A Twist Of Fate

Two unknown scientists solved the secret of life in a few weeks of frenzied inspiration in 1953. Here's how they did it

By MICHAEL D. LEMONICK

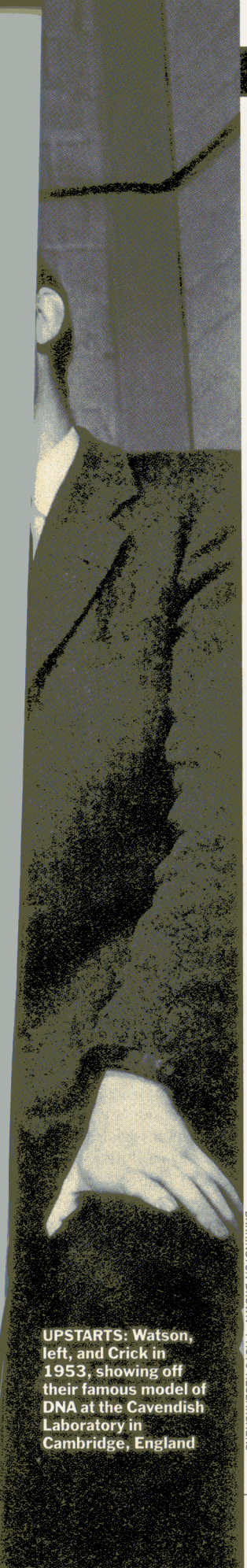
ON FEB. 28, 1953, FRANCIS CRICK walked into the Eagle pub in Cambridge, England, and announced that he and James Watson had "found the secret of life." At least that's what Watson remembers; Crick's memory is different. The exact words don't matter that much because the fact is, they had done it. Earlier that day, the two scientists had pieced together the correct solution to a problem that researchers around the world were racing to solve. They had built a model of deoxyribonucleic acid (DNA) that showed by its very structure how DNA could be everything they fiercely believed it to be: the carrier of the genetic code and thus the key molecule of heredity, developmental biology and evolution. Watson and Crick weren't necessarily the smartest scientists in the contest (though they were plenty smart). They weren't the most experienced; their track records in this area of science, in fact, were essentially nonexistent. They didn't have the best equipment. They didn't even know much biochemistry.

But despite these dismal odds, they made a discovery that in the half-century since has transformed science, medicine and much of modern life—though the full impact has yet to be felt. The tale of how this unlikely pair solved the most basic mystery of molecular biology is a reminder that brilliant minds and top-notch training aren't necessarily enough to penetrate the secrets of nature. You also need resilience, dogged persistence, plus a fair amount of luck—and as Watson inadvertently proved with the 1968 best seller *The Double Helix*, his controversial inside account of the discovery, a bit of arrogance doesn't hurt.

By the time Watson arrived in Cambridge in the fall of 1951, the brash and brilliant 23-year-old was obsessed with DNA. He had originally set out to become a naturalist (since childhood, he had had an interest in birds), but during his third year at the University of Chicago, Watson read a book titled *What Is Life?*, by Erwin Schrödinger, a founder of quantum physics. Stepping boldly outside his field of expertise, Schrödinger argued that one of life's essential features is the storage and transmission of information—that is, a genetic code that passes from parent to child. And because it had to be both complex and compact enough to fit inside a single cell, this code had to be written at the molecular level.

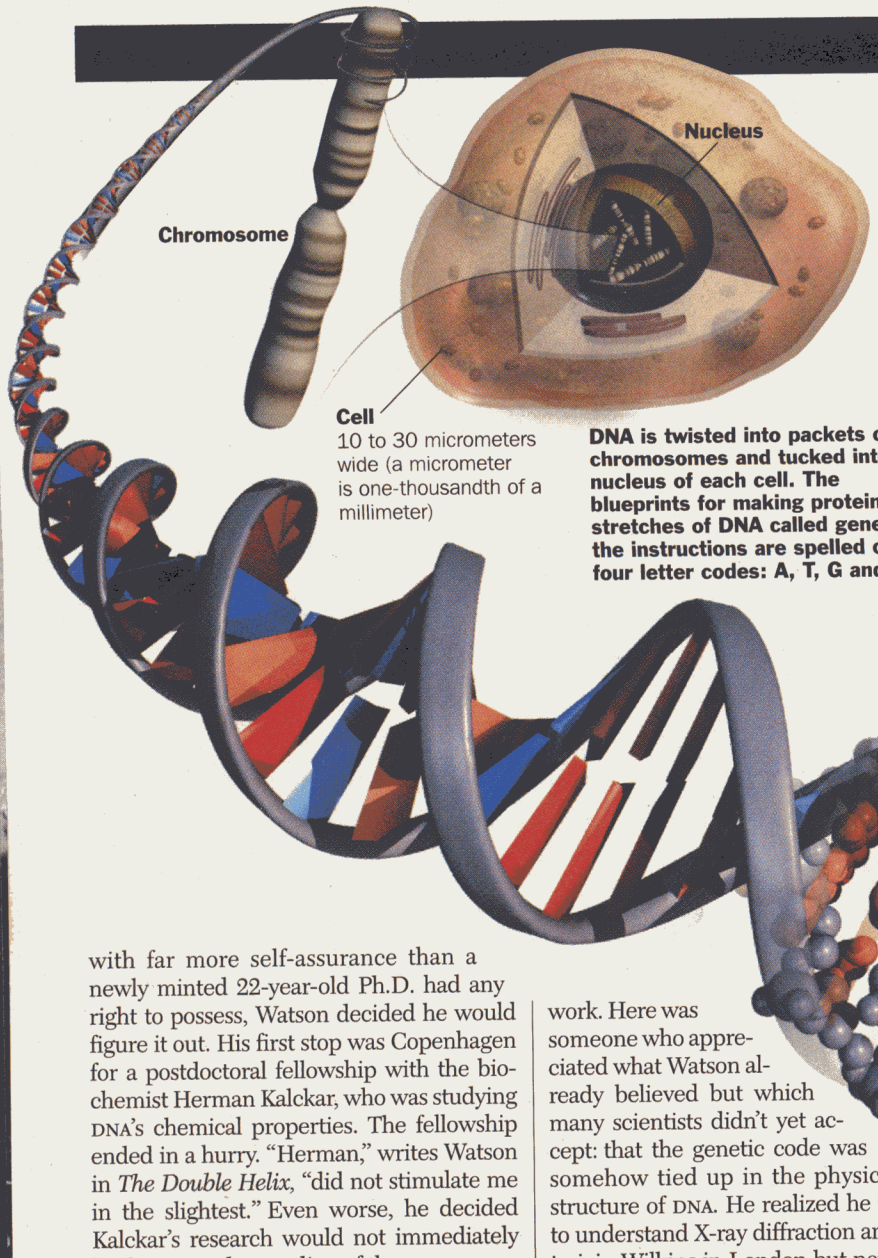
Impressed by these arguments, Watson switched from birds to genetics and went to Indiana University in 1947 to study viruses, the simplest form of life on the planet and thus the one in which the code might be especially easy to find. By then, scientists had strong evidence that Schrödinger's genetic code was carried by DNA, thanks to a series of brilliant experiments on pneumococcal bacteria, first by Fred Griffith of the British Health Ministry and later by Oswald Avery at the Rockefeller Institute (now Rockefeller University) in New York City.

But while biologists freely used the word gene to mean the "smallest unit of genetic information," they didn't have a clue what a gene actually is. And



UPSTARTS: Watson, left, and Crick in 1953, showing off their famous model of DNA at the Cavendish Laboratory in Cambridge, England

BARRINGTON BROWN—PHOTO RESEARCHERS



DNA is twisted into packets called chromosomes and tucked into the nucleus of each cell. The blueprints for making proteins are stretches of DNA called genes; the instructions are spelled out in four letter codes: A, T, G and C

HOW DNA WORKS

The beauty of DNA is that its form is its function. It's a self-reproducing molecule that carries the instructions for making living things from one generation to the next

with far more self-assurance than a newly minted 22-year-old Ph.D. had any right to possess, Watson decided he would figure it out. His first stop was Copenhagen for a postdoctoral fellowship with the biochemist Herman Kalckar, who was studying DNA's chemical properties. The fellowship ended in a hurry. "Herman," writes Watson in *The Double Helix*, "did not stimulate me in the slightest." Even worse, he decided Kalckar's research would not immediately lead to an understanding of the gene.

During a conference in Naples, Italy, in the spring of 1951, Watson happened to sit in on a lecture by Maurice Wilkins of King's College, London, who was using X-ray diffraction to try to understand the physical structure of the DNA molecule. When you shine X rays on any sort of crystal—and some biological molecules, including DNA, form crystals—the invisible rays bounce off atoms in the sample to create complex patterns on a piece of photographic film. In principle, you can look at the patterns and get important clues about the structure of the molecules that make up the crystal. In practice, the patterns in DNA are hellishly hard to disentangle.

But Watson was elated. Wilkins' image suggested that DNA had a regular crystalline structure. By figuring out what that structure is, moreover, one might be in a better position to understand how genes work. Here was someone who appreciated what Watson already believed but which many scientists didn't yet accept: that the genetic code was somehow tied up in the physical structure of DNA. He realized he needed to understand X-ray diffraction and wanted to join Wilkins in London but never got an opportunity to ask him. So Watson wangled the next best position—a fellowship at the Cavendish Laboratory in Cambridge, where the director, Sir William Lawrence Bragg, had (with his father Sir William) developed X-ray crystallography in 1912-14.

IT WAS THERE, IN THE FALL OF 1951, that Watson initially met Crick. (He actually met Crick's wife Odile first. Her only comment afterward: "He had no hair!"—a reference to Watson's crew cut.) Like Wilkins, Crick was a physicist who switched into biology; like Wilkins and Watson, Crick had been impressed with Schrödinger's *What Is Life?* He wasn't actually studying DNA, though; at age 35, thanks in part to a hiatus for military work in World War II, he was still pursuing his Ph.D. on the X-ray diffraction of hemoglobin, the iron-carrying protein in blood. Watson, meanwhile, had gone to Cambridge to use X-ray diffraction to understand the structure of another protein, myoglobin.

But whatever their formal duties, both men were determined to figure out what genes were, and both were convinced that understanding the structure of DNA would help them do that. "Now, with me around the lab always wanting to talk about genes," writes Watson in *The Double Helix*, "Francis no longer kept his thoughts about DNA in a back recess of his brain ... No one should mind if, by spending only a few hours a week thinking about DNA, he helped me solve a smashingly important problem."

The two men turned out to be utterly compatible. "Jim and I hit it off immediately," writes Crick in his book, *What Mad*

Pursuit, "partly because our interests were astonishingly similar and partly, I suspect, because a certain youthful arrogance, a ruthlessness and an impatience with sloppy thinking came naturally to both of us." (Crick had got in trouble more than once at the Cavendish for pointing out the sloppy thinking of his bosses.)

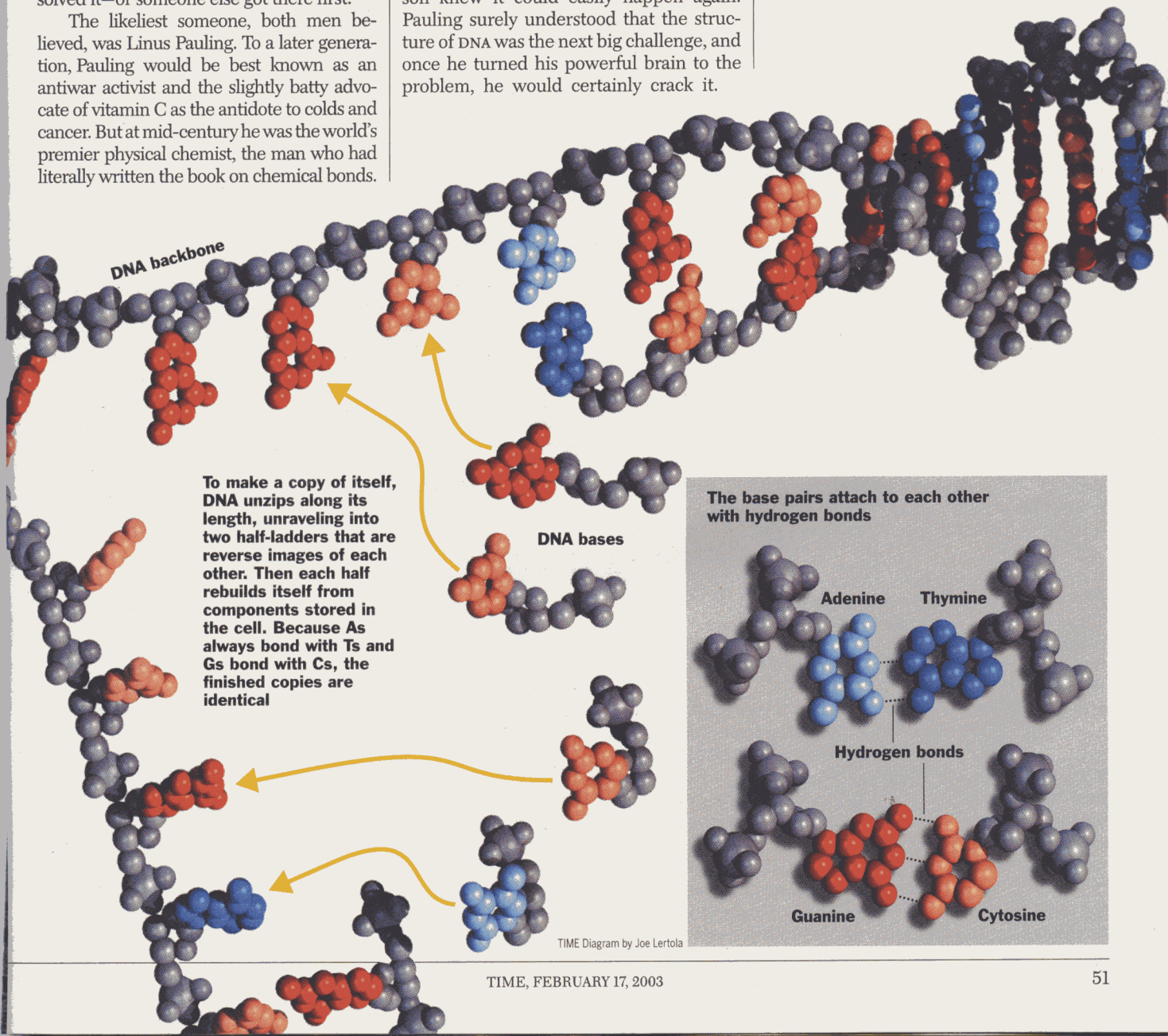
Both men also loved to think out loud, for hours at a stretch, during walks along the river Cam, at meals at the Cricks' flat, at the Eagle and, of course, in the lab, where their incessant chatter drove their colleagues crazy. (Watson and Crick were quickly relegated to a separate office, where they would disturb only each other.) Most important, both were as tenacious as pit bulls. Once they clamped their minds onto the problem of DNA structure, they couldn't let go until they solved it—or someone else got there first.

The likeliest someone, both men believed, was Linus Pauling. To a later generation, Pauling would be best known as an antiwar activist and the slightly batty advocate of vitamin C as the antidote to colds and cancer. But at mid-century he was the world's premier physical chemist, the man who had literally written the book on chemical bonds. A few months before Watson arrived, in fact, Pauling embarrassed the Cavendish by winning the race to figure out the structure of keratin, the protein that makes up hair and fingernails. (It was a long, complex corkscrew of atoms known as the alpha-helix.) While he did rely on X-ray crystallographs for hints to what was going on at the molecular level, Pauling depended more heavily on scaled-up models he built by hand, using his deep knowledge of the ways atoms can bond together. Cavendish scientists, relying mostly on X rays, hadn't bothered to consult their colleagues in the chemistry department about what was or wasn't possible for atoms to do, and became hopelessly sidetracked.

The defeat was humiliating—"the biggest mistake," Bragg would one day say, "of my scientific career"—and Crick and Watson knew it could easily happen again. Pauling surely understood that the structure of DNA was the next big challenge, and once he turned his powerful brain to the problem, he would certainly crack it.

"Within a few days of my arrival," writes Watson, "we knew what to do: imitate Linus Pauling and beat him at his own game." To do so, they would need X rays of DNA, but they would have to look outside Cambridge. The Cavendish's crystallographers were interested in proteins; DNA was the province of King's College, London; and while actively competing with Americans was fine, it just wouldn't do to poach—openly, at least—on fellow Brits.

Fortunately, Crick was on good terms with Wilkins, the man whose DNA images had originally sparked Watson's interest. Unfortunately, Wilkins was on very bad terms with his King's College colleague, the accomplished but prickly Rosalind Franklin. At 31, she was already one of the world's most talented crystallographers



TIME Diagram by Joe Lertola

INTERVIEW

"You Have To Be Obsessive"

SUZANNE DECHILLO—THE NEW YORK TIMES

James Watson, author of *The Double Helix*, talks with TIME's Michael Lemonick about his career as scientist, teacher and administrator

WHY DID YOU AND FRANCIS CRICK SOLVE THE STRUCTURE OF DNA BEFORE ANYONE ELSE? People say we didn't deserve to solve it, and it's true that we were lucky, but we did deserve it, for a number of reasons. First, we thought it was the most important problem around. Others didn't realize that. Second, most people thought it couldn't be solved by building models—they thought you needed to get the answer primarily from X-ray crystallography of DNA. Rosalind Franklin's made that mistake. But we said, "It worked for Linus Pauling when he solved the structure of the alpha helix, so why not for us?" Third, we had each other. It helps to have someone else to take over the thinking when you get frustrated. Fourth, we were willing to ask for help and talk to our competitors. Again, Rosalind was so intelligent that she rarely sought advice. If you're the brightest person in the room, you're in trouble.

Fifth, you have to be obsessive. Jeff Goldblum played me in a BBC movie, and he was really unpleasant. But people told me, "You *were* unpleasant." It goes along with obsession, I'm afraid. Finally, both Francis and I knew we would have careers even if we failed, so we weren't desperate. Hence we were willing to trust that an idea that was only 90% certain was worth taking a chance on.

WHAT RECEPTION DID YOUR DISCOVERY GET? Almost total silence. The number of references to the original papers was essentially zero until the 1960s. People waited for the explanation of how DNA duplicated itself and how its code was turned into proteins before they fully accepted our structure. They didn't understand that it was simply too good not to be true. That's one reason we didn't get the Nobel for nine years.

WAS THAT DISTRESSING? It was actually quite pleasant. We didn't have a lot of competition, and we could work on related ideas, like RNA, with a very small number of other researchers who knew how important it all was.

YOU NEVER DID GET THE STRUCTURE OF RNA. Right. But by the time I gave up, I was involved in training the wonderful graduate students I had at Harvard, where I'd joined the faculty in 1956.

PART OF WHAT ATTRACTED TOP STUDENTS WAS THE PROSPECT OF WORKING WITH YOU, RIGHT? Well, not me, necessarily. We had a very strong department by then. I admit that I'd learned the practice from Sal Luria, my own adviser, of not putting my name on my student's papers. That means the students feel they're working for themselves, not for someone else. That might have influenced some of them.

YOU ALSO BECAME DIRECTOR OF THE COLD SPRING HARBOR LABORATORY IN 1968. Yes. The lab was in financial trouble, and they couldn't get anyone else to run it. I wanted to keep it alive, because this is such an important meeting place for biologists. I've been coming here for workshops and conferences since I was 20. One thing we did was to focus on the problem of understanding cancer; not only is it important, but cancer money is easier to get than other money. More recently, we've refocused on stopping cancer, since we understand so much about it by now.

WHAT'S YOUR SECOND GREATEST ACCOMPLISHMENT? Writing *The Double Helix*. I think the book will last. No one else could have written it. Well, Francis could have written the story, but he has a different personality. He's interested in the result; I'm more interested in how the result came about.

ANYTHING ELSE YOU'RE PROUD OF? I'm very proud of being the first director of the Human Genome Project. It's just bound to give explanations for all sorts of phenomena. As a child, I always wanted explanations. Why does something happen—not what happens, but why? I really never would have guessed when we started how quickly it would go and how profound some of the implications would be. It's almost a cliché to say it, but it's true nevertheless that understanding the genome will completely change medicine.

ARE THERE ANY GREAT FRONTIERS LEFT IN BIOLOGY? Absolutely. We've hardly skimmed off all the good stuff, so I don't feel a bit sorry for kids who are being born today. The way to do great science is to stay away from subjects that are overpopulated, and go to the frontiers. We have more frontiers now than when I was getting started. How the mind works, for example, is still a mystery. We understand the hardware, but we don't have a clue about the operating system. There are enough questions to keep people occupied for the next hundred years. ■

and had recently returned to her home country to take a position at King's after a stint at a prestigious Paris lab.

Franklin believed deeply in the primacy of experimental data: Pauling might have been lucky with his flashy model building, but the best way to understand DNA, she insisted, was to make high-quality X-ray images first and speculate afterward about what they meant. "Only a genius of [Pauling's] stature," writes Watson, summarizing Franklin's attitude, "could play like a ten-year-old boy and still get the right answer." Wilkins made the mistake of declaring publicly that Franklin's images suggested that DNA had a helical shape. Franklin was incensed. He had no right, she believed, to even be working on X-raying DNA, something she was led to believe was her exclusive domain at King's College.

They remained collaborators in name but essentially stopped talking. To find out what she was doing, Wilkins had to go to a seminar Franklin gave in November 1951. He invited Watson to come along. (Crick, whose interest in DNA was well known, thought it might cause too much of a flap if he showed up.) Wilkins had warned Watson that Franklin was difficult; for his part, Watson had a generally piggish attitude toward women at the time. He liked "popsies"—young, pretty things without brains—but strong, independent women rather baffled him. In *The Double Helix*, he puts Franklin down in a passage that he later had the decency to renounce:

"By choice she did not emphasize her feminine qualities. Though her features were strong, she was not unattractive and might have been quite stunning had she taken even a mild interest in clothes. This she did not. There was never lipstick to contrast with her straight black hair, while at the age of 31 her dresses showed all the imagination of English bluestocking adolescents."

Then came the professional assessment: "Clearly Rosy [a nickname she abhorred, and which her adolescent-minded antagonists therefore insisted on using] had to go or be put in her place. The former was obviously preferable because, given her belligerent moods, it would be very difficult for [Wilkins] to maintain a dominant position that would allow him to think unhindered about DNA."

FOR THE MOMENT, THOUGH, THE men were stuck with "Rosy's" data, and Watson briefed Crick as soon as possible on what he had seen and heard. But Watson, overconfident to the point of arrogance, hadn't bothered to take notes. "If a subject interested me," he would write, "I could usually recollect what I needed. This time, however, we were in trouble, because I did not know enough of the crystallographic jargon." A key point was the amount of water present in Franklin's DNA samples. Watson remembered the number incorrectly, by a lot.

Armed with this crucially wrong information, the two began working in earnest. Conventional biochemistry had long since told scientists what DNA was made of: four types of organic molecules, known as bases—adenine, cytosine, thymine, guanine, or A, C, T and G—almost certainly strung somehow along a "backbone" of sugar and phosphate. The question was, How? "Perhaps a week of solid fiddling with the molecular models would be necessary," writes Watson, "to make us absolutely sure we had the right answer. Then it would be obvious to the world that Pauling was not the only one capable of true insight into how biological molecules were constructed."

A few weeks later, Crick and Watson were pretty sure they had it. DNA was a triple helix. They invited Wilkins to take a look at their model, and to their surprise, Franklin came along too. It didn't take long for everyone to realize that Watson's memory had betrayed him. The amount of water a DNA molecule had to contain was a whopping 10 times the quantity he had assumed. The structure Crick and Watson had so confidently come up with was impossible.

Their mistake had two immediate effects. First, Bragg, already fed up with Crick's impertinence, forbade the pair to work actively on DNA. Second, Franklin, previously suspicious of Crick and even more so of Watson, was convinced that the latter, at least, was a blithering idiot. Chagrined, Watson and Crick turned over their model-making kits to the King's group and urged Wilkins and

THE CHAIN OF EVENTS

It was a race to the finish—and the start of a new era of discovery

1951

MAY Watson attends Maurice Wilkins' lecture on X-ray crystallography of DNA

APRIL **Linus Pauling** deciphers the molecular structure of the protein keratin

OCT. Watson arrives at the Cavendish Laboratory in Cambridge, where he meets Francis Crick

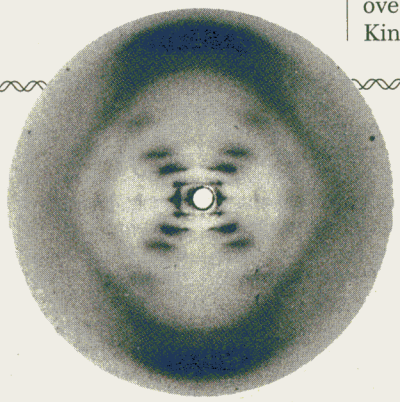
NOV. Watson and Wilkins attend a seminar by Rosalind Franklin. Watson fails to remembers correctly key data about the water content of DNA

NOV. Watson and Crick build a model of DNA as a triple helix. Franklin immediately spots their major blunder

DEC. Watson and Crick are told to back off the DNA project. They send the molds for their models to Wilkins and Franklin in London

1952

MAY The State Department prevents Pauling from leaving the U.S. because of his political views



NORMAN ARCHIVE FOR THE HISTORY OF MOLECULAR BIOLOGY

MAY Franklin takes her famous **X-ray image** of DNA in its B form

MAY Franklin and Wilkins have a formal falling out. The lab's director assigns Wilkins to work with the B form of DNA and Franklin to concentrate on the A form

1953

JAN. 28 Watson and Crick learn that Pauling has concluded that DNA is a three-stranded molecule

JAN. 30 Watson goes to London to tell Wilkins and Franklin about Pauling's mistake. Wilkins shows Watson Franklin's best image of the B form, which strongly suggests a double helix

FEB. 8 Watson and Crick learn of a report on DNA studies at King's College that convinces them the molecule has two chains

FEB. 19 Watson tinkers with a "pretty" model, unsure of the placement of the backbone or which bases pair with which. That week Watson learns he has been using the wrong chemical form of one of the key bases

FEB. 28 In a eureka moment, Watson realizes the base pairs don't match like with like—A-A or G-G—rather they pair A-T and G-C. Crick concurs, and their model falls into place

APR. 25 Watson and Crick report their discovery in a letter to the journal *Nature*

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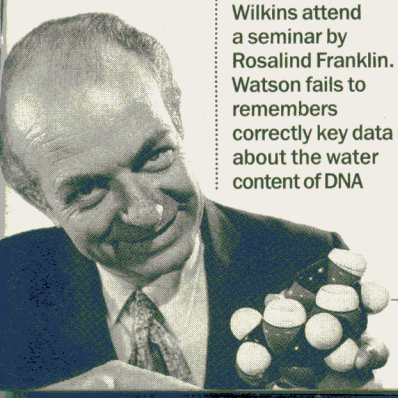
RALPH MORSE—TIMEPIX



Franklin to use them. Watson and Crick may have been ambitious for themselves, but they were passionate about knowing the structure of DNA. If they couldn't make the discovery, they would have to acquiesce to Wilkins' and Franklin's doing it. But the Cavendish botch job had cemented Wilkins' and Franklin's view that building models was not the way to solve the structure of DNA. They never used the kits.

Watson turned grudgingly to work on the structure of the tobacco mosaic virus, and Crick went back to hemoglobin. But no mere lab director could keep them from talking about DNA between themselves. And while their blunder the first time around had been dispiriting, it didn't discourage them. After all, they had no reputations to be tarnished. And if they had come to the wrong conclusions based on incomplete information and a dumb mistake, that was just an incentive to get better information and be more careful next time.

Besides, they couldn't give up, because Pauling was now on the case for sure. He had written to Wilkins, then to Wilkins' boss, J.T. Randall, asking for copies of King's X-ray images. Both men declined. But Pauling was coming to a Royal Society meeting in May 1952; it would be tougher to refuse him in person. As Pauling was preparing to board a plane in New York, however, the U.S. government seized his passport, citing what they considered his dangerous left-wing political views. While that setback might delay Pauling, Watson and Crick knew it would not stop him.

THE KING'S COLLEGE GROUP, meanwhile, pushed ahead with its DNA research. Franklin kept working to perfect her X-ray images. In May 1952 she took one that would prove crucially important—though until the day she died, she would never realize it. By increasing the humidity in her lab apparatus, she and graduate student Raymond Gosling discovered that DNA could assume two forms. When sufficiently moist, the molecule would stretch and get thinner, and the pictures that resulted were much sharper than anything anyone had ever seen. They called the wetter version the B form of DNA.

Wilkins was intrigued; the pictures convinced him more firmly than ever that the DNA molecule was helical, and he proposed to collaborate with Franklin in exploring the B form in detail. But Franklin, who still thought there was no evidence of a helix in her pictures, went into a rage, according to Wilkins. "She exploded," writes Brenda Maddox in her sympathetic 2002 biography *Rosalind Franklin: The Dark Lady of DNA*. "Rosalind had good reason ... Undervalued at King's, she had just achieved extraordinary results by working in virtual isolation. Now what she saw as a less able colleague of higher rank was proposing to elbow in and spoil the clarity of her investigation." Alarmed by what had become a very public quarrel, lab director Randall declared that from now on Wilkins would work with the B form of DNA and Franklin would have exclusive rights to the A form. Unwittingly and indirectly, he had just handed Watson and Crick a crucial piece of information.

Through the summer and fall of 1952, Watson and Crick kept talking, trying to fit together the still unconnected pieces of the DNA puzzle. One piece was a discovery that had been made years earlier by the Austrian refugee Erwin Chargaff. Analyzing the DNA of many different organisms, he found that while the overall proportions of the four DNA bases varied among species, the number of adenine molecules always equaled the number of thymine, and guanine and cytosine were similarly matched. (Chargaff visited Cambridge during this period and was appalled at how little basic chemistry Watson and Crick knew—and offended by how little this seemed to bother them.)

But progress on the greater problem was slow. "On a few walks our enthusiasm would build up to the point that we fiddled with the models when we got back to our office," writes Watson. "But almost immediately Francis saw that the reasoning which had momentarily given us hope led nowhere ... Several times I carried on alone for a half hour or so, but without Francis' reassuring chatter my inability to think in three dimensions became all too apparent."

In December 1952, they got some bad news. In a letter to his son Peter, then a graduate student at Cam-

PROFESSOR OSCAR L. MILLER/SPL—PHOTO RESEARCHERS

THE CHAIN OF EVENTS

1953
George Gamow suggests that DNA holds the code for making proteins

1959
The first human chromosome abnormality, Down syndrome, is identified

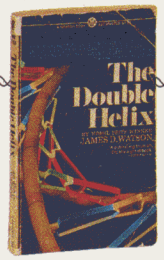
1960
Messenger RNA, the link between DNA and the protein-making factories of cells, is discovered

1961
Marshall Nirenberg identifies the first of 64 three-letter genetic codes for proteins

1962
Crick, Watson and Maurice Wilkins win **Nobel Prize**

1967
Allan Wilson and Vincent Sarich, using the tools of molecular biology, estimate that humans and great apes diverged about 5 million years ago, not 25 million, as many anthropologists believed

1968
Watson's ***The Double Helix*** is published and becomes a best seller



1969
A Harvard Medical School team isolates the first gene, a segment of bacterial DNA that plays a role in sugar metabolism

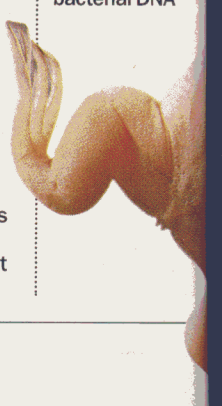
1970
University of Wisconsin researchers synthesize a gene from scratch

1972
Paul Berg and colleagues cut and splice genes from viruses to create the first molecules of recombinant DNA

Bruce Ames discovers that cancer-causing chemicals also cause mutations in DNA, the basis of the Ames test for carcinogens

Peter Vogt and Peter Duesberg identify the first cancer-causing gene, in a virus

1973
In the first successful genetic engineering experiment, Stanley Cohen and Herbert Boyer insert a gene from an **African clawed toad** into bacterial DNA

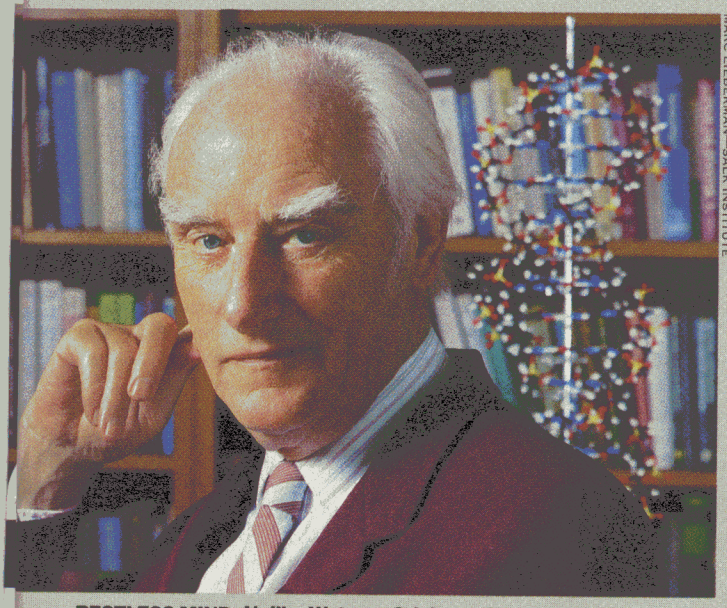


FRANCIS CRICK

Beyond the Double Helix

I have never seen Francis Crick in a modest mood." James Watson's mischievous opening line of *The Double Helix* raised many eyebrows at the time, but even Crick wouldn't quarrel with it now. Still brash and outspoken at 86, even without the booming laugh that once echoed through Cambridge's Cavendish lab, Crick has no reason for modesty. In the years since their discovery of the double helix, Crick, unlike Watson, has continued to do significant research, mostly by pondering big—and often controversial—theoretical questions rather than by toiling in the lab. Says his longtime colleague and fellow Nobel laureate Sydney Brenner: "He's the only molecular biologist I know who has managed to make a living as a theoretician."

Ranging widely over the biological landscape, Crick helped explain how genes build proteins.



MARC LIEBERMAN—SALK INSTITUTE

RESTLESS MIND: Unlike Watson, Crick continued to do significant research, exploring proteins, consciousness and the origins of life

With a colleague, Leslie Orgel, he speculated on the origins of life, concluding that it began not on Earth but elsewhere in the universe. And for the past two decades, Crick has been pursuing that most baffling of topics, consciousness, an interest he jokingly says some regard "as a sign of approaching senility."

The scientifically inclined son of middle-class parents from Britain's Midlands—his father was a shoe manufacturer—Crick started out studying physics and during World War II worked on radar and magnetic mines. But like Watson, he switched fields after reading Erwin Schrödinger's *What Is Life?* After their triumph in 1953, Crick went on to study the larger issue of how the millions of base pairs along DNA's twisted strands convey the message of the genes.

Together with Brenner and others, Crick provided an initial solution: DNA's sequence of four bases, taken three at a time, direct the formation of 20 amino acids; then, guided by DNA's single-chain cousins, messenger and transfer RNA (whose existence Crick predicted), these molecules link up to form more complex proteins. In the process, Crick asserted, genetic information always flows one way, from DNA to RNA to protein, an idea he called molecular biology's "central dogma."

In 1966 Crick, always restless, decided there were greater opportunities in embryology, the study of how a single fertilized egg develops into an adult organism. A decade later, he made another major change by moving to the Salk Institution in La Jolla, Calif., to explore the brain. He began by looking at dreams and soon shocked Freudians by concluding that dreams were simply the brain's nightly housecleaning to make room for new memories.

Crick's ideas on the origins of life are no less provocative. Concluding that conditions on the young Earth were far from favorable for the spontaneous generation of lifelike organisms, and trying to explain why the genetic code is the same in all earthly creatures, he and Orgel revived a theory known as panspermia ("seeds everywhere"). In their version, called directed panspermia, a distant civilization arising long ago on a planet where conditions were benign, sent unmanned rocket ships to seed the primitive earth's oceans with sporelike organisms that multiplied and evolved.

Still scattering ideas like so many nucleotides, Crick has just co-authored an article in *Nature Neuroscience* outlining a broad program for probing consciousness by concentrating on visual perception. Says neuroscientist Nikos Logothetis: "Even in old age, he is one of the most brilliant minds I've ever met." Also one of the most stubborn. Though he was flooded with invitations to join in celebrations of his and Watson's historic discovery, Crick has rejected them all. He's too busy, he grumps, to take part in "circuses." —*By Frederic Golden*

PHOTO RESEARCHERS

1975

Scientists meet at the Asilomar conference center in California and call for guidelines regulating recombinant-DNA research

1976

Boyer and Robert Swanson found Genentech, the world's first genetic-engineering company

1977

Walter Gilbert and Frederick Sanger separately develop methods for sequencing DNA

1978

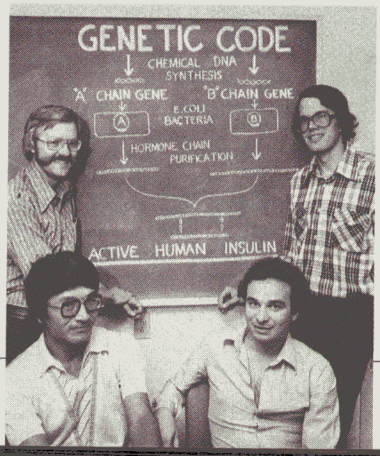
Genentech scientists help clone the gene for human insulin

1980

Martin Cline and co-workers create a transgenic mouse by transferring functional genes from one animal into another

1982

The U.S. Food and Drug Administration approves the first genetically engineered drug, a form of insulin produced by bacteria



JAMES W. COLLISON

- Stanley Prusiner discovers prions, the infectious proteins responsible for scrapie and mad-cow disease
- Thomas Cech, and later Sidney Altman, show that RNA can act as an enzyme

1983

Kary Mullis devises the polymerase chain reaction (PCR), enabling scientists to multiply rapidly snippets of DNA

TERRY WHY—PHOTOTAKE

1984

Alec Jeffreys and colleagues develop **genetic fingerprinting**—using DNA to positively identify individuals

- Elizabeth Blackburn and Carol Greider discover telomerase, an enzyme that extends the life of cells

Continued

bridge, Pauling revealed that he would soon publish a paper on the structure of DNA. It looked as if Watson and Crick had lost the race. Peter received his father's paper on Jan. 28 and walked into Watson and Crick's office to tell them about it. "Giving Francis no chance to ask for the manuscript," writes Watson, "I pulled it out of Peter's outside coat pocket and began reading." The senior Pauling had come up with a three-stranded molecule with the sugar-phosphate backbone at the center. Almost immediately, Watson realized it didn't make sense. "I could not pinpoint the mistake, however, until I looked at the illustrations for several minutes. Then I realized that the phosphate groups in Linus' model were not ionized ... Pauling's nucleic acid in a sense was not an acid at all."

But of course DNA *was* an acid. Pauling, the world's greatest chemist, had made a mistake in basic chemistry—an unimaginable blooper. Watson and Crick retired to the Eagle to drink a toast to Pauling's failure. They were more nervous than ever, though. The paper was scheduled to be published in March; once it was out, someone would notice the error, and Pauling would work that much harder to vindicate himself. They had at most six weeks to figure out DNA.

Watson also knew he had to warn Wilkins and Franklin about Pauling's near miss. On Friday, Jan. 30, he went to London. Wilkins wasn't in his lab, so Watson dropped in on Franklin. What happened next—from Watson's point of view, at least—was recorded in great detail in *The Double Helix*. The passage shows how formidable Franklin could be but also demonstrates Watson's adolescent

ROSALIND FRANKLIN

Mystery Woman: The Dark Lady of DNA

Who was Rosalind Franklin? The story of her life is short, tragically so, but it doesn't lack for tellers. Was she difficult Rosy, the Cruella De Vil of *The Double Helix*, who nearly knocked Watson's block off? Was she Dr. R.E. Franklin, the humble supporting player whom Watson and Crick thanked in the second-to-last sentence of their famous article in *Nature*? Or was she Franklin the feminist icon, the tormented genius who was cheated out of biochemistry's ultimate prize?

This much we know: Franklin was brilliant, beautiful, wealthy and tough to get along with. Born in 1920 into a prominent Jewish family in London, she graduated from Cambridge in 1941, then went on to do groundbreaking work on the molecular structure of coal, first in England and later in France, a country she vastly preferred to her homeland. She earned a reputation for meticulous lab work and a brusque manner. Words like difficult, bossy and impatient crop up frequently in the recollections of those who knew her. Prickly is a particular favorite.

Her impatience extended into the laboratory. Safety standards were lower in those days, and, in her eagerness to get results, Franklin often didn't bother with protective gear, even when working with radiation. Bold as she was in her work, however, Franklin was curiously standoffish with regard to the opposite sex. According to her biographer, Brenda Maddox, Franklin was still ignorant of the facts of life as late as her third year in college—this from a student of biochemistry.

In 1951 Franklin returned from Paris to study nucleic acids at King's College in London, where she produced the clearest X-ray images of crystallized DNA that anyone had ever obtained. She discovered and photographed the hydrated B form of DNA, and she established, crucially, that DNA's structure depended on an external backbone, with the bases on the inside. But here the stories diverge. According to *The Double Helix*, Franklin was unable to interpret her images properly and was unwilling to share them with others, to a point where Watson and Crick were forced to go around her to get at her data. According to Maddox, however, Franklin was perfectly capable of interpreting the X-ray images, although she was slow to come around to the helical model of DNA's drier, more crystalline A form, in which the structure is harder to see. Be that as it may, Maddox argues, Watson and Crick appropriated Franklin's work without her permission and without proper acknowledgment. And Maddox goes further: she argues that Franklin was close to seeing the whole picture herself. "It is clear," Maddox writes, "that she would have got there by herself before long."

She might have—but she didn't. Franklin was the intellectual equal of Watson and Crick, but she lacked the advantage of a sympathetic collaborator, and she simply wasn't the prizewinning type. She was a bloodhound, cautious and implacable, whereas Crick and Watson were greyhounds who lived for the sprint. When they made their triumphant announcement, Franklin was gracious in defeat, accepting her peripheral role with an equanimity that surprised her colleagues. When she encountered Watson and Crick later in life, they met as friends. She probably never knew what a central

GERRY GROPP—SIPA

1985

Robert Gallo and Luc Montagnier each publish the genetic sequence of HIV, the virus that causes AIDS

1986

Leroy Hood invents the first automatic DNA sequencer

■ The FDA approves the first genetically engineered vaccine for humans for hepatitis B

1987

Allan Wilson, Rebecca Cann and Mark Stoneking determine that all living humans share a common ancestor: "mitochondrial Eve"

1988

Harvard University acquires the first patent for a genetically altered animal: a mouse that is highly susceptible to breast cancer

1989

The first genetic screening test (to determine sex) is performed on embryos before they are implanted in the uterus

1990

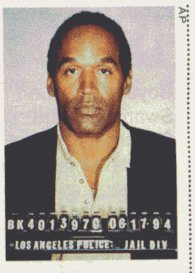
The Human Genome Project, an international effort to map and sequence human DNA, is officially launched

1993

Researchers at George Washington University clone the first human embryos, and nuture them in vitro for several days

1994

The FDA allows the first genetically modified food product to market, the **Flavr Savr tomato.** A bland taste and high price make it a commercial dud



AP

1995

PCR and DNA fingerprinting play a starring role in the **O.J. Simpson** murder trial

■ Craig Venter and colleagues are first to decode the genome of a free-living organism, the bacterium *Haemophilus influenzae*

■ DNA microarrays are invented, permitting rapid analysis of large quantities of DNA

■ Mutations in the BRCA1 and BRCA2 genes are linked to hereditary breast, ovarian and prostate cancers

1997

Ian Wilmut and others report they have cloned a sheep, **Dolly**

ALONE: Franklin vacationing in France, two years before Watson and Crick's triumph

VITTORIO LUZZATI—NATIONAL PORTRAIT GALLERY, LONDON

part her X rays had played in their discovery.

Ironically, Franklin thought of her stint at King's as the low point of her career. By the time the news about DNA broke, she had moved on to a lab at the University of London, where she studied the structure of viruses. There she finally met the Crick to her Watson, the crystallographer Aaron Klug, with whom she did the best work of her career. In 1955 Don Caspar, a young researcher from the California Institute of Technology, visited the lab, and they became close. At 35, Franklin had still never had a fulfilling romantic relationship with a man, and Caspar might well have become her first—but fate intervened. In the summer of 1956, Franklin felt a stabbing pain in her abdomen. It was ovarian cancer, which was well advanced. It was almost certainly the price she paid for having worked so closely with X-ray radiation earlier in her career. She died on April 16, 1958. She was 37.

Franklin's life was short, but its epilogue has been long. Watson, Crick and Maurice Wilkins were awarded the Nobel Prize for Medicine in 1962. (Nobels are awarded only to living scientists, and Franklin died too early to share the glory.) In an uncharacteristically heartfelt afterword to *The Double Helix,* Watson admits that his "initial impressions of her, both scientific and personal ... were often wrong." She has been the subject of two biographies, a BBC movie and numerous articles, all aimed at giving her the credit she was denied during her lifetime. In 2000, King's College christened its new life-sciences building the Franklin-Wilkins building. But in life Franklin never felt a need to be defended. Prickly she may have been, even brusque and difficult, but she was never troubled by bitterness over what might have been. Who was Rosalind Franklin? The snippy, standoffish, supporting player? The brilliant, wronged woman? Or somebody else entirely? There are deeper mysteries in life than DNA, and some of them may never be solved.

—By Lev Grossman

delight in needling her. He tried to engage Franklin in debate about the idea that DNA was helical, which she still insisted was unsupported by evidence. "Rosy by then was hardly able to control her temper," he writes, "and her voice rose as she told me that the stupidity of my remarks would be obvious if I would stop blubbering and look at her X-ray evidence.

"I decided to risk a full explosion," he continues. "Without further hesitation I implied that she was incompetent in interpreting X-ray pictures. If only she would learn some theory, she would understand how her supposed antihelical features arose from the minor distortions needed to pack regular helices into a crystalline lattice." The explosion occurred. "Suddenly, Rosy came from behind the lab bench that separated us and began moving toward me. Fearing that in her hot anger she might strike me, I grabbed up the Pauling manuscript and hastily retreated toward the open door. My escape was blocked by Maurice [Wilkins], who, searching for me, had just then stuck his head through." Franklin shut the door on both men. "Walking down the passage," Watson continues, "I told Maurice how his unexpected appearance might have prevented Rosy from assaulting me. Slowly he assured me that this very well might have happened. Some months earlier she had made a similar lunge toward him."

United in their belief that Rosy was impossible—there's no evidence that either

THE CHAIN OF EVENTS

1998

Two teams grow embryonic stem cells in a Petri dish

1999

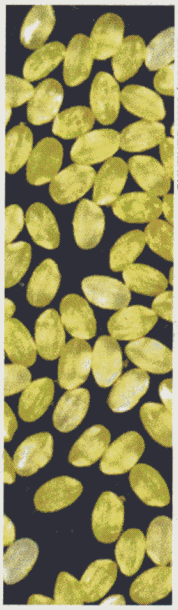
First known American death caused by gene therapy: Jesse Gelsinger, 18, dies of multiple-organ failure after receiving an experimental treatment

AP

- Ingo Potrykus and Peter Beyer create **golden rice,** a bioengineered strain enriched with beta-carotene

2000

Venter and Francis Collins announce together that they have sequenced the human genome

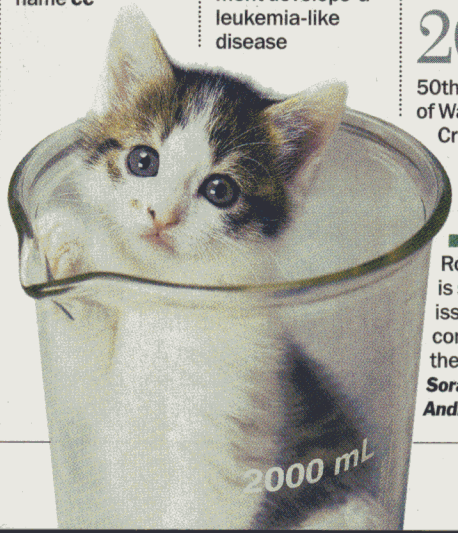


ETH ZURICH, SWITZERLAND

2002

Scientists at Texas A&M University clone a house cat, which they name **cc**

- Gene-therapy trials in France and the U.S. for the bubble-boy disease are halted after a child undergoing treatment develops a leukemia-like disease
- Raelian sect claims the birth of the first cloned human baby, named Eve, but offers no proof



RICHARD OLSENIUS—TEXAS A&M UNIVERSITY

2003

50th anniversary of Watson and Crick's discovery of the double helix

- Britain's Royal Mint is scheduled to issue a £2 coin commemorating the event

—By Sora Song and Andrea Dorfman

man felt he had contributed to her reaction—Watson and Wilkins began chatting. "Now that I need no longer merely imagine the emotional hell he had faced during the past two years," writes Watson, "he could treat me almost as a fellow collaborator rather than as a distant acquaintance." In the course of that conversation, Wilkins trotted out one of Franklin's images of the B form of DNA. Labeled Photograph 51, it was her best—and, writes Watson, "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. Moreover, the black cross of reflections which dominated the picture could arise only from a helical structure."

DNA must be a helix after all, and on a cold train ride back to Cambridge, Watson decided that two helical sugar-phosphate backbones made more sense than three. "Thus by the time I had cycled back to college and climbed over the back gate, I had decided to build two-chain models. Francis would have to agree. Even though he was a physicist, he knew that important biological objects came in pairs."

It wasn't just the clarity of Franklin's picture that excited Watson. It was also the fact that the pattern repeated itself every 34 angstroms (an angstrom is one ten-billionth of a meter). That gave Crick and Watson crucial information about the angles between bonded molecules. Even better, the image suggested that the bases attached to the backbone were neatly stacked one on top of the other.

But were the two backbones on the inside of DNA or on the outside? Inside was a lot more straightforward; with the attached bases pointing outward, whatever code they might carry would be easily accessible. There seemed no chemically viable way to parse it, however, although Watson spent several days trying. Finally, he writes, "as I took apart a particularly repulsive backbone-centered molecule, I decided that no harm could come from spending a few days building backbone-out models." This would raise the tricky question of how to pack strings of bases against one another. But Watson put aside that worry for the moment.

On Feb. 8, 1953, the Cricks had Wilkins and Watson to lunch, and the Cavendish scientists learned several things. First, it was O.K. with Wilkins if they proceeded with their model building (a good thing, since they had already started and had no intention of stopping now). More important, they evidently also learned that the King's group had prepared a report on its DNA studies for the Medical Research Council, which funded the work. It wasn't a confidential document, so Watson and Crick got hold of a copy. In it were some more crucial clues, including the fact that DNA had a particular type of structural symmetry that implied that the molecule was made of two chains running in opposite directions.

But there remained the problem of how to fit the bases together. Watson kept trying to do it by pairing like with like—an A attached to one backbone linked to an A on the other. Chemically, it would work. The bases were different enough in size and shape, though, that this scheme led to either a gap between bases or misshapen backbones. Worse yet, when Watson happened to show his idea to Jerry Donohue, an American crystallographer doing a stint at the Cavendish, Donohue informed him that the bases came in more than one chemical form. Watson was using the form prescribed in standard textbooks. But the textbooks, Donohue insisted, were wrong.

It took about a week for Watson and Crick to see that Donohue was right. The Cavendish machine shop would have to build new pieces for their models. Watson couldn't wait. He spent the afternoon of Feb. 27 cutting his own pieces out of cardboard. Then he went out to the theater.

On Feb. 28, armed with his new cardboard bases, Watson began trying to match like with like again—and then he had an insight. "Suddenly," he writes, "I became aware that an adenine-thymine pair held together by two hydrogen bonds was identical in shape to a guanine-cytosine pair held together by at least two hydrogen bonds." If the bases were joined up this way, the backbones wouldn't be bumpy. Moreover, such an arrangement neatly explained what Chargaff had discovered in 1950. If A and T were always paired, there naturally had to be equal amounts of these two bases; same thing for G and C.

"Even more exciting," writes Watson, "this type of double helix suggested a replication scheme ... always pairing adenine with thymine and guanine with cytosine meant that the base sequences of the two intertwined chains were complementary to each other. Given the base sequence of one chain, that of its partner was automatically determined. Conceptually, it was thus very easy to visualize how a single chain could be the template for the synthesis of a chain with the complementary sequence."

He consulted Donohue. It made sense. Crick showed up about 40 minutes later; it made sense to him too. There were still details to work out, and Watson feared a repeat of their botch job in late 1951. "Thus," he writes, "I felt slightly queasy when at lunch Francis winged into the Eagle to tell everyone within hearing distance that we had found the secret of life."

But of course they had. Wilkins and Franklin would be informed within a few days—although they never told Franklin of the crucial role her photograph had played. The rest of the world would learn about the double helix in a one-page letter to *Nature*, which appeared on April 25, 1953. It began with the now famous understatement: "We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest."

In retrospect, what they found is utterly straightforward and so elegant that Pauling or Wilkins or Franklin or someone would have come up with it, possibly within weeks. The reason we remember Watson and Crick instead is summed up nicely by Crick himself. "The major credit I think Jim and I deserve," he writes, "is for selecting the right problem and sticking to it. It's true that by blundering about we stumbled on gold, but the fact remains that we were looking for gold." ■

BARRINGTON BROWN—PHOTO RESEARCHERS

NOBELISTS IN WAITING: Crick, left, and Watson have coffee at the Cavendish laboratory after their paper appeared in *Nature*