetics class, and he was spurred to read the short book *What Is Life?* (1944) by Erwin Schrödinger.

The eminent physicist (Nobel Prize 1933) probed the question of the difference between nonliving matter and life and focused in particular on the mystery of heredity. Writing before Avery's discovery, Schrödinger inferred that the three-dimensional arrangement of atoms in some polymer had to explain the two main properties of heredity. Those properties were the stability of life, such that traits were passed faithfully from generation to generation; and the mutability of life, the ability of life to evolve over time. Such great powers begged a physical explanation.

Watson was driven to "finding out the secret of the gene." Rejected from graduate school at both Harvard and Caltech, Watson enrolled (at age 19) at

Indiana University where he did learn a lot of genetics, but again very little chemistry. After a solid but unremarkable PhD project, Watson's mentor suggested that the best place for him to get the training he wanted in the biochemistry of nucleic acids was in Europe, specifically in Denmark. Watson sailed for Copenhagen in September 1950.

The first and most important thing Watson learned in Copenhagen was that he was in the wrong place, or at least that he had arrived at the wrong time, to learn what he needed. His mentor, distracted by an impending divorce, left Watson to fend for himself. After several unproductive months, his advisor suggested that Watson accompany him that spring to the zoological station in Naples. He spent most of his time enjoying the sun, walking the streets, or reading articles.

Watson was not the only scientist seeking a little time in the sun. Maurice Wilkins also went to Naples that spring to attend a meeting on the structure of biomolecules, courtesy of his boss in London who could not make the trip himself. Watson sat in on the meeting, trying to make sense of the technical talks. He heard nothing revealing or inspiring, until Wilkins took the podium and talked about his and his student Raymond Gosling's efforts to make X-ray diffraction images of DNA.

In this technique, a narrow X-ray beam is focused on a molecular crystal or fiber that contains a regular array of atoms. The atoms diffract the X-ray in different directions depending on their identity and position within the molecule. Analysis of the resulting diffraction pattern on photographic film can reveal the detailed structure of the molecule. Wilkins had discovered that purified DNA could be drawn out into very thin threadlike fibers containing many molecules. Near the end of his talk, Wilkins showed a photograph of an X-ray diffraction pattern of one such fiber of DNA that seemed to contain a lot of detail.

Watson was thrilled. Before that moment, Watson had feared that DNA might be an irregular structure, very difficult or even impossible to decipher. The features in the picture suggested that DNA had a regular, repeating structure that could be solved. It had never occurred to him or his mentors that he needed to learn about X-ray crystallography. To get into the game, he had to get out of Copenhagen and go to where the action was.

Watson evaluated his options. He tried to approach Wilkins in Naples about coming to London, but Wilkins slipped away before Watson could put the question to him. Shortly after he returned to Copenhagen, a spectacular flurry of papers appeared on the structures of proteins by Linus Pauling. Caltech would certainly be one place to learn crystallography, but Watson doubted that Pauling would be willing to waste his time on someone with so little training. The other hub of structural work was in Cambridge, England. Watson's graduate advisor made the introductions and the eager crystallographer-to-be happily said goodbye to Denmark.

CAMBRIDGE

Watson joined the laboratory of Max Perutz, one of the leaders of the Cambridge group, where he met an assortment of researchers working on the structures of biomolecules, primarily proteins. Among them was Francis Crick, a 35-year-old graduate student. Crick's first attempt at a PhD—in physics—was derailed by the war when he was recruited into the Admiralty and spent seven years designing magnetic and acoustic mines. His abandoned PhD project became a direct casualty of the war when the building housing the apparatus he had constructed was destroyed by a direct hit from a parachute mine. It was a mercy killing. Crick thought his project—to determine the viscosity of water under different conditions—the "dullest problem imaginable."

After the war, Crick was also drawn toward biology by reading Schrödinger's little book. He was persuaded by the argument that just like nonliving matter, life must also operate by the laws of physics and chemistry. He hoped that his training in physics would give him some foundation for studying the molecules of life. Crick went to Cambridge in 1947 but had still not earned his PhD when he met the much younger Watson (aged 23) in October of 1951.

The two men hit it off right away. Both loved to talk, and talk they did—at the ritual tea and coffee breaks, at lunch in the nearby Eagle pub, whenever they were together, often several hours a day. In Crick, Watson found a partner who not only believed that DNA was more important than proteins, but also could tutor him in the interpretation of X-ray crystallographic data. In Watson, Crick had a partner who was up-to-date on the latest findings in genetics. Their animated conversations did not go unnoticed. Crick had a booming laugh and spoke faster and louder than anyone else around the laboratory or the building. The pair was soon assigned their own office.

Even though Crick's thesis work was on proteins, he and Watson quickly decided that they should tackle the structure of DNA together. They agreed that they could not solve it by staring at X-ray pictures alone. They were impressed by Pauling's approach to protein structure, which involved building Tinkertoy-like models and using the rules of chemistry to figure out which atoms sit next to each other. They decided they would take that approach as well. They also resolved to search for the simplest structure that was consistent with whatever data were available. They hoped that it might be some kind of helix, as Pauling had found in proteins. There was no sense in worrying about much more complicated structures until they ruled out simpler ones.

A few important details were known about the chemical formula of DNA. Just two years earlier, chemists at Cambridge had determined that the polymer was made up of a backbone consisting of alternating phosphate and sugar (deoxyribose) groups, to which the nitrogen-containing bases adenine, guanine, cytosine, and thymine were attached. The polymer was a long chain of smaller units known as nucleotides, consisting of a base attached to a sugar and phosphate group (Figure 5.2).

Watson and Crick assumed that the nucleotides occurred in an irregular order. If the order were always the same, then all DNA molecules would be identical and could not carry gene-specific or species-specific information. But despite that irregular order, DNA had to form some regular structure as indicated by X-ray pictures.

Among the many unknowns was the number of chains. Wilkins told Crick that the diameter of the DNA molecule was thicker than it would be if made of only one chain. There might be two, three, or even four chains. In any case, some sort of chemical bonds had to hold the chains together. It was unknown whether those might be ionic bonds involving the negatively charged phosphate groups, or weaker hydrogen bonds. Nor was it known whether the bases or sugar–phosphate backbones were inside or outside the chains.

There were a lot of possibilities. To narrow them down, the pair needed access to good X-ray pictures. Rather than try to make their own images, which could take many months, if they succeeded at all, they decided to reach out to Wilkins. There were potential priority and turf issues in asking to see Wilkins' data. Crick and Wilkins had been friends for several years, however, and Wilkins readily agreed to make the short train ride from London up to Cambridge to chat.

Wilkins shared his suspicion that DNA was made of three chains, but he did not share Watson and Crick's enthusiasm for building models. Wilkins thought that more and better pictures of DNA were needed. The trouble was, he confided to Watson and Crick, he and Rosalind Franklin, who had joined the unit early that year, were not getting along at all. The two scientists had opposite personalities. Wilkins was quiet, had the habit of looking away from people as he spoke, and shunned conflict. Franklin was direct, sometimes brusque, and she enjoyed the give-and-take of debate. After sizing up Wilkins,

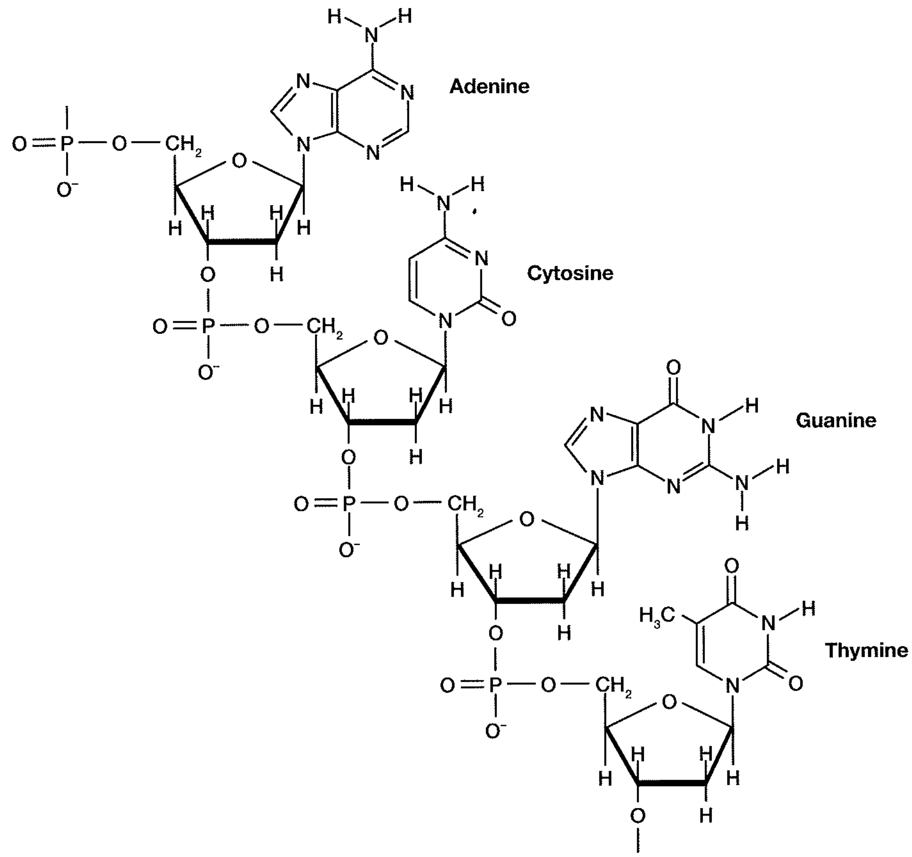

FIGURE 5.2 DNA Is Composed of Nucleotides The backbone is made up of alternating sugar (2-deoxyribose) and phosphate groups. Each sugar has attached to it a side group consisting of either a purine base (adenine or guanine) or a pyrimidine base (cytosine or thymine).

Franklin rejected the notion that she and Wilkins would work together, although Wilkins had given her all of his good crystalline DNA. Franklin had taken over supervision of Raymond Gosling, and told Wilkins to take no more X-ray pictures of DNA.

If Watson and Crick wanted fresh pictures, they would have to get them from Franklin. Wilkins told the duo that Franklin was scheduled to give a seminar on her work in a few weeks, and invited Watson to attend. Having been in Cambridge for only a few weeks, Watson needed to bone up on his crystallography so that Franklin's talk would not fly over his head.

The key clue Watson was looking for was whether DNA was in fact a helix. Franklin's X-ray photographs were sharper than Wilkins', but she did not offer a firm interpretation on that score. Later, as Franklin wrestled with interpretations of the so-called crystalline or A form of DNA, she had doubts. She did discuss how she had been working on two forms of DNA, what she called the "crystalline" form that was prepared similarly to Wilkins' samples, and a "wet" form that was prepared and analyzed under higher humidity. Franklin had performed careful measurements on the water content of each DNA form, but that was about all Watson took away. Franklin clearly believed that more X-ray crystallography was the key to the mystery, and did not mention any model building of the type Watson and Crick were planning.

The next day Crick grilled Watson for the details of the talk. As was his habit, Watson had not made any written notes. Crick was annoyed that he had not recorded the exact water content of the DNA, which would affect the placement of water molecules in any model. Nonetheless, Crick started scribbling on some scratch paper and said that only a few structures could be compatible with the water values Watson recalled. Crick was confident that they could come up with a model—perhaps as soon as in a week or so.

Day by day the two men worked through the issues. The first was where to place the sugar–phosphate chains; they decided that they should go in the interior of the molecule. That way, the different-sized bases would be facing out and would be easier to fit in the structure than if they were in the interior. Then they struggled with what held the chains together. Eventually, they came up with magnesium ions that could bridge phosphate groups between chains (although there were no data on what ions were present in the samples). But how many chains? They determined that three chains braided together best fit Wilkins and Franklin's X-ray measurements.

In just a matter of days, they had a model. Word spread through the building. The key test would be to see how it fit Franklin's data. Crick invited Wilkins up to Cambridge for a look. Wilkins agreed to come the next day, and told Crick that he would be bringing Franklin.

Crick opened the discussion, but as he spoke, Franklin soon grew impatient. She was not impressed by Crick's explanation and firmly disagreed that there was sufficient evidence that DNA was helical. Then, she quickly dismissed the magnesium ions in the model by pointing out that they would be surrounded by water molecules and could not form a tight structure. Worse, Watson had not remembered the correct water content. He was off by a factor of 24. Both he and Crick knew that if there were more water in the molecule, as Franklin said, the number of possible structures mushroomed.

Their breakthrough was a complete bust.

The consequences were more than just embarrassment. The Cambridge upstarts had trespassed onto King's College London's turf and flopped. The possibility of escalating tensions between the two government-supported research units did not seem worth the risk to Crick and Watson's superiors. The word came down from above that they were to abandon their work on DNA and leave it to the crystallographers in London.

Their quest was over almost as soon as it had started.

ON THE SIDELINES

There was no use in trying to appeal the ban. Crick's large personality grated on some in the research unit, and he had still not finished his PhD. It was wiser for him to keep his head down and get back to working on his thesis on the structure of hemoglobin. Watson, who had not even been two months in Cambridge before the triple-helix fiasco, needed to gain a more solid foundation in how to solve structures. He began work on the structure of a plant virus. For most of the next year (1952), the two largely stuck to other structures.

Franklin continued to work hard on the alternate forms of DNA and on getting better pictures. However, she found the tension at King's increasingly stressful and started looking for a new position elsewhere. She and Wilkins continued to avoid one another.

The London pair did not have DNA to themselves. Sooner or later, most believed, Pauling would turn his attention from his triumphal work on proteins to DNA. Watson and Crick learned that the great chemist was scheduled to come to a meeting in London in May 1952, and perhaps to visit the King's College crystallographers. The duo was eager to find out whether Pauling had in fact begun to tackle DNA. But at the last minute, Pauling did not show.

As his British hosts would learn, Pauling had his own problems—with the U.S. Department of State. Alarmed by the rapid spread of nuclear weapons, Pauling had used his eminence to become a vocal critic of the arms race between the United States and the Soviet Union. He urged for negotiations to curtail the power, spread, and testing of nuclear weapons. The U.S. government had become suspicious that Pauling was a communist sympathizer (he was not), and denied him a passport to attend the London meeting.

The action led to an international furor. Pauling had served the war effort admirably, even earning a commendation from President Truman. To deny him the opportunity to share his world-leading work with his peers was scandalous. It also meant that Pauling did not get a chance to visit with and hear the latest from Franklin, who had obtained some much better X-ray pictures.

Crick and Watson soon learned that another player in the game would be coming through Cambridge. Erwin Chargaff had published a series of papers on the composition of DNA. By working out methods for chemically separating and measuring the bases, Chargaff discovered that the ratio of the amounts of the four bases in DNA was not 1:1:1:1, as would be expected if DNA was a repeating sequence of four bases (ACGTACGT . . .) as had once been proposed. He had also determined that the base ratios were different in different species' DNA. Moreover, he had discovered that the ratio of the amount of adenine to thymine and the ratio of the amount of cytosine to guanine were about 1:1 each. Watson had read Chargaff's papers, Crick had not, by the time they sat down to lunch in one of Cambridge's dining halls.

The encounter did not go well. Chargaff was not impressed by what the pair had to say; rather, what did impress him was "their extreme ignorance." Chargaff realized that Crick was ignorant of what his chemical analyses had revealed.

"Well, of course, there is the 1:1 ratios," Chargaff said.

"What is that?" Crick replied.

"Well it is all published," Chargaff said, and went on to explain the ratios. In the course of the discussion, it became clear to him that Crick did not even know the chemical structures of the four different bases.

Chargaff later said, "I never met two men who knew so little—and aspired so much." The encounter reinforced Chargaff's opinion of "a typical British intellectual atmosphere, little work and lots of talk."

Chargaff offered no interpretation of the 1:1 ratios. Crick, however, was electrified. It immediately occurred to him that if there were some sort of complementary pairing of the bases in the structure, there would have to be 1 to 1 ratios among the bases. Soon afterward, Crick tried to figure out how the bases might pair by stacking the structures on top of one another. He could not figure it out and retreated back into his protein work.

While the pair were not working officially on DNA, the topic was never far from Crick and Watson's minds. In the summer, Crick ran into Rosalind Franklin at a meeting in Cambridge. In the line for tea, she told Crick that she was convinced that the form of DNA that Wilkins had photographed (the A form as it would be known) was not a helix. She thought it was perhaps an unwound version of the wet or B form, which she did believe was a helix, but had not spent much time analyzing. Crick was not convinced, and suggested to her that a pattern she was examining could be an experimental anomaly and should be dismissed. Franklin, however, continued to try to explain the result in terms of a rod, sheet, or even a figure eight of DNA.

Pauling finally received a passport and made it to Europe that summer, which gave Watson a chance to find out if he was, in fact, taking on DNA. Pauling gave no signs of interest in DNA, but Watson learned from Pauling's wife that their son Peter was coming to join their very own research unit in Cambridge. Peter was assigned a desk right between Watson and Crick. Both men enjoyed Peter's company, and hoped to be able to keep tabs on any developments out of Pauling's lab in California.

Just before Christmas, their hopes and fears were both realized. Peter received a letter from home in which his father mentioned that he had a structure for DNA. No further details were given, but Watson and Crick's hearts both sank. They shared the news with their bosses. Pauling had won the protein structure race, and now it seemed that the brilliant American had repeated the feat with DNA.

BACK IN THE GAME

The wait was agony. For several weeks there was no more news from California until one day at the end of January 1953, Peter walked in with a copy of his father's submitted manuscript. He announced that the structure was a triple helix with the sugar–phosphate backbone in the center. Watson was surprised, as it sounded very much like the structure they had built and abandoned a year earlier. Maybe they had it right after all? He snatched the manuscript from Peter's pocket and began reading.

Watson sensed right away something was not right. He studied the illustrations and realized that the phosphate groups were not ionized; they were bound to hydrogen atoms. This went against what Watson thought he knew about nucleic acids—in fact, with no net charge deoxyribonucleic acid would not be an acid at all. Pauling, the undisputed greatest chemist in the world, had blundered. Watson thought, "We are still in the game."

Crick shared the news with his bosses in the research unit, telling them that Pauling had it wrong, but would surely keep at it until it was right. Two days later, Watson went to London to tell Wilkins about Pauling's mistake.

Wilkins was occupied, so Watson went down the hallway to Franklin's lab. He tried to show her the manuscript and where Pauling had gone wrong. She objected right away to the mention of a helix, asserting that there was no evidence that DNA was a helix. Watson countered that a helix was the simplest structure, and that her dismissal of a helix was a mistake. Franklin was visibly aggravated, so Watson started to leave just as Wilkins appeared. Franklin turned away and closed the lab door behind her.

Wilkins confided to Watson that Franklin would soon leave King's College, and that she had begun to share her data in preparation for turning the work back over to Wilkins. Just days earlier, Franklin's student (and Wilkins' former student) Raymond Gosling had brought him one rather sharp X-ray image of an alternate form of DNA, the wet, B form. Gosling had obtained the image in May 1952 by wrapping the DNA fibers around a paper clip to keep them taut in front of the X-ray source. Watson asked what the images looked like, and Wilkins brought out a picture, numbered B51.

Watson's mouth fell open. The picture was simpler than images of the A form, with a sharp cross pattern in the center, a telltale sign of a helix (Figure 5.3). Over dinner, Watson tried to urge Wilkins back into the game by saying that Pauling would be back on the trail very soon. Wilkins was not persuaded—he wanted to wait until Franklin left. On the train ride home, Watson tried to sketch as much of the X-ray image as he could remember. He was determined to start making models again.

The next day, Watson ran into the heads of the Cambridge unit and told them about the picture and Wilkins' reluctance to get on with solving the structure. The answer seemed closer than ever, so he brought up the prospect of the British losing to Pauling again. This time, he did not get a restraining order—he was encouraged to get on with building models again.

THE DOUBLE HELIX

Watson told Crick what he had gathered from the photograph and from Wilkins about the B form of DNA—and that was a lot. The dark patches at the top and bottom of the photograph were produced by reflection of the X-rays off the bases. By knowing the distance and orientation of the DNA sample from the X-ray source and the film, the distance between the bases could be calculated to be 3.4 angstroms (1 Å = 1 ten-millionth of a millimeter). The spots that made up the cross pattern revealed that ten bases were stacked on top of one another in each turn of the helix. And from the

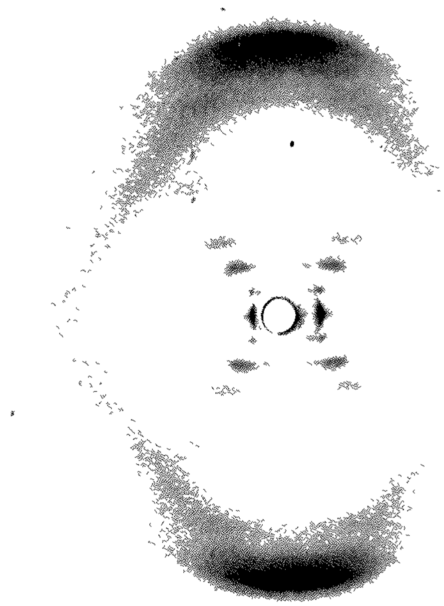

FIGURE 5.3 Photograph B51 Taken May 2, 1952, by Raymond Gosling of the B form of DNA, the X-ray diffraction pattern contains several key pieces of information. The closer the spots are, the greater is the actual distance between features. The pronounced crossing pattern of the spots is a diagnostic signature of a helical structure. The vertical distance from the center and the broad dark smears at the top and bottom corresponds to the 3.4-angstrom distance between stacked bases. The distance between horizontal rows of spots corresponds to the 34-angstrom distance between each turn of the helix. The two values together indicate that one turn consists of ten base pairs (34/3.4). King's College London Archives/Science Source.

diamond-shaped blank areas outside of the crossing pattern, it could be deduced that the phosphate backbone was on the outside of the helix.

The number of chains was not certain. That clue was found in a report in which Franklin had summarized her previous year's work for the British funding agency that supported it. The report was circulated among the research units, so Perutz (the head of the unit) received a copy. Crick and Watson asked to see it and Perutz shared it, since the report was not confidential. Crick quickly spotted a key data point whose significance had eluded Franklin: the structure had a 2-fold axis of symmetry, which meant that two chains ran in antiparallel, not parallel directions.

The overall structure was taking shape, but how the chains were held together and how the bases fit inside the helix were still not clear. One problem was that adenine and guanine were bulky, two-ringed molecules (purines) while cytosine and thymine were single rings (pyrimidines). Watson began exploring the placement of the bases. Studying the chemistry of each base in a textbook, he realized that the bases could form hydrogen bonds with themselves (in an end-to-end configuration, not by stacking as Crick had explored earlier). Adenine on one chain, for example, could form two hydrogen bonds with an adenine residue on the adjacent chain. Watson started imagining how two chains of DNA held together in this way would be identical (Figure 5.4A). As he worked alone into the middle of the night, his pulse began to race . . . Maybe one chain served as the template for the synthesis of the other? It was an appealing, even beautiful model. Watson finally fell asleep, happy.

His model was dead by lunchtime. When Watson explained his model to Jerry Donohue, another American in the Cambridge group, Donohue pointed out the chemical forms of the bases Watson had gleaned from the textbook were wrong and could not form the hydrogen bonds with themselves as Watson proposed. Crick further deflated Watson by pointing out that his scheme did not explain Chargaff's 1:1 ratios (adenine = thymine, cytosine = guanine). Watson had to go back to the drawing board—actually, to cardboard. Watson spent the afternoon making cardboard cutout models of each of the four bases.

The next morning, a Saturday, Watson was the first to arrive at the office. He cleared away a flat surface and began aligning the bases in various combinations. Suddenly he realized that an adenine–thymine pair held together by two hydrogen bonds had the same shape as a cytosine–guanine pair held together by at least two hydrogen bonds. He called over to Jerry Donohue to check his chemistry, and was ecstatic when Donohue had no objections.

Watson realized he had solved three problems at once. The base pairs would all fit nicely on top of one another without distorting the interior of the helix, the hydrogen bonds would hold the helix together, and the base pairs explained Chargaff's ratio. Moreover, the pairing rules suggested a way for copying DNA in that each chain was the complement of the other (Figure 5.4B).

When Crick arrived, he barely made it through the door when Watson told him they had the answer. The duo celebrated with lunch at the Eagle Pub, where Crick told everyone they had found "the secret of life."

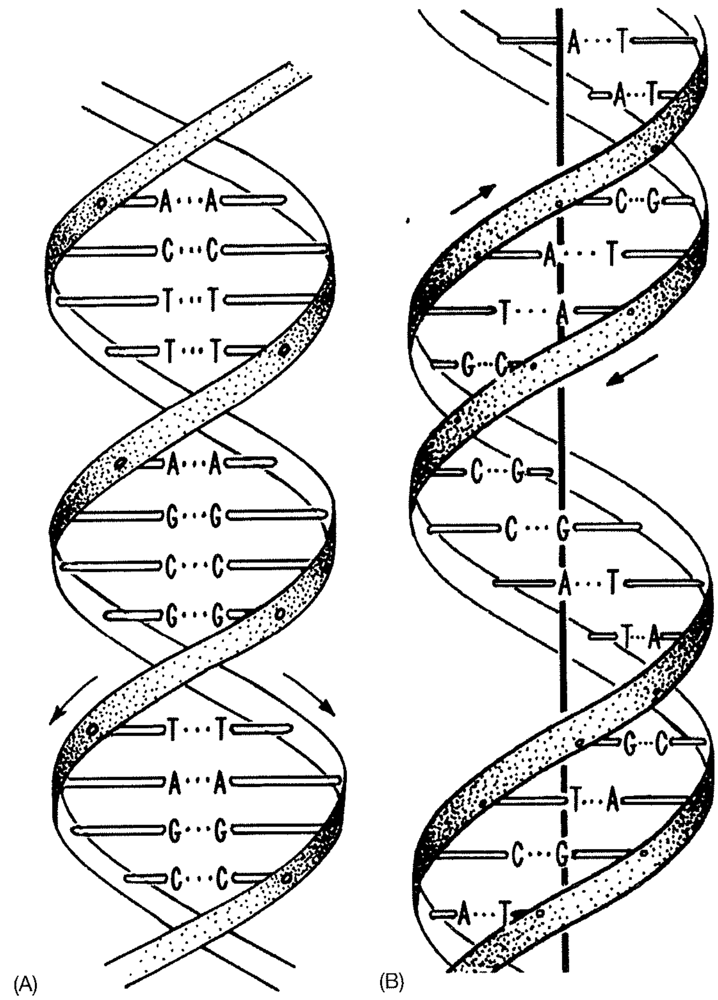

FIGURE 5.4 Two Models for Base-Pairing (A) Watson's first double helix model had a like-with-like base-pairing scheme. (B) Watson's second base-pairing scheme had adenine–thymine and cytosine–guanine base pairs that were the same size and fit Chargaff's ratios.

SHARING THE NEWS

Over the next two weeks, Watson and Crick assembled the physical double helix model of DNA. They invited Wilkins and Franklin to see it. Wilkins came first and liked it right away. He did not express a trace of resentment or regret that the Cambridge duo had solved the structure first.

Franklin came to Cambridge a couple of weeks later. Unbeknownst to Watson and Crick, while they were tinkering with models, Franklin had been making considerable progress in deciphering her X-ray pictures of the B form. She had concluded it was a helix with two chains and that the phosphate backbones were on the outside, but she had not deciphered the antiparallel arrangement or the base-pairing rules. Given the tenseness of previous encounters, Watson was apprehensive when Franklin took her first glimpse of their model. But to his amazement, Franklin instantly accepted the model. The tensions between Franklin, Watson, and Crick seemed to melt away as they discussed the details of the model and her crystallographic data.

Franklin later told Raymond Gosling, "We all stand on each other's shoulders."

Chargaff was not informed. Just after the breakthrough, one of the senior Cambridge scientists received a note from Chargaff asking what his "scientific clowns" were up to.

It was arranged for three papers to be published in the April 25, 1953, issue of *Nature,* the first by Watson and Crick, the second by Wilkins and his collaborators, and the third by Franklin and Gosling. In their article, barely longer than one page, Watson and Crick noted, "It has not escaped our notice that the specific pairing mechanism we have postulated immediately suggests a possible copying mechanism for the genetic material." Five weeks later, they followed with a second paper that specifically spelled out how the chains of the helix might be separated and serve as templates for duplication.

In 1962, Watson, Crick, and Wilkins were awarded the Nobel Prize in Physiology or Medicine for solving the structure of DNA. Tragically, Franklin, whose crystallographic work had made the solution possible, died four years earlier from cancer at age 37 and was ineligible to receive the prize.

END-OF-CHAPTER QUESTIONS

1. Which important clue or clues to the structure of DNA did each of the six main scientists obtain? Which key clues did each overlook or lack, and why?
   a. Erwin Chargaff
   b. Linus Pauling

c. Maurice Wilkins
d. Rosalind Franklin
e. James Watson
f. Francis Crick

2. Long before the structure of DNA was solved, the physicist Erwin Schrödinger suggested that the three-dimensional arrangement of atoms in some polymer had to explain the two main properties of heredity. Those properties were (i) the stability of life, such that traits were passed faithfully from generation to generation; and (ii) the mutability of life, such that traits could change.

   How did Watson and Crick's structure explain these two properties?

3. What problems existed with Watson's like-with-like base-pairing scheme?
4. Much has been written and said about the issue of credit concerning the discovery of the structure of DNA, particularly with respect to Rosalind Franklin. For each of the following accepted facts of the story, discuss the effect of each action on the solution of the structure of DNA, and whether the actions taken were appropriate or fair.
   a. Max Perutz shared Franklin's nonconfidential report to the British funding body with Watson and Crick (without Franklin's knowledge).
   b. Maurice Wilkins showed photograph B51, taken by Gosling and Franklin, to James Watson (without Franklin's knowledge or asking her permission).
   c. Watson and Crick's acknowledgments in their first report stated: "We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin, and their co-workers at King's College, London."
   d. The Nobel Committee awarded the 1962 Nobel Prize in Physiology or Medicine to Watson, Crick, and Wilkins "*for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material.*" Franklin, who died four years earlier, was ineligible under the rules of the prizes.