academic ability, and to home in on that," says Fuller. "There's a history of people with no qualifications who are now senior."

Past as prologue

At the end of April, hundreds of former LMB researchers will converge on Cambridge to celebrate the 50th anniversary of Watson and Crick's DNA paper. They include numerous Nobel laureates whose prizewinning research came after their time at LMB, as well as prominent department heads, institute directors, and journal editors. There is no doubt in their minds that LMB is unique. "I don't think if you had put the same people in a U.S. institution that they would have done as well," says Rubin.

But can it continue to be so special? Thirty years ago, "the field was much smaller. It was *the* place for U.S. postdocs to go, and the best went," Rubin explains. "Now there are many good places." Although funds still flow relatively freely, paperwork, regulations, and other constraints have crept in, Henderson notes. And while he and his colleagues pride themselves on their small labs, which range in size from 1 to 10 people, they worry that they will fall behind. "There's so much more you can do with more manpower," says Pelham.

Biological incubator. Hundreds of budding molecular biologists got their start at the Laboratory of Molecular Biology, opened in 1962.

To keep pace with the burgeoning scientists and staff—about 400, more than twice the number 30 years ago—the building has doubled in size every decade since 1962. A new building is in the works. Says Klug, "I am worried that we will get too big and lose the ethos on which the lab has been built."

LMB now relies on a glossy annual report rather than word of mouth to publicize its accomplishments. Commercial considerations are also gaining prominence. For instance, 25 years ago MRC didn't bother to patent Milstein's technique for making monoclonal antibodies, now a fundamental tool in many industries. The same was true of Sanger's sequencing technology. Today, patenting is encouraged, says Henderson, and several companies, such as Celltech, are associated with the lab.

Klug and Henderson suspect that the place is good for at least a couple of more Nobels. Even today, with universities, medical foundations, and other organizations working to create hotbeds of scientific creativity, LMB still earns strong kudos. Says Yale's Joan Steitz: "There have been very good research institutions that have tried to capture the flavor and spirit, but they haven't got it."

–ELIZABETH PENNISI

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NEWS

DNA's Cast of Thousands

Watson and Crick's discovery revealed much, suggested more, but left many details unanswered. Ever since, researchers have been discovering the proteins that unlock DNA and the genetic code

When James Watson and Francis Crick elucidated the structure of DNA, they discovered an elegantly simple molecule. With cardboard cutouts, metal, and wire, they showed how DNA's two chains wound around each other, with the paired bases inside, one full rotation every 10 bases. Their model immediately suggested how DNA copied itself and enabled genetic information to flow from one generation to the next. They boasted that they had found the "secret of life"—essentially, biology's master molecule that controlled the fate of the cell and, consequently, of the organism.

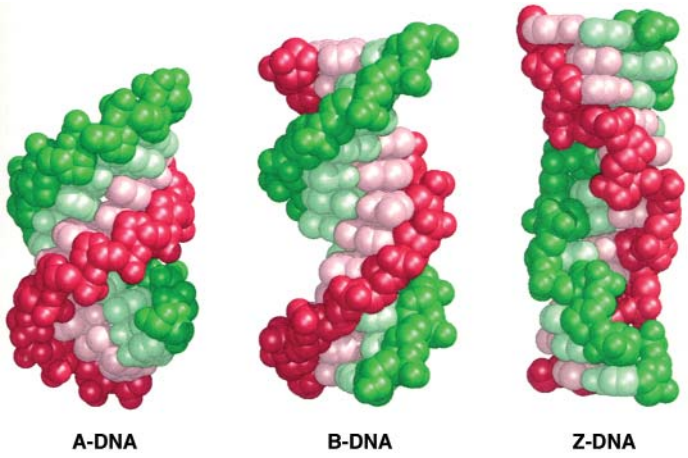
Fifty years of research since then has shown that, despite its precision design, this molecule can't dance without a team of choreographers. Like a puppet, DNA comes alive only when numerous proteins pull its "strings." At the time of their discovery, Watson and Crick had only the haziest of ideas about how this double helix interacted with proteins. But rebuilt today, Watson and Crick's bare-bones model would be draped with proteins that kink and curl, repair, and otherwise animate DNA.

DNA ascendant

The age of DNA began well before Crick and Watson were born. In the 1860s, Friedrich Miescher, a Swiss working in Tübingen, Germany, isolated a strange, phosphorus-rich material from the cell nucleus. Within decades, it was clear that this peculiar substance—later identified as nucleic acids—was fundamental to the cell's chemistry. Somehow.

Throughout the early part of the 20th century, biochemists argued about DNA's role. Some postulated that it was the stuff of genes; others insisted that proteins carried

Naked DNA. Watson and Crick's first model of DNA didn't begin to reveal the complex set of proteins the molecule needs to do its job.



Chameleon. Although the B-DNA is most common and the one first described, certain conditions force this molecule into A- or Z-DNA configurations.

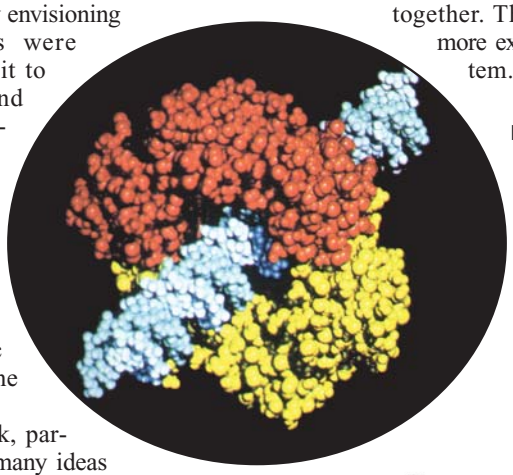
the genetic code. Even though Oswald Avery, Colin MacLeod, and Maclyn McCarty of Rockefeller University in New York City demonstrated in 1944 that DNA and not proteins carried the genetic code, the debate continued; even Crick and Watson at first disagreed on this point.

Soon after Watson joined him at the University of Cambridge, U.K., in 1951, Crick was persuaded. Across two continents, they and others set out to discover just what DNA looked like. Tapping a newly developed imaging technique called x-ray crystallography, Rosalind Franklin and Maurice Wilkins of King's College in London produced images that showed DNA was helical. Others were busy envisioning how DNA's bases were arranged to enable it to function. Watson and Crick's discovery settled once and for all that genes were made of DNA. But it took eight more years—and the efforts of many researchers—to crack the genetic code contained in the nucleotide bases.

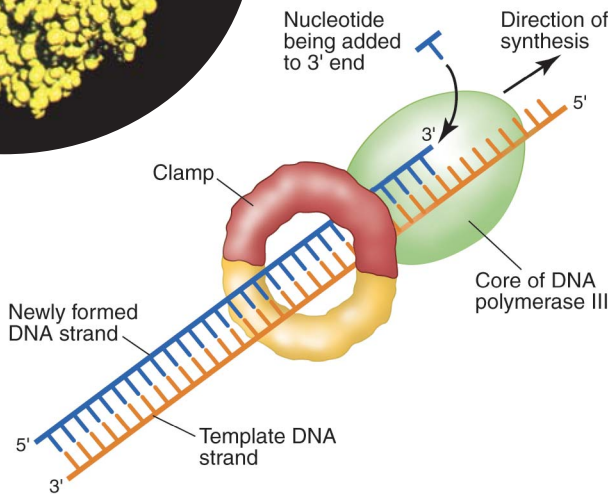
Watson and Crick, particularly Crick, had many ideas about how DNA worked, something their landmark 1953 paper hinted at in its last sentence: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." The idea was that, as the double helix uncoiled, each strand of an existing DNA molecule could act as a template for building another copy of the molecule. In the late 1950s, Matthew Meselson and Franklin Stahl of the California Institute of Technology in Pasadena showed this to be the case.

Shortly afterward, Arthur Kornberg of Stanford University and his colleagues demonstrated that an enzyme they had discovered several years earlier orchestrates the synthesis of each new DNA strand. The enzyme, DNA polymerase, adds just the right nucleotide base to the separated DNA strands, making sure the new one exactly matches its template. More than 20 additional proteins are also known to perform distinct functions in copying DNA. Some help unwind DNA, for example; others mark the starting point of replication. And since then researchers have found at least two more DNA polymerases: one specializes in making new DNA; another helps repair damaged DNA.

Some mistakes are introduced long after DNA polymerase has finished its job—for instance, when radiation or toxic chemicals cause the wrong base or bases to be substituted or others to be deleted altogether. This necessitates a more extensive repair system. Faced with such errors, the cell calls in its molecular repairers. These enzymes mark the bad DNA, cut it out, and replace it with the right code. One of the best-studied examples is that of bacteria as they recover from exposure to ultraviolet light. First, a complex of UvrABC proteins recognizes the damage. Then the UvrABC enzyme cuts at two sites a few bases to either side of the defective DNA and whisks away that piece. DNA polymerase then fills in the gap with the correct bases.



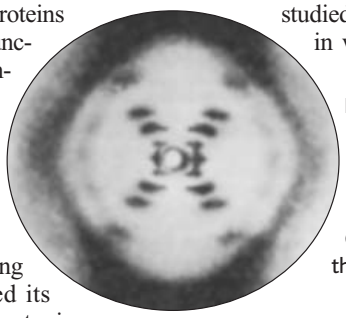
Duplicating DNA. The ring section of DNA polymerase helps this enzyme's core work more efficiently as it carries out DNA replication. The crystal structure shows the ring (red and yellow) sliding down the DNA.



DNA's messenger

Watson and Crick's discovery left wide open the question of how DNA specifies which proteins are made. It was more than a decade before the "code" itself was worked out, along with all the intricate details of the gene-to-protein transition.

The first clues that genes specified amino acids came from V. M. Ingram of the University of Cambridge. He studied the sickle cell trait, in which two defective genes can lead to severe anemia, while one causes just mild problems. In 1957, he tracked the defect down to a single amino acid change, a mistake in whatever specified the order of amino acids in the hemoglobin protein. The work suggested that DNA was that template. Then, in 1961, Marshall Nirenberg of the U.S. National Institutes of Health in Bethesda, Maryland, realized that a three-base sequence in DNA, UUU, specified the amino acid phenylalanine; soon the rest of the triplets were deciphered.



First glimpse. This x-ray diffraction pattern hinted that DNA was helical, thereby helping Watson and Crick come up with the right structure.

We now know that DNA's triplet code is transmitted through an intermediary called messenger RNA (mRNA), a closely related, single-stranded nucleic acid. The mRNA ferries this information out of the nucleus to the ribosome, which builds the protein one amino acid at a time.

Early on, there were clues that a short-lived molecule might be involved. The prime suspect was RNA, because it

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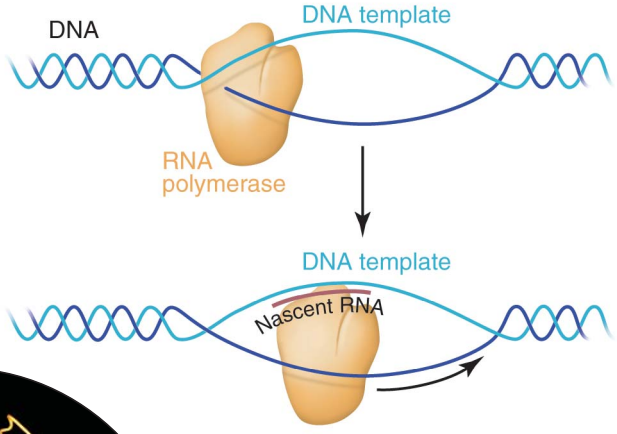
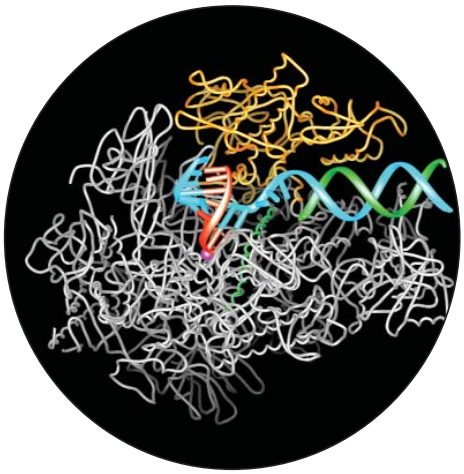
appears in large quantities outside the nucleus where proteins are being made by the ribosome. But researchers had no idea how the RNA got there or what it really did. Then, in 1960, four groups, Jerard Hurwitz of Memorial Sloan-Kettering Cancer Center in New York City and Sam Weiss of the University of Chicago among them, independently discovered that the enzyme RNA polymerase strings together the RNA's bases much as DNA polymerase does for DNA. A year later, Sol Spiegelman of the University of Illinois, Urbana-Champaign, showed that RNA polymerase reads this code from the DNA template, providing one of the strongest clues that RNA was somehow involved with DNA.

At about the same time in Paris, the Pasteur Institute's François Jacob and Jacques Monod proposed that a short-lived messenger molecule shuttled DNA's coding information from the nucleus to the cytoplasm. Working with Meselson and Sydney Brenner at the Laboratory of Molecular Biology, Jacob then verified the idea. Thus, by the early 1960s, there was little doubt that mRNA linked the gene to a protein's production and that RNA polymerase was central to this process.

Again, the process is proving to be even more complicated than researchers initially realized. It turns out that there are three RNA polymerases: one for protein-coding genes and two for genes that code for RNAs that are never translated into proteins. In addition, RNA polymerase has help. For instance, in bacteria, RNA polymerase works much more efficiently when it links up with a protein, called cAMP-CAP. And in the more complex eukaryotes, a whole series of steps precedes RNA polymerase activity. Other proteins and protein-RNA complexes are needed to process the RNA that peels off the DNA before it's ready to exit the nucleus. A key change is the removal of noncoding bases transcribed from the noncoding sections of DNA.



Reading the code. To transfer a gene's coding data into protein production, an enzyme called RNA polymerase (peach) latches onto DNA, unwinds the double helix, and begins to build messenger RNA based on a template strand of the DNA (top). It moves along the DNA as the nascent RNA forms (bottom). The crystal structure shows the RNA polymerase (gray) with its clamp (orange) building the RNA based on the DNA strand (blue).

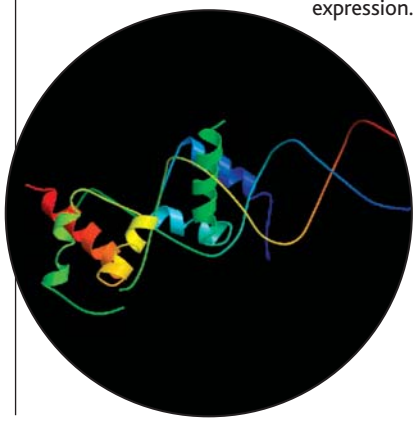


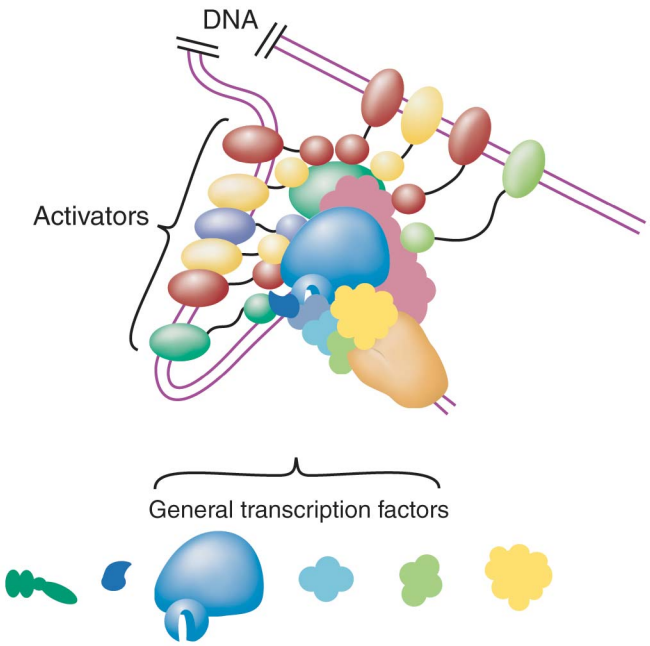
DNA's advisers

The entire DNA code is not expressed all at once. The human's 31,000 or so genes are turned on and off, singly and in combination, depending on which suites of proteins are needed for specific cell functions. Few researchers gave much thought to the idea that proteins might regulate genetic activity until 1961. In the same paper in which Monod and Jacob suggested the existence of mRNA, they proposed that cells also have regulatory elements that affect gene expression. Then, in 1967, Walter Gilbert and Benno Müller-Hill of Harvard University isolated a protein that bound to DNA and repressed gene activity. Independently, Harvard's Mark Ptashne isolated another transcription factor, as these proteins are now called. Scores more have since been discovered. Some latch onto DNA where the synthesis of mRNA begins, to either suppress or stimulate gene activity; others work from afar.

Over time, researchers have come to realize that multiple proteins, interacting in different ways, exert exquisite control over gene expression. The same factor can alternate between activating and repressing transcription, depending on its protein partners. For example, in normal human colon cells a protein called groucho links with a transcription factor called Lef/Fcf and keeps an oncogene called *Myc* quiet. But if β-catenin takes the place of groucho, *Myc* is turned on.

Transcription factors often make their mark by bending the DNA so that the enzymes that translate the DNA code into protein can position themselves at the right place on DNA and still interact with one another. For example, in a prerequisite for ex-





Simple to complex. Researchers first thought individual proteins latched onto and regulated DNA activity (W-shaped ribbon). But now they realize that these proteins rarely act alone. Varying combinations of transcription factors, along with protein activators or repressors, exert dynamic and finely tuned control over gene expression.

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pression of most eukaryotic genes, the transcription factor TFIID causes the DNA molecule to bend, paving the way for other transcription factors.

Often, transcription factors work in combination. A half-dozen factors link together to activate the β-interferon gene, for instance. Their association is facilitated by several copies of yet another protein called HMGI, which causes DNA to bend sharply so that the various transcription factors align themselves elbow to elbow as they work. And four varieties of specific transcription factors together with more than a half-dozen other proteins are required to switch on the *TTR* genes in liver cells, so they make that blood protein.

1974, Stanford's Roger Kornberg (son of Arthur) proposed that chromatin was quite structured—made up of repeating units, each containing 200 base pairs of DNA wrapped around pairs of two of four different histones. Those units are now called nucleosomes, and they pack and organize DNA so that under an electron microscope, it looks like beads on a string.

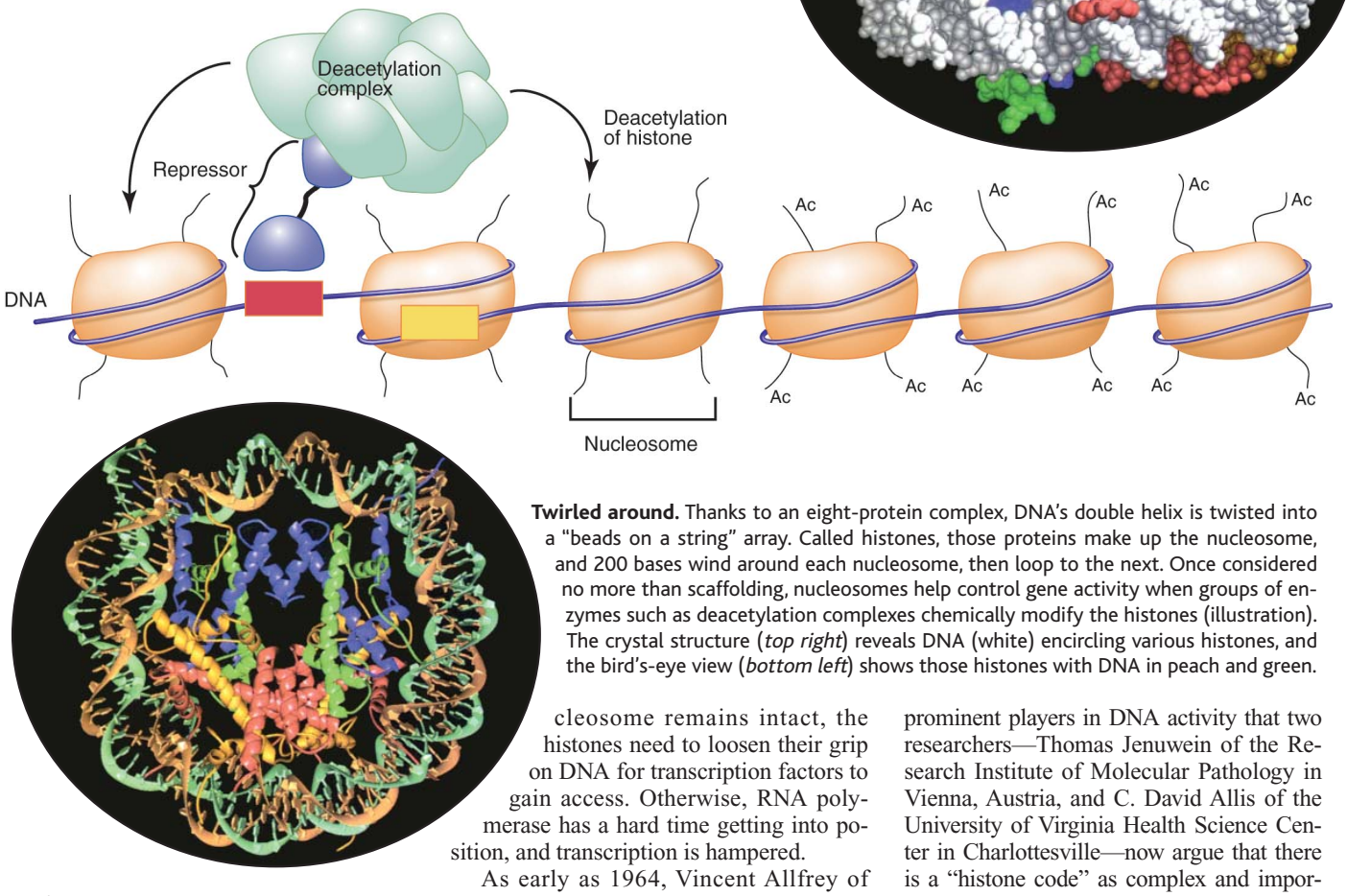
For the next 20 years, few researchers thought histones were anything more than structural supports. Because the nucleosomes remained intact during transcription, they didn't seem to be involved in gene regulation. But it turns out that although the nucleosome remains intact, the histones need to loosen their grip on DNA for transcription factors to gain access. Otherwise, RNA polymerase has a hard time getting into position, and transcription is hampered.

ity, whereas the removal of a histone's acetyl groups silences nearby genes.

Today, that cast has expanded to include enzymes that add and remove methyl groups and others that do the same with phosphates. Histones are becoming such prominent players in DNA activity that two researchers—Thomas Jenuwein of the Research Institute of Molecular Pathology in Vienna, Austria, and C. David Allis of the University of Virginia Health Science Center in Charlottesville—now argue that there is a "histone code" as complex and important as the DNA code, one that fine-tunes gene activity and adds more depth to the information encoded in the genes. The idea is slowly catching on, leaving pioneering molecular biologists to shake their heads.

Forty years ago, Brenner and others were convinced that the central questions in molecular biology would be answered well before the turn of the century. Now they know better. The nature of the histone code is just one of many problems whose complexities are left to be unraveled.

–ELIZABETH PENNISI



Twirled around. Thanks to an eight-protein complex, DNA's double helix is twisted into a "beads on a string" array. Called histones, those proteins make up the nucleosome, and 200 bases wind around each nucleosome, then loop to the next. Once considered no more than scaffolding, nucleosomes help control gene activity when groups of enzymes such as deacetylation complexes chemically modify the histones (illustration). The crystal structure (*top right*) reveals DNA (white) encircling various histones, and the bird's-eye view (*bottom left*) shows those histones with DNA in peach and green.

CREDITS: (TOP TO BOTTOM) FROM K. LUGER *ET AL.*, *NATURE* **389** (1997); ADAPTED FROM *MOLECULAR CELL BIOLOGY*, LODISH *ET AL.*; T. J. RICHMOND

DNA's attire

At the time of Watson and Crick's discovery, it was already clear that DNA was not really naked in the cell nucleus but was adorned with proteins. For decades, these proteins were considered mere dressing. Indeed, 50 years later researchers are still figuring out how they interact to regulate gene expression.

In the cell nucleus, those proteins—primarily histones—together with DNA make up a complex called chromatin, so named because of how it stains in cells. In

As early as 1964, Vincent Allfrey of Rockefeller University realized that histones were often chemically modified by the addition of many acetyl side groups, which seemed to cause them to slacken their hold on DNA. The observation was all but forgotten, however, until 1996, when a slew of researchers discovered that histones, too, are also puppets: Various proteins cause them to change shape, which in turn alters gene activity. In a matter of months, the cast of puppeteers included four enzymes that add acetyl groups to histones and five that remove them. Acetylation prompts gene activ-