The New Genetics

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of General Medical Sciences

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Foreword

Consider just three of Earth's inhabitants: a bright yellow daffodil that greets the spring, the single-celled creature called *Thermococcus* that lives in boiling hot springs, and you. Even a science-fiction writer inventing a story set on a distant planet could hardly imagine three more different forms of life. Yet you, *Thermococcus* and the daffodil are related! Indeed, all of the Earth's billions of living things are kin to each other.

And every living thing does one thing the same way: To make more of itself, it first copies its molecular instruction manual—its genes—and then passes this information on to its offspring. This cycle has been repeated for three and a half billion years.

But how did we and our very distant relatives come to look so different and develop so many different ways of getting along in the world? A century ago, researchers began to answer that question with the help of a science called genetics. Get a refresher course on the basics in **Chapter 1, "How Genes Work."**

It's likely that when you think of heredity you think first of DNA, but in the past few years, researchers have made surprising findings about

another molecular actor that plays a starring role. Check out the modern view of RNA in **Chapter 2, "RNA and DNA Revealed: New Roles, New Rules."**

When genetics first started, scientists didn't have the tools they have today. They could only look at one gene, or a few genes, at a time. Now, researchers can examine all of the genes in a living organism—its genome—at once. They are doing this for organisms on every branch of the tree of life and finding that the genomes of mice, frogs, fish and a slew of other creatures have many genes similar to our own.

So why doesn't your brother look like your dog or the fish in your aquarium? It's because of evolution. In **Chapter 3, "Life's Genetic Tree,"** find out how evolution works and how it relates to genetics and medical research.

Can DNA and RNA help doctors predict whether we'll get diseases like cancer, diabetes or asthma? What other mysteries are locked within the 6 feet of DNA inside nearly every cell in our bodies? **Chapter 4, "Genes Are Us,"** explains what researchers know, and what they are still learning, about the role of genes in health and disease.

Finally, in **Chapter 5, "21st-Century Genetics,"** see a preview of things to come. Learn how medicine and science are changing in big ways, and how these changes influence society.

From metabolism to medicines to agriculture, the science of genetics affects us every day. It is part of life … part of *your* life!

How Genes Work

People have known for many years that living things inherit traits from their parents. That common-sense observation led to agriculture, the purposeful breeding and cultivation of animals and plants for desirable characteristics. Firming up the details took quite some time, though. Researchers did not understand exactly how traits were passed to the next generation until the middle of the 20th century.

Now it is clear that **genes** are what carry our traits through generations and that genes are made of **deoxyribonucleic acid (DNA)**. But genes themselves don't do the actual work. Rather, they serve as instruction books for making functional molecules such as **ribonucleic acid (RNA)** and **proteins**, which perform the chemical reactions in our bodies.

Proteins do many other things, too. They provide the body's main building materials, forming the cell's architecture and structural components. But one thing proteins can't do is make copies of themselves. When a cell needs more proteins, it uses the manufacturing instructions coded in DNA.

The DNA code of a gene—the sequence of its individual DNA building blocks, labeled A (adenine), T (thymine), C (cytosine) and G (guanine) and collectively called **nucleotides**—spells out the exact order of a protein's building blocks, **amino acids**.

Occasionally, there is a kind of typographical error in a gene's DNA sequence. This mistake—which can be a change, gap or duplication—is called a **mutation**.

Genetics in the Garden

The monk Gregor Mendel first described how traits are inherited from one generation to the next.

In 1900, three European scientists independently discovered an obscure research paper that had been published nearly 35 years before. Written by Gregor Mendel, an Austrian monk who was also a scientist, the report described a series of breeding experiments performed with pea plants growing in his abbey garden.

Mendel had studied how pea plants inherited the two variant forms of easy-to-see traits. These included flower color (white or purple) and the texture of the peas (smooth or wrinkled). Mendel counted many generations of pea plant offspring and learned that these characteristics were passed on to the next generation in orderly, predictable ratios.

When he cross-bred purple-flowered pea plants with white-flowered ones, the next generation had only purple flowers. But directions for making white flowers were hidden somewhere in the peas of that generation, because when those purple-flowered

A mutation can cause a gene to encode a protein that works incorrectly or that doesn't work at all. Sometimes, the error means that no protein is made.

But not all DNA changes are harmful. Some mutations have no effect, and others produce new versions of proteins that may give a survival advantage to the organisms that have them. Over time, mutations supply the raw material from which new life forms evolve (see Chapter 3, "Life's Genetic Tree").

Beautiful DNA

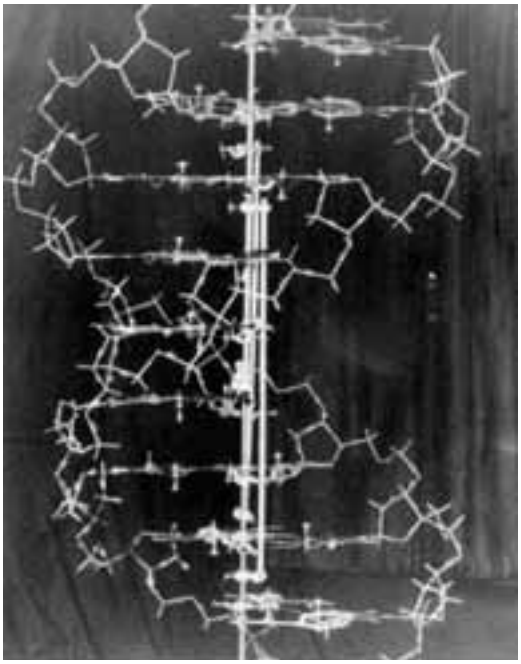
Up until the 1950s, scientists knew a good deal about heredity, but they didn't have a clue what DNA looked like. In order to learn more about DNA and its structure, some scientists experimented with using X rays as a form of molecular photography.

Rosalind Franklin, a physical chemist working with Maurice Wilkins at King's College in London, was among the first to use this method to analyze genetic material. Her experiments

plants were bred to each other, some of their offspring had white flowers. What's more, the second-generation plants displayed the colors in a predictable pattern. On average, 75 percent of the second-generation plants had purple flowers and 25 percent of the plants had white flowers. Those same ratios persisted, and were reproduced when the experiment was repeated many times over.

Trying to solve the mystery of the missing color blooms, Mendel imagined that the reproductive cells of his pea plants might contain discrete "factors," each of which specified a particular trait, such as white flowers. Mendel reasoned that the factors, whatever they were, must be physical material because they passed from parent to offspring in a mathematically orderly way. It wasn't until many years later, when the other scientists unearthed Mendel's report, that the factors were named genes.

Early geneticists quickly discovered that Mendel's mathematical rules of inheritance applied not just to peas, but also to all plants, animals and people. The discovery of a quantitative rule for inheritance was momentous. It revealed that a common, general principle governed the growth and development of all life on Earth.



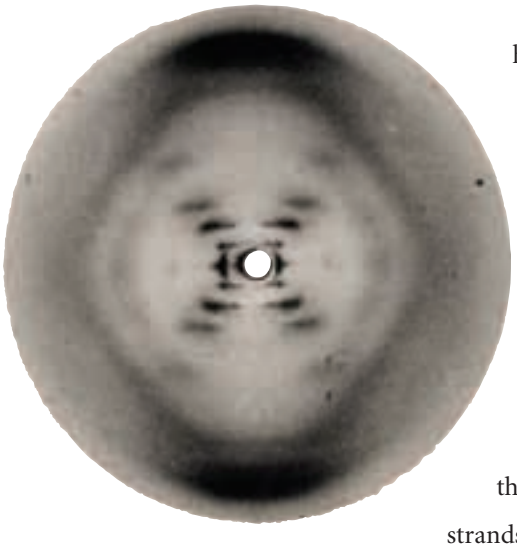
COLD SPRING HARBOR LABORATORY ARCHIVES

▲ In 1953, Watson and Crick created their historic model of the shape of DNA: the double helix.

produced what were referred to at the time as "the most beautiful X-ray photographs of any substance ever taken."

Other scientists, including zoologist James Watson and physicist Francis Crick, both working at Cambridge University in the United Kingdom, were trying to determine the shape of DNA too. Ultimately, this line of research revealed one of the most profound scientific discoveries of the 20th century: that DNA exists as a double helix.

The 1962 Nobel Prize in physiology or medicine was awarded to Watson, Crick and Wilkins for this work. Although Franklin did not earn a share of the prize due to her untimely death at age 38, she is widely recognized as having played a significant role in the discovery.



▲ Rosalind Franklin's original X-ray diffraction photo revealed the physical structure of DNA.

OREGON STATE UNIVERSITY LIBRARIES SPECIAL COLLECTIONS

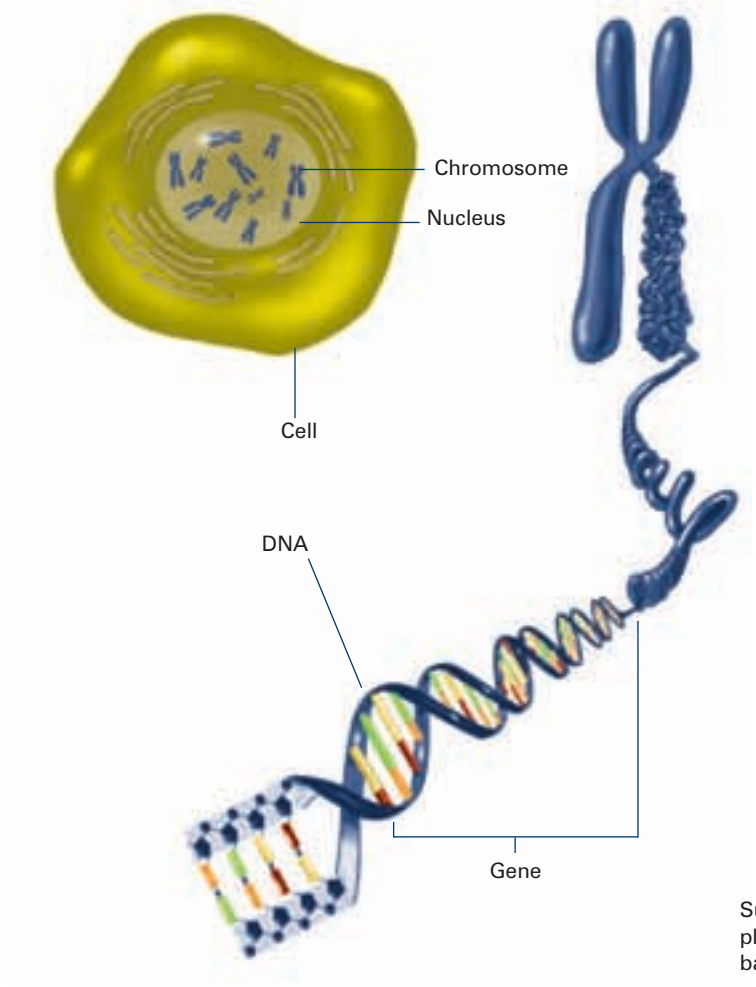
The spiral staircase-shaped double helix has attained global status as the symbol for DNA. But what is so beautiful about the discovery of the twisting ladder structure isn't just its good looks. Rather, the structure of DNA taught researchers a fundamental lesson about **genetics**. It taught them that the two connected strands—winding together like parallel handrails—were complementary to each other, and this unlocked the secret of how genetic information is stored, transferred and copied.

In genetics, complementary means that if you know the sequence of nucleotide building blocks on one strand, you know the sequence of nucleotide building blocks on the other strand: A always matches up with T and C always links to G (see drawing, page 7).

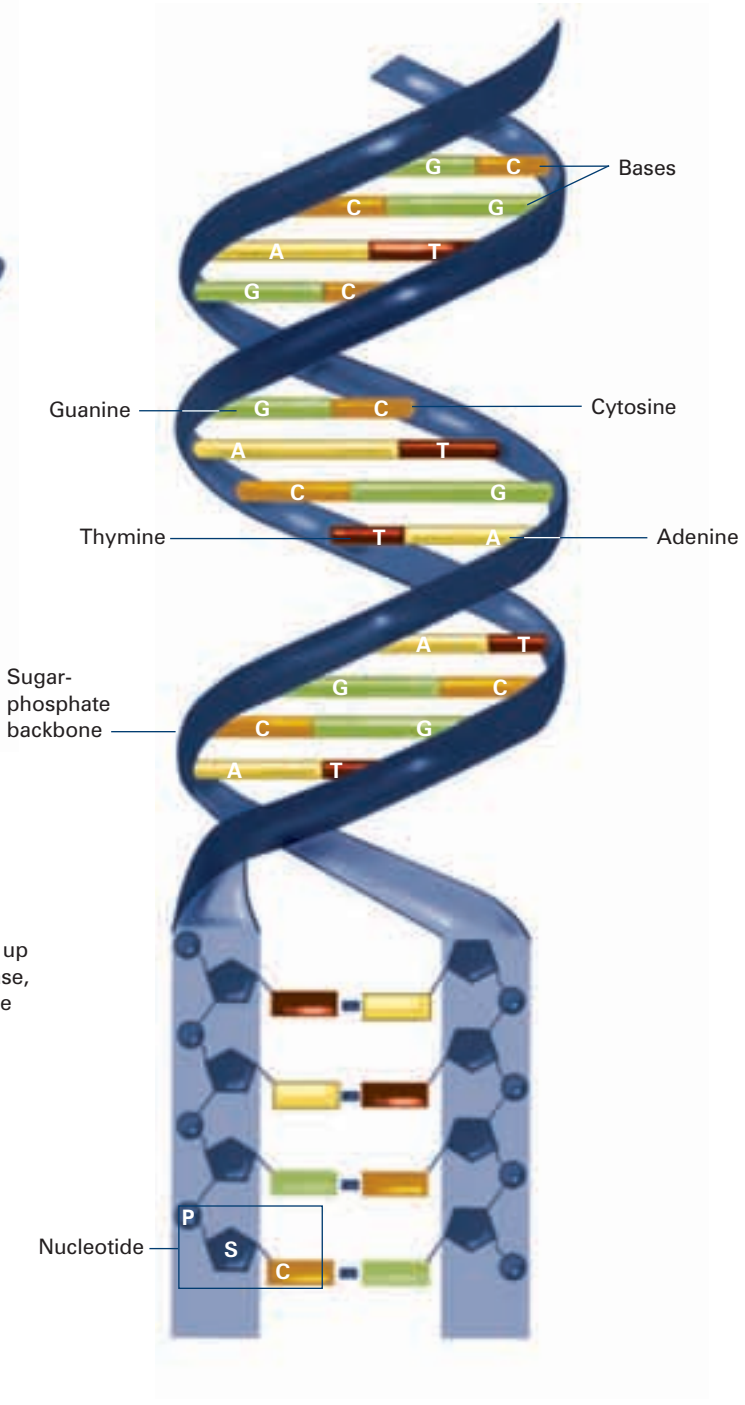
Long strings of nucleotides form genes, and groups of genes are packaged tightly into structures called **chromosomes**. Every cell in your body except for eggs, sperm and red blood cells contains a full set of chromosomes in its **nucleus**.

If the chromosomes in one of your cells were uncoiled and placed end to end, the DNA would be about 6 feet long. If all the DNA in your body were connected in this way, it would stretch approximately 67 billion miles! That's nearly 150,000 round trips to the Moon.

DNA Structure



The long, stringy DNA that makes up genes is spooled within chromosomes inside the nucleus of a cell. (Note that a gene would actually be a much longer stretch of DNA than what is shown here.)



DNA consists of two long, twisted chains made up of nucleotides. Each nucleotide contains one base, one phosphate molecule and the sugar molecule deoxyribose. The bases in DNA nucleotides are adenine, thymine, cytosine and guanine.

▲ Humans have 23 pairs of chromosomes. Male DNA (pictured here) contains an X and a Y chromosome, whereas female DNA contains two X chromosomes.

CYTOGENETICS LABORATORY, BRIGHAM AND WOMEN'S HOSPITAL

Copycat

It's astounding to think that your body consists of trillions of cells. But what's most amazing is that it all starts with one cell. How does this massive expansion take place?

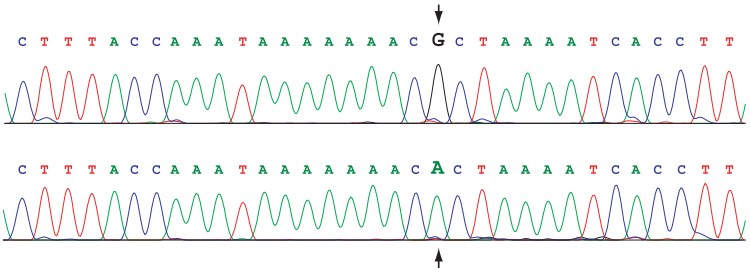
As an embryo progresses through development, its cells must reproduce. But before a cell divides into two new, nearly identical cells, it must copy its DNA so there will be a complete set of genes to pass on to each of the new cells.

To make a copy of itself, the twisted, compacted double helix of DNA has to unwind and separate its two strands. Each strand becomes a pattern, or template, for making a new strand, so the two new DNA molecules have one new strand and one old strand.

The copy is courtesy of a cellular protein machine called **DNA polymerase**, which reads the template DNA strand and stitches together the complementary new strand. The process, called **replication**, is astonishingly fast and accurate, although occasional mistakes, such as deletions or duplications, occur. Fortunately, a cellular spell-checker catches and corrects nearly all of these errors.

Mistakes that are not corrected can lead to diseases such as cancer and certain genetic disorders. Some of these include Fanconi anemia, early aging diseases and other conditions in which people are extremely sensitive to sunlight and some chemicals.

DNA copying is not the only time when DNA damage can happen. Prolonged, unprotected sun exposure can cause DNA changes that lead to skin cancer, and toxins in cigarette smoke can cause lung cancer.



▲ When DNA polymerase makes an error while copying a gene's DNA sequence, the mistake is called a mutation. In this example, the nucleotide G has been changed to an A.

It may seem ironic, then, that many drugs used to treat cancer work by attacking DNA. That's because these chemotherapy drugs disrupt the DNA copying process, which goes on much faster in rapidly dividing cancer cells than in other cells of the body. The trouble is that most of these drugs do affect normal cells that grow and divide frequently, such as cells of the immune system and hair cells.

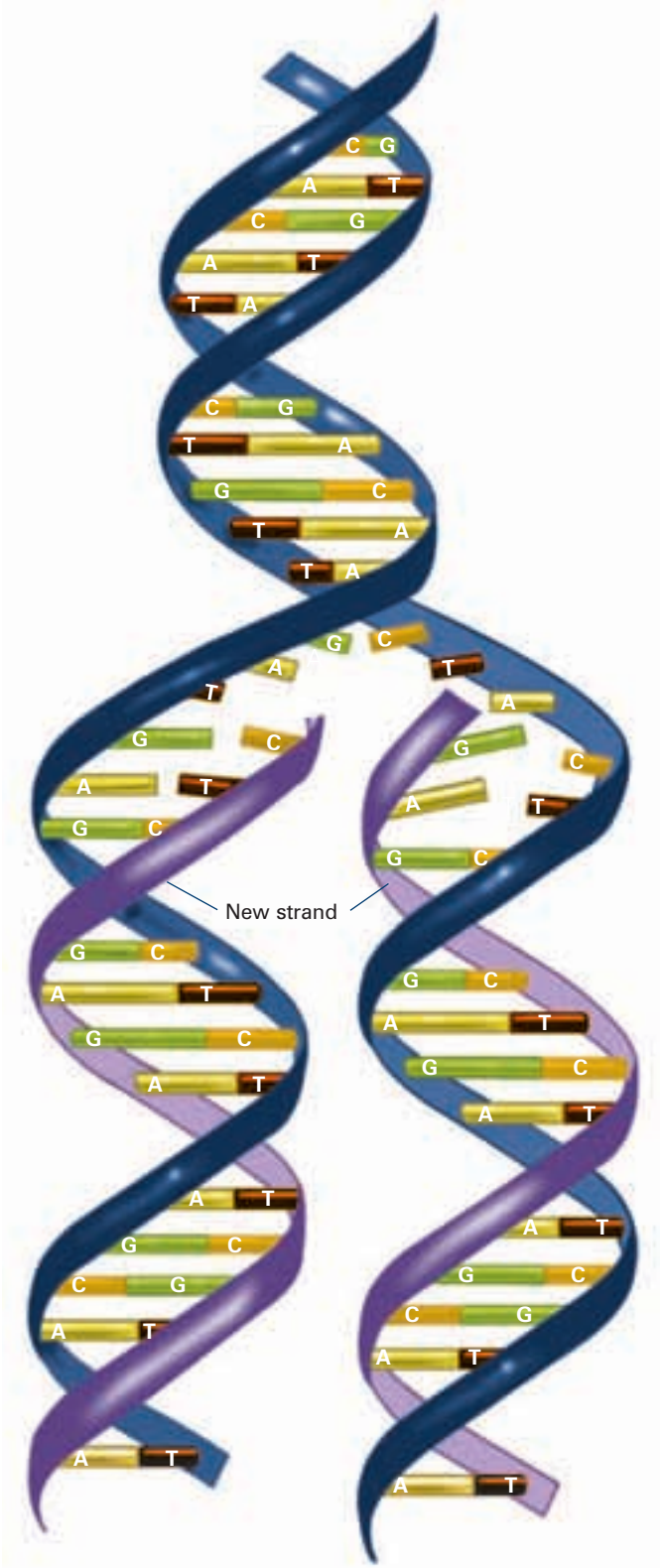
Understanding DNA replication better could be a key to limiting a drug's action to cancer cells only.

Let's Call It Even

After copying its DNA, a cell's next challenge is getting just the right amount of genetic material into each of its two offspring.

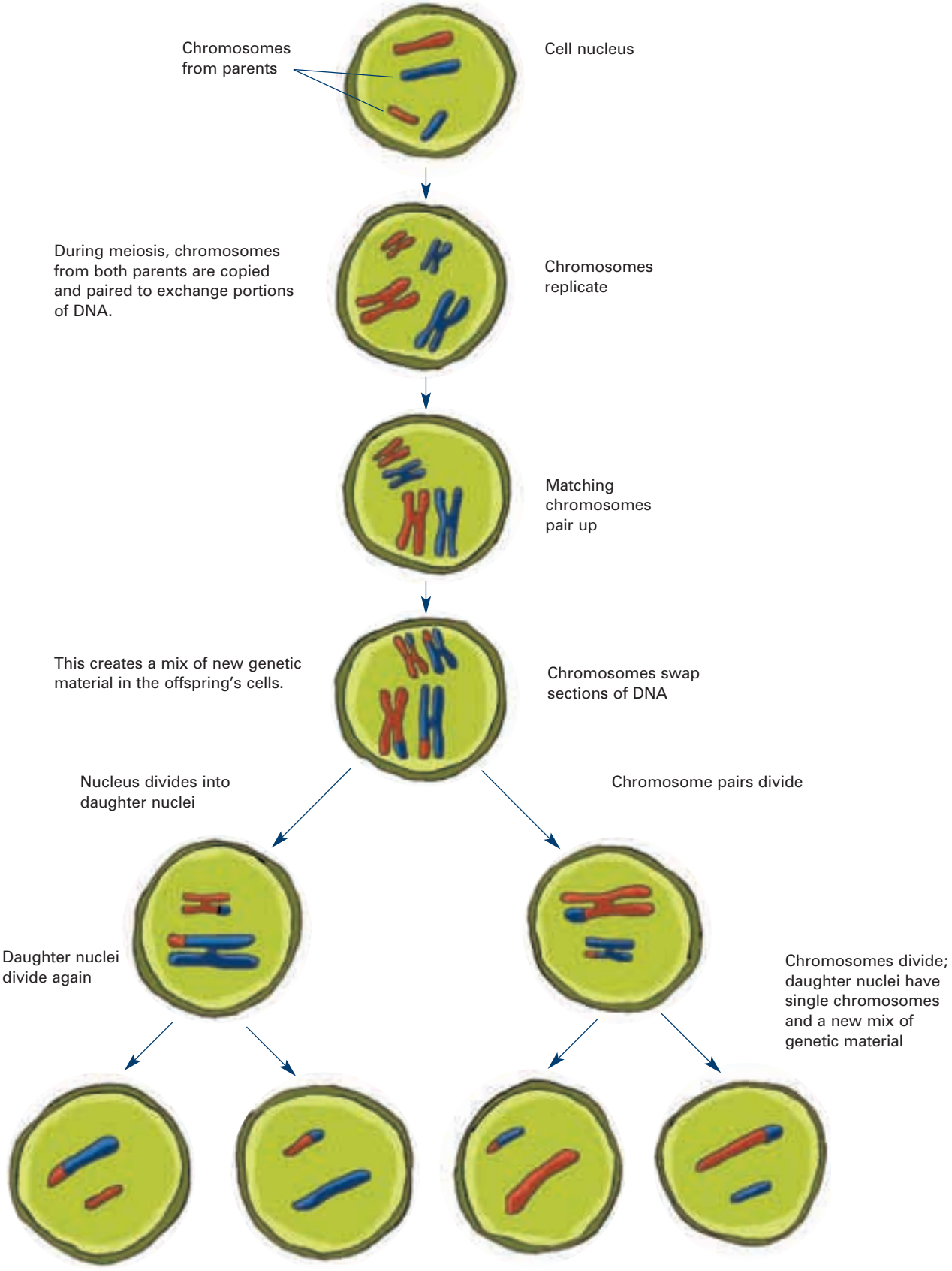
Most of your cells are called **diploid** ("di" means two, and "ploid" refers to sets of chromosomes) because they have two sets of chromosomes (23 pairs). Eggs and sperm are different; these are known as **haploid** cells. Each haploid cell has only one set of 23 chromosomes so that at fertilization the math will work out: A haploid egg cell will combine with a haploid sperm cell to form a diploid cell with the right number of chromosomes: 46.

Chromosomes are numbered 1 to 22, according to size, with 1 being the largest chromosome. The 23rd pair, known as the sex chromosomes, are called X and Y. In humans, abnormalities of chromosome number usually occur during **meiosis**, the time when a cell



▲ During DNA replication, each strand of the original molecule acts as a template for the synthesis of a new, complementary DNA strand.

Meiosis


Chromosomes from parents
Cell nucleus
During meiosis, chromosomes from both parents are copied and paired to exchange portions of DNA.
Chromosomes replicate
Matching chromosomes pair up
This creates a mix of new genetic material in the offspring's cells.
Chromosomes swap sections of DNA
Nucleus divides into daughter nuclei
Chromosome pairs divide
Daughter nuclei divide again
Chromosomes divide; daughter nuclei have single chromosomes and a new mix of genetic material

reduces its chromosomes from diploid to haploid in creating eggs or sperm.

What happens if an egg or a sperm cell gets the wrong number of chromosomes, and how often does this happen?

Molecular biologist Angelika Amon of the Massachusetts Institute of Technology in Cambridge says that mistakes in dividing DNA between daughter cells during meiosis are the leading cause of human birth defects and miscarriages. Current estimates are that 10 percent of all embryos have an incorrect chromosome number. Most of these don't go to full term and are miscarried.

In women, the likelihood that chromosomes won't be apportioned properly increases with age. One of every 18 babies born to women over 45 has three copies of chromosome 13, 18 or 21 instead of the normal two, and this improper balancing can cause trouble. For example, three copies of chromosome 21 lead to Down syndrome.

To make her work easier, Amon—like many other basic scientists—studies yeast cells, which separate their chromosomes almost exactly the same way human cells do, except that yeast do it much faster. A yeast cell copies its DNA and produces daughter cells in about $1\frac{1}{2}$ hours, compared to a whole day for human cells.

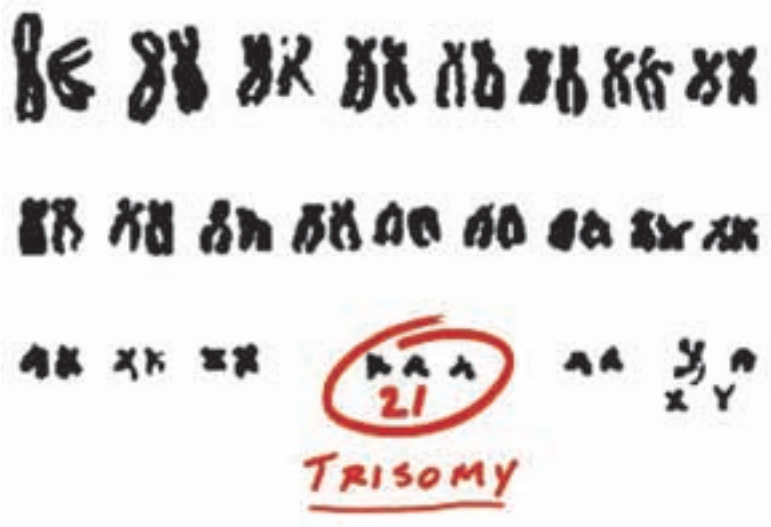
The yeast cells she uses are the same kind bakeries use to make bread and breweries use to make beer!

Amon has made major progress in understanding the details of meiosis. Her research shows how, in healthy cells, gluelike protein complexes called cohesins release pairs of chromosomes at exactly the right time. This allows the chromosomes to separate properly.

These findings have important implications for understanding and treating infertility, birth defects and cancer.

Getting the Message

So, we've described DNA—its basic properties and how our bodies make more of it. But how does DNA serve as the language of life? How do you get a protein from a gene?



▲ Trisomy, the hallmark of Down syndrome, results when a baby is born with three copies of chromosome 21 instead of the usual two.

There are two major steps in making a protein. The first is **transcription**, where the information coded in DNA is copied into RNA. The RNA nucleotides are complementary to those on the DNA: a C on the RNA strand matches a G on the DNA strand.

The only difference is that RNA pairs a nucleotide called uracil (U), instead of a T, with an A on the DNA.

A protein machine called **RNA polymerase** reads the DNA and makes the RNA copy. This copy is called messenger RNA, or mRNA, because it delivers the gene's message to the protein-producing machinery.

At this point you may be wondering why all of the cells in the human body aren't exactly alike, since they all contain the same DNA. What makes a liver cell different from a brain cell? How do the cells in the heart make the organ contract, but those in skin allow us to sweat?

Cells can look and act differently, and do entirely different jobs, because each cell "turns on," or expresses, only the genes appropriate for what it needs to do.

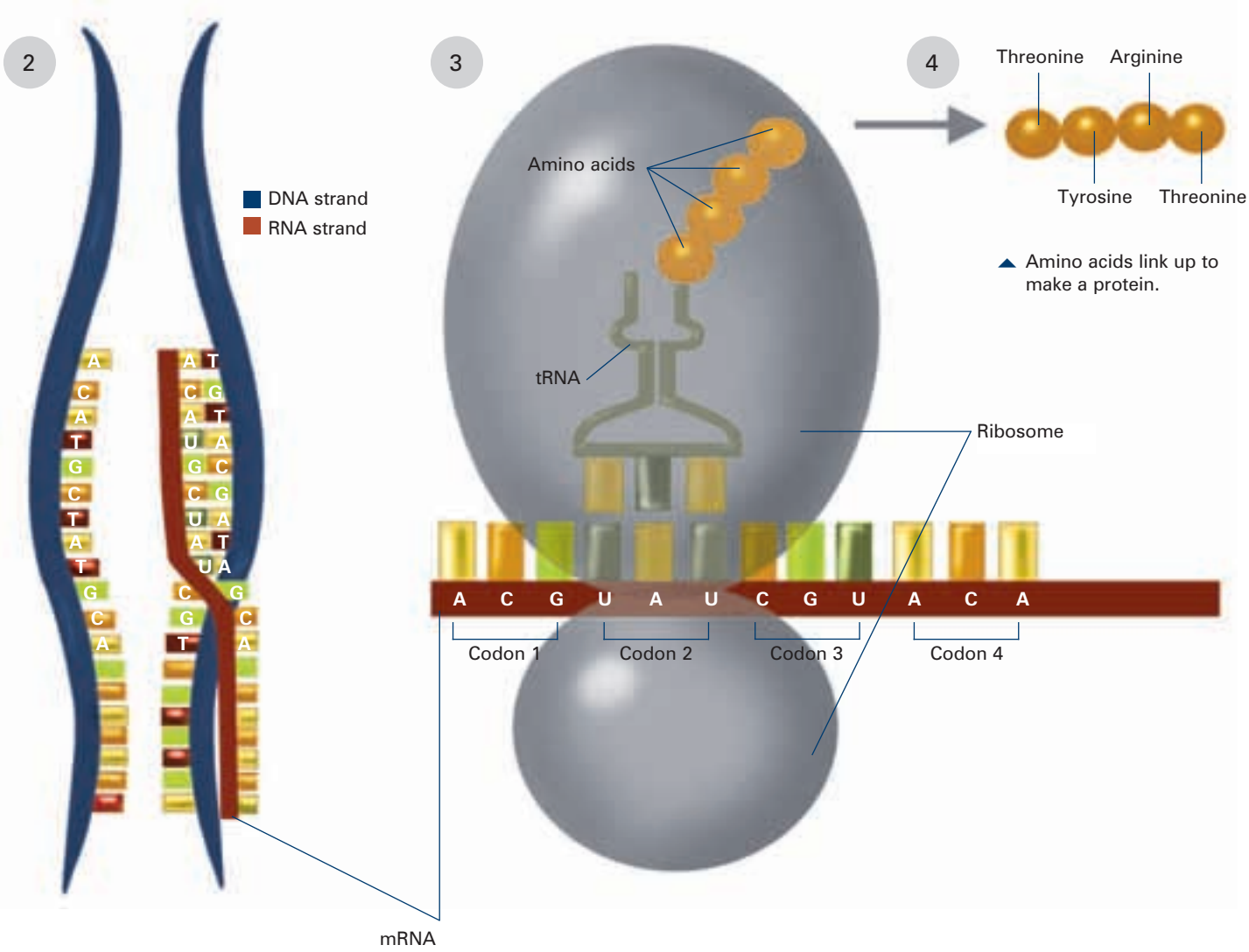
That's because RNA polymerase does not work alone, but rather functions with the aid of many helper proteins. While the core part of RNA polymerase is the same in all cells, the helpers vary in different cell types throughout the body.

You'd think that for a process so essential to life, researchers would know a lot about how transcription works. While it's true that the basics are clear—biologists have been studying gene transcribing by RNA polymerases since these proteins were first discovered in 1960—some of the details are actually still murky.

▲ RNA polymerase transcribes DNA to make messenger RNA (mRNA).

The biggest obstacle to learning more has been a lack of tools. Until fairly recently, researchers were unable to get a picture at the atomic level of the giant RNA polymerase protein assemblies inside cells to understand how the many pieces of this amazing, living machine do what they do, and do it so well.

But our understanding is improving fast, thanks to spectacular technological advances. We have new X-ray pictures that are far more sophisticated than those that revealed the structure of DNA. Roger Kornberg of Stanford University in California used such methods to determine the structure of RNA polymerase. This work earned



▲ The mRNA sequence (dark red strand) is complementary to the DNA sequence (blue strand).

▲ On ribosomes, transfer RNA (tRNA) helps convert mRNA into protein.

▲ Amino acids link up to make a protein.