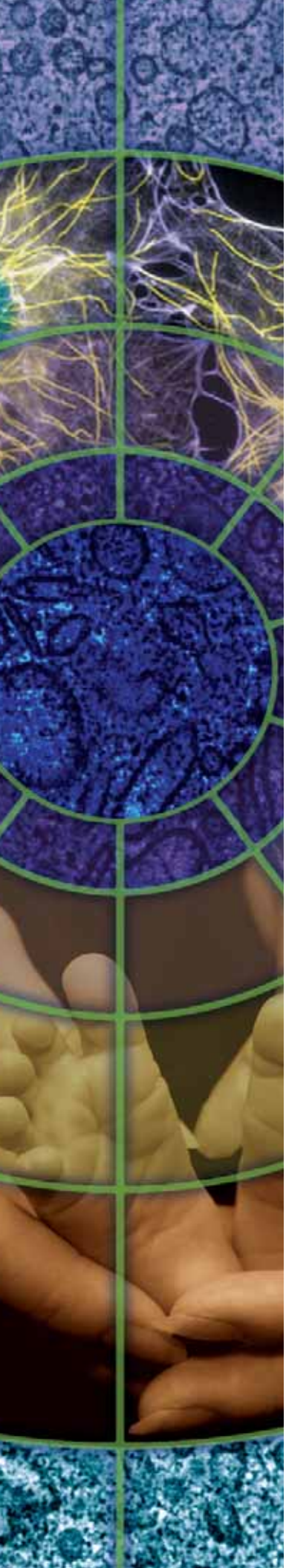
Inside the Cell

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

What Is NIGMS?

The National Institute of General Medical Sciences (NIGMS) supports basic biomedical research on genes, proteins, and cells. It also funds studies on fundamental processes such as how cells communicate, how our bodies use energy, and how we respond to medicines. The results of this research increase our understanding of life and lay the foundation for advances in the diagnosis, treatment, and prevention of disease. The Institute's research training programs produce the next generation of biomedical scientists, and NIGMS has programs to encourage minorities underrepresented in biomedical and behavioral science to pursue research careers. NIGMS supported the research of most of the scientists mentioned in this booklet.



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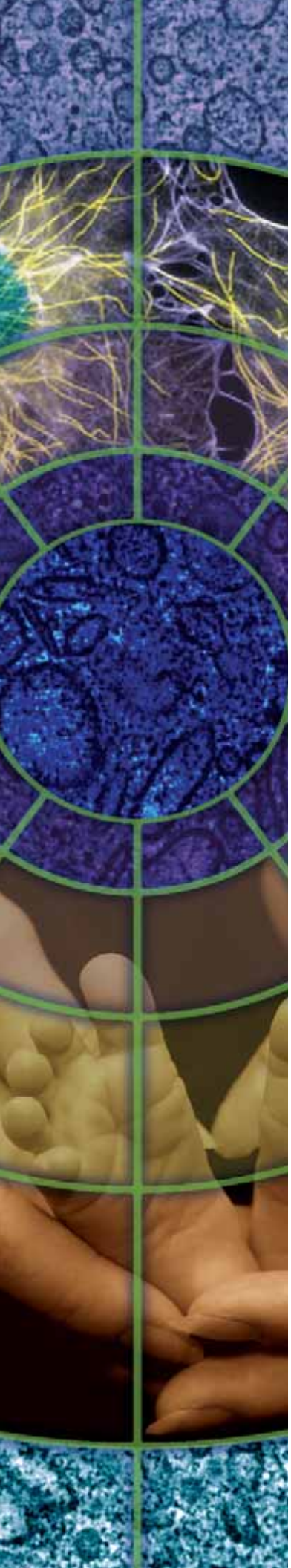


Contents

The Microscopic Metropolis Inside You

At this very moment, electricity is zapping through your brain, voracious killers are coursing through your veins, and corrosive chemicals sizzle in bubbles from your head to your toes. In fact, your entire body is like an electrical company, chemical factory, transportation grid, communications network, detoxification facility, hospital, and battlefield all rolled into one. The workers in each of these industries are your cells.

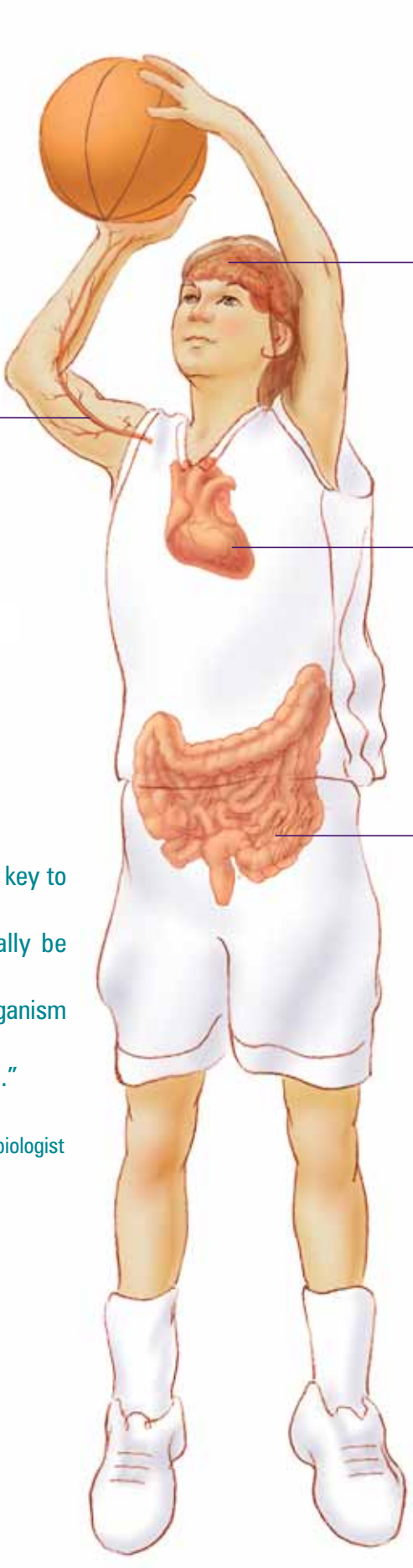
Cells are the smallest form of life—the functional and structural units of all living things. Your body contains trillions of cells, organized into more than 200 major types.

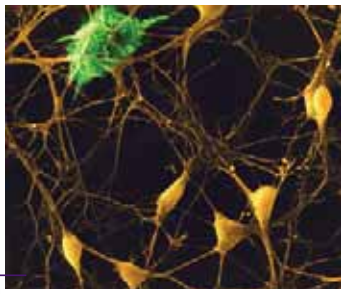
At any given time, each cell is doing thousands of jobs. Some of these tasks are so essential for life that they are carried out by virtually all cells. Others are done only by cells that are highly skilled for the work, whether it is covering up your insides (skin cells), preventing you from sloshing around like a pile of goo (bone cells), purging your body of toxic chemicals (liver cells), or enabling you to learn and remember (brain cells). Cells also must make the products your body needs, such as sweat, saliva, enzymes, hormones, and antibodies.

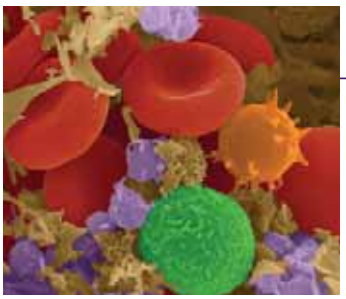
In **Chapter 1, "An Owner's Guide to the Cell,"** we'll explore some of the basic structures that allow cells to accomplish their tasks and some of the ways scientists study cells. In **Chapter 2, "Cells 101: Business Basics,"** we'll focus on the functions shared by virtually all cells: making fuel and proteins, transporting materials, and disposing of wastes. In **Chapter 3, "On the Job: Cellular Specialties,"** we'll learn how cells specialize to get their unique jobs done. In **Chapters 4, "Cellular Reproduction: Multiplication by Division,"** and **5, "The Last Chapter: Cell Aging and Death,"** we'll find out how cells reproduce, age, and die.

Much of the research described in this booklet is carried out by cell biologists at universities and other institutions across the nation who are supported by U.S. tax dollars, specifically those distributed by the National Institute of General Medical Sciences (NIGMS), a component of the National Institutes of Health. NIGMS is keenly interested in cell biology because knowledge of the inner workings of cells underpins our understanding of health and disease.

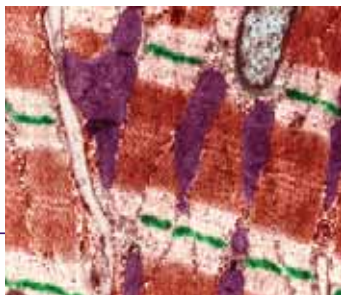
Although scientists daily learn more about cells and their roles in our bodies, the field is still an exciting frontier of uncharted territory and unanswered questions. Maybe someday, you will help answer those questions.



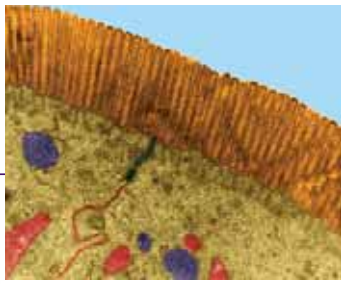




Blood Cells



Heart Muscle Cells



Small Intestine Cells

"Long ago it became evident that the key to every biological problem must finally be sought in the cell; for every living organism is, or at some time has been, a cell."

— E.B. Wilson (1856–1939) famous cell biologist

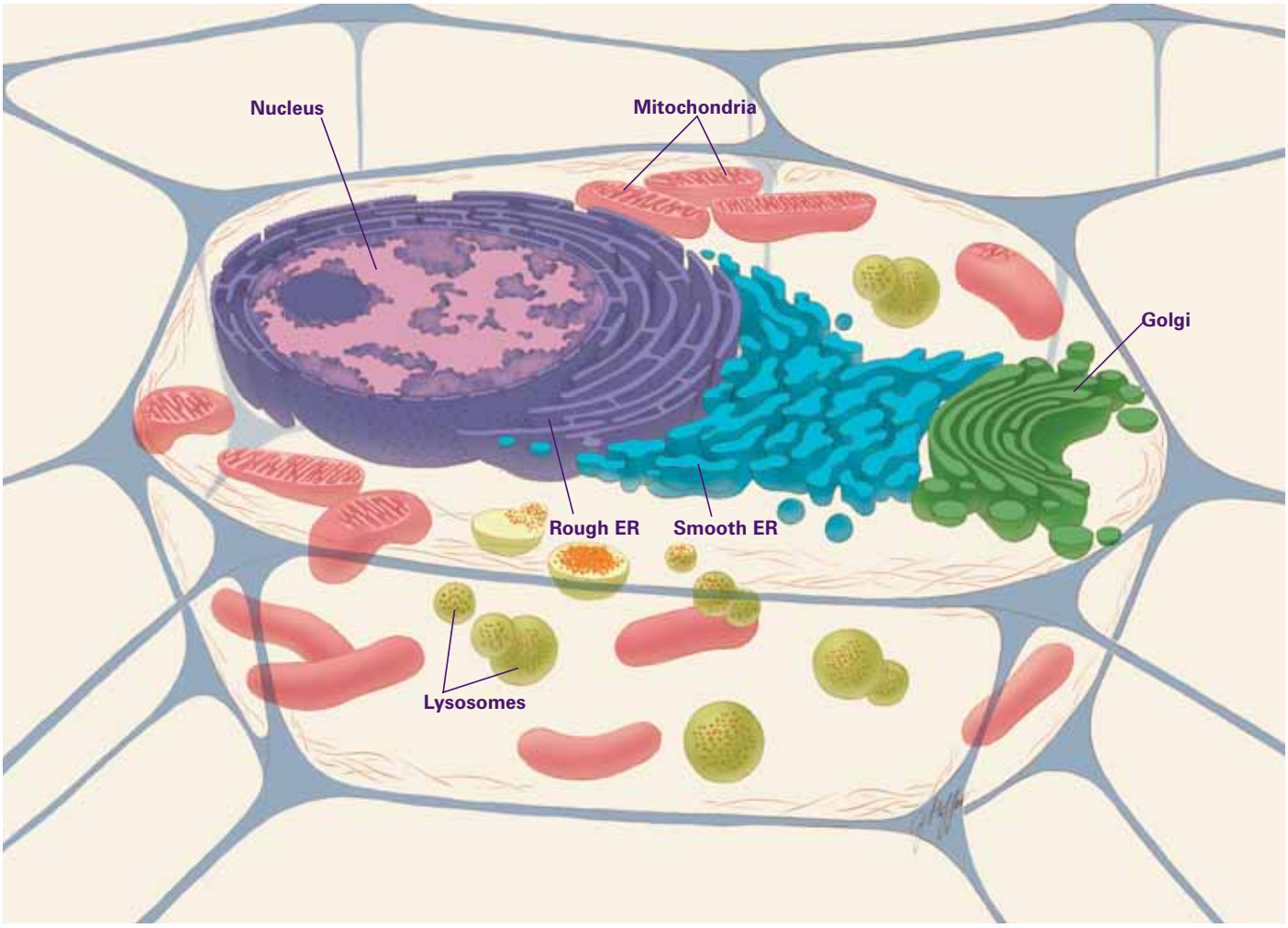
Your body contains many different cell types, each customized for a particular role. Red blood cells carry life-giving oxygen to every corner of your body, white blood cells kill germ invaders, intestinal cells squirt out chemicals that chisel away at your food so you can absorb its nutrients, nerve cells sling chemical and electrical messages that allow you to think and move, and heart cells constantly pump blood, enabling life itself.

An Owner's Guide to the Cell

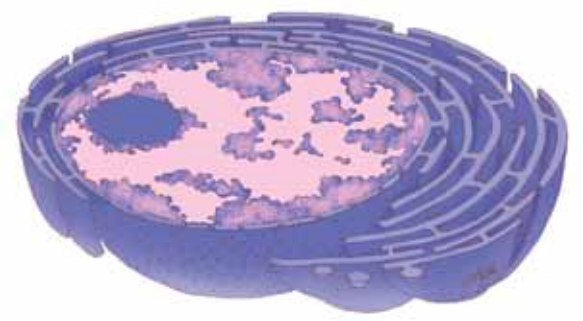
Welcome! I hope the transformation wasn't too alarming. You have shrunk down to about 3 millionths of your normal size. You are now about 0.5 **micrometers** tall (a micrometer is 1/1000 of a millimeter). But don't worry, you'll return to your normal size before you finish this chapter.

At this scale, a medium-sized human **cell** looks as long, high, and wide as a football field. But from where we are, you can't see nearly that far. Clogging your view is a rich stew of molecules, fibers, and various cell structures called **organelles**. Like the internal **organs** in your body, organelles in the cell each have a unique biological role to play.

Now that your eyes have adjusted to the darkness, let's explore, first-hand and up close, the amazing world inside a cell.



A typical animal cell, sliced open to reveal cross-sections of organelles.

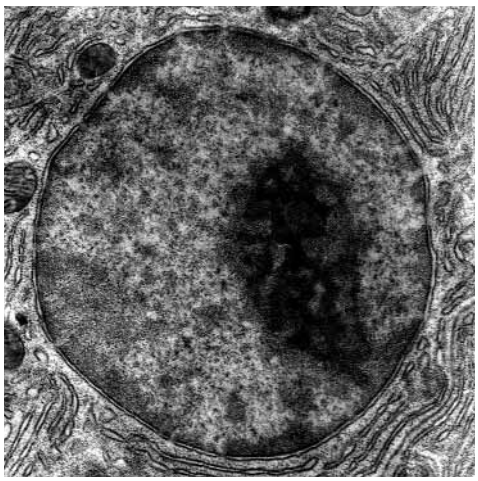


Nucleus: The Cell's Brain

Look down. Notice the slight curve? You're standing on a somewhat spherical structure about 50 feet in diameter. It's the **nucleus**—basically the cell's brain.

The nucleus is the most prominent organelle and can occupy up to 10 percent of the space inside a cell. It contains the equivalent of the cell's gray matter—its genetic material, or **DNA**. In the form of **genes**, each with a host of helper molecules, DNA determines the cell's identity, masterminds its activities, and is the official cookbook for the body's **proteins**.

Go ahead—jump. It's a bit springy, isn't it? That's because the nucleus is surrounded by two pliable **membranes,** together known as the **nuclear envelope**. Normally, the nuclear envelope

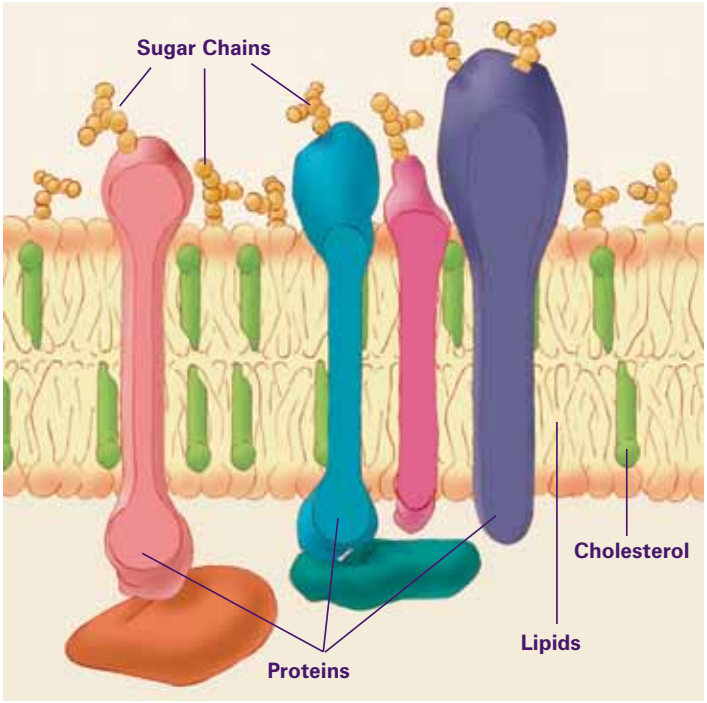


is pockmarked with octagonal pits about an inch across (at this scale) and hemmed in by raised sides. These **nuclear pores** allow chemical messages to exit and enter the nucleus. But we've cleared the nuclear pores off this area of the nucleus so you don't sprain an ankle on one.

If you exclude the nucleus, the rest of the cell's innards are known as the **cytoplasm**.

EUKARYOTIC CELLS	PROKARYOTIC CELLS
The cells of "complex" organisms, including all plants and animals	"Simple" organisms, including bacteria and blue-green algae
Contain a nucleus and many other organelles, each surrounded by a membrane (the nucleus and mitochondrion have two membranes)	Lack a nucleus and other membrane-encased organelles
Can specialize for certain functions, such as absorbing nutrients from food or transmitting nerve impulses; groups of cells can form large, multicellular organs and organisms	Usually exist as single, virtually identical cells
Most animal cells are 10–30 micrometers across, and most plant cells are 10–100 micrometers across	Most are 1–10 micrometers across

Virtually all forms of life fall into one of two categories: **eukaryotes** or **prokaryotes**.



The membrane that surrounds a cell is made up of proteins and lipids. Depending on the membrane's location and role in the body, lipids can make up anywhere from 20 to 80 percent of the membrane, with the remainder being proteins. **Cholesterol**, which is not found in plant cells, is a type of lipid that helps stiffen the membrane.

Cell Membrane: Specialist in Containing and Communicating

You may not remember it, but you crossed a membrane to get in here. Every cell is contained within a membrane punctuated with special gates, channels, and pumps. These gadgets let in—or force out—selected molecules. Their purpose is to carefully protect the cell's internal environment, a thick brew (called the **cytosol**) of salts, nutrients, and proteins that accounts for about 50 percent of the cell's volume (organelles make up the rest).

The cell's outer membrane is made up of a mix of proteins and **lipids** (fats). Lipids give membranes their flexibility. Proteins transmit chemical messages into the cell, and they also monitor and maintain the cell's chemical climate. On the outside of cell membranes, attached to some of the proteins and lipids, are chains of sugar molecules that help each cell type do its job. If you tried to bounce on the cell's outer surface as you did on the nuclear membrane, all these sugar molecules and protruding proteins would make it rather tricky (and sticky).

Endoplasmic Reticulum: Protein Clothier and Lipid Factory

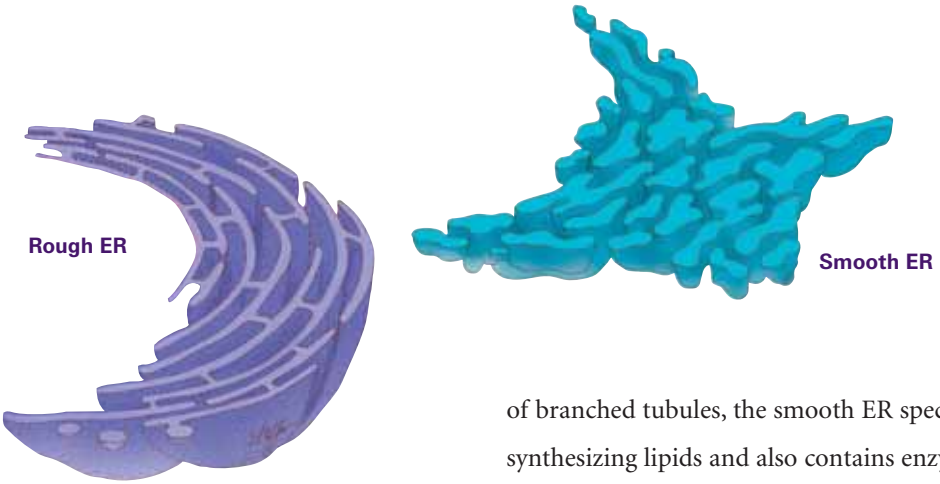
If you peer over the side of the nucleus, you'll notice groups of enormous, interconnected sacs snuggling close by. Each sac is only a few inches across but can extend to lengths of 100 feet or more. This network of sacs, the **endoplasmic reticulum** (ER), often makes up more than 10 percent of a cell's total volume.

Take a closer look, and you'll see that the sacs are covered with bumps about 2 inches wide. Those bumps, called **ribosomes**, are sophisticated molecular machines made up of more than 70 proteins and 4 strands of **RNA**, a chemical relative of DNA. Ribosomes have a critical job: assembling all the cell's proteins. Without ribosomes, life as we know it would cease to exist.

To make a protein, ribosomes weld together chemical building blocks one by one. As naked, infant protein chains begin to curl out of ribosomes, they thread directly into the ER. There, hard-working **enzymes** clothe them with specialized strands of sugars.

Now, climb off the nucleus and out onto the ER. As you venture farther from the nucleus, you'll notice the ribosomes start to thin out. Be careful! Those ribosomes serve as nice hand- and footholds now. But as they become scarce or disappear, you could slide into the smooth ER, unable to climb out.

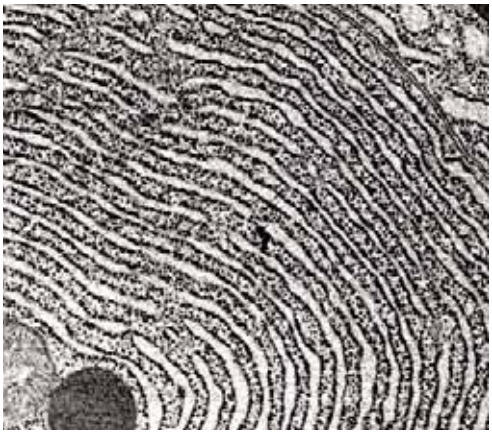
In addition to having few or no ribosomes, the smooth ER has a different shape and function than the ribosome-studded rough ER. A labyrinth



The endoplasmic reticulum comes in two types: Rough ER is covered with ribosomes and prepares newly made proteins; smooth ER specializes in making lipids and breaking down toxic molecules.

of branched tubules, the smooth ER specializes in synthesizing lipids and also contains enzymes that break down harmful substances. Most cell types have very little smooth ER, but some cells—like those in the liver, which are responsible for neutralizing toxins—contain lots of it.

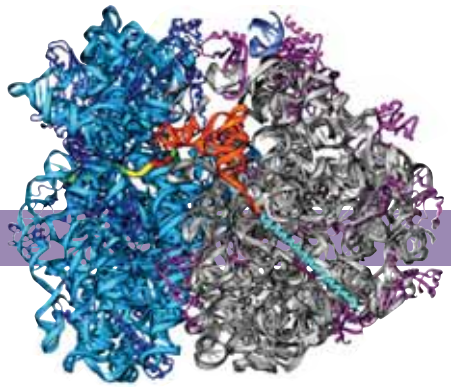
Next, look out into the cytosol. Do you see some free-floating ribosomes? The proteins made on those ribosomes stay in the cytosol. In contrast, proteins made on the rough ER's ribosomes end up in other organelles or are sent out of the cell to function elsewhere in the body. A few examples of proteins that leave the cell (called secreted proteins) are **antibodies**, insulin, digestive enzymes, and many **hormones**.



SUSUMU ITO

Rough ER

Rx: Ribosome Blockers



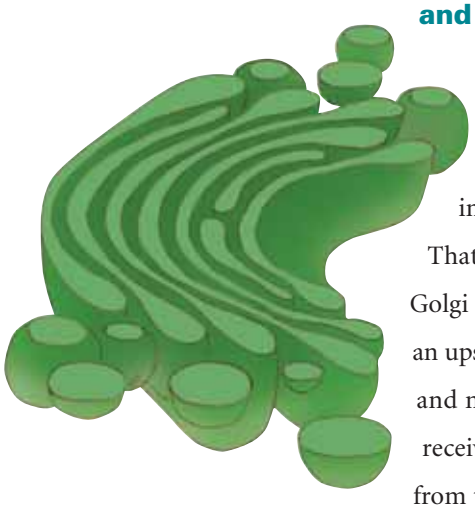
In a dramatic technical feat, scientists obtained the first structural snapshot of an entire ribosome in 1999. This more recent image captures a bacterial ribosome in the act of making a protein (the long, straight spiral in the lightest shade of blue). It also shows that—unlike typical cellular machines, which are clusters of proteins (shown here as purple ribbons)—ribosomes are composed mostly of RNA (the large, light blue and grey loopy ladders). Detailed studies of ribosomal structures could lead to improved antibiotic medicines.

IMAGE COURTESY OF HARRY NOLLER

All cellular organisms, including **bacteria**, have ribosomes. And all ribosomes are composed of proteins and ribosomal RNA. But the precise shapes of these biological machines differ in several very specific ways between humans and bacteria. That's a good thing for researchers trying to develop bacteria-killing medicines called antibiotics because it means that scientists may be able to devise therapies that knock out bacterial ribosomes (and the bacteria along with them) without affecting the human hosts.

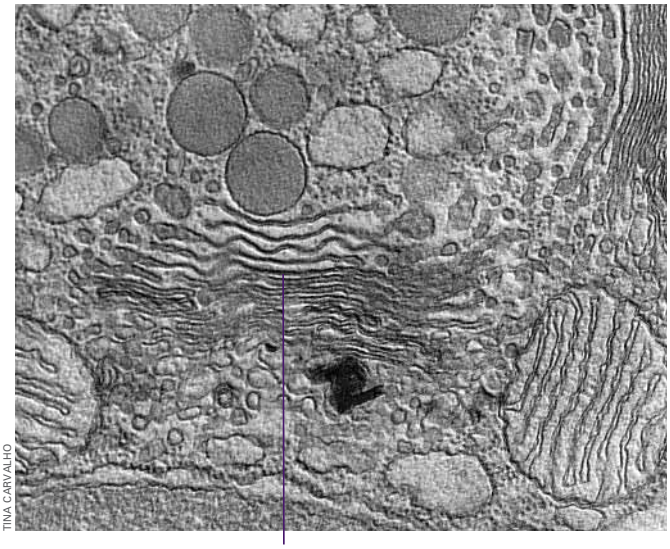
Several antibiotic medicines currently on the market work by inhibiting the ribosomes of bacteria that cause infections. Because many microorganisms have developed resistance to these medicines, we urgently need new antibiotics to replace those that are no longer effective in fighting disease.

Using sophisticated imaging techniques like X-ray crystallography, researchers have snapped molecular pictures of antibiotics in the act of grabbing onto a bacterial ribosome. Studying these three-dimensional images in detail gives scientists new ideas about how to custom design molecules that grip bacterial ribosomes even more strongly. Such molecules may lead to the development of new and more effective antibiotic drugs. —*Alison Davis*



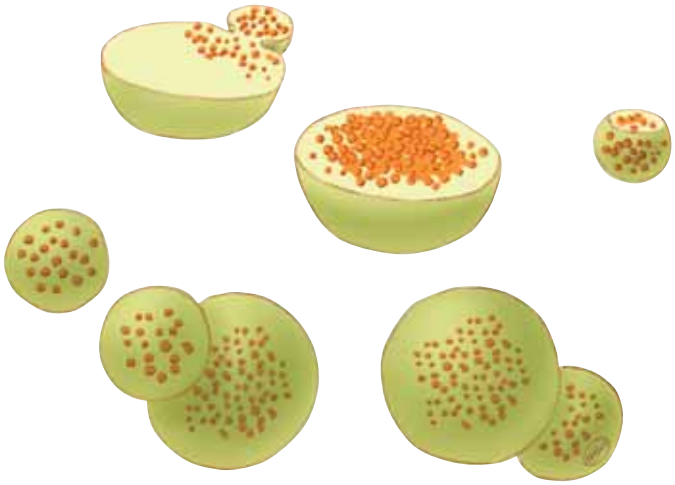
Golgi: Finishing, Packaging, and Mailing Centers

Now, let's slog through the cytosol a bit. Notice that stack of a half dozen flattened balloons, each a few inches across and about 2 feet long? That's the **Golgi** complex, also called the Golgi apparatus or, simply, the Golgi. Like an upscale gift shop that monograms, wraps, and mails its merchandise, the Golgi receives newly made proteins and lipids from the ER, puts the finishing touches on them, addresses them, and sends them to their final destinations. One of the places these molecules can end up is in **lysosomes**.



TINA CARVALHO

Golgi



Lysosomes: Recycling Centers and Garbage Trucks

See that bubble about 10 feet across? That's a lysosome. Let's go—I think you'll like this. Perhaps even more than other organelles, lysosomes can vary widely in size—from 5 inches to 30 feet across.

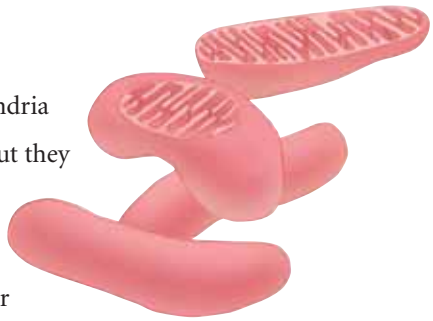
Go ahead, put your ear next to it. Hear the sizzling and gurgling? That's the sound of powerful enzymes and acids chewing to bits anything that ends up inside.

But materials aren't just melted into oblivion in the lysosome. Instead, they are precisely chipped into their component parts, almost all of which the cell recycles as nutrients or building blocks. Lysosomes also act as cellular garbage trucks, hauling away unusable waste and dumping it outside the cell. From there, the body has various ways of getting rid of it.

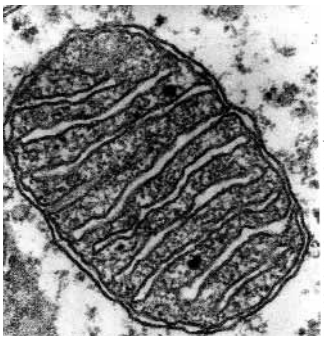
Mitochondria: Cellular Power Plants

Blink. Breathe. Wiggle your toes. These subtle movements—as well as the many chemical reactions that take place inside organelles—require vast amounts of cellular energy. The main energy source in your body is a small molecule called **ATP**, for adenosine triphosphate.

ATP is made in organelles called **mitochondria**. Let's see if we can find some. They look like blimps about as long as pickup trucks but somewhat narrower. Oh, a few of them are over there. As we get nearer, you may hear a low whirring or humming sound, similar to that made by a power station. It's no coincidence. Just as power plants convert energy from fossil fuels or hydroelectric dams into electricity, mitochondria convert energy from your food into ATP.



Like all other organelles, mitochondria are encased in an outer membrane. But they also have an inner membrane. Remarkably, this inner membrane is four or five times larger than the outer membrane. So, to fit inside the organelle, it doubles over in many places, extending long, fingerlike folds into the center of the organelle. These folds serve an important function: They dramatically increase the surface area available to the cell machinery that makes ATP. In other words, they vastly increase the ATP-production capacity of mitochondria.

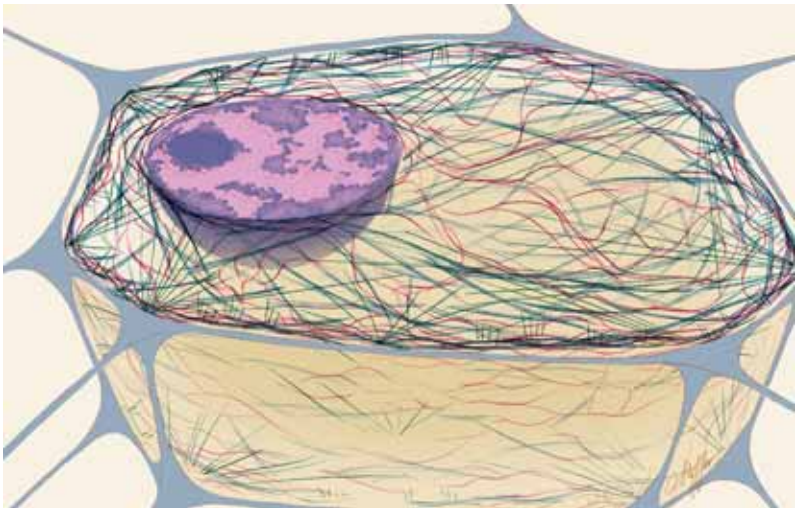


D.S. FRIEND, BRIGHAM AND WOMEN'S HOSPITAL

The mazelike space inside mitochondria is filled with a strong brew of hundreds of enzymes, DNA (mitochondria are the only organelles to have their own genetic material), special mitochondrial ribosomes, and other molecules necessary to turn on mitochondrial genes.

	ACTUAL SIZE (AVERAGE)	PERCEIVED SIZE WHEN MAGNIFIED 3 MILLION TIMES
Cell diameter	30 micrometers*	300 feet
Nucleus diameter	5 micrometers	50 feet
Mitochondrion length	Typically 1–2 micrometers but can be up to 7 micrometers long	18 feet
Lysosome diameter	50–3,000 **nanometers***	5 inches to 30 feet
Ribosome diameter	20–30 nanometers	2–3 inches
Microtubule width	25 nanometers	3 inches
Intermediate filament width	10 nanometers	1.2 inches
Actin filament width	5–9 nanometers	0.5–1 inch

*A micrometer is one millionth (10^{-6}) of a meter. A nanometer is one billionth (10^{-9}) of a meter.



The three fibers of the cytoskeleton—microtubules in blue, intermediate filaments in red, and actin in green—play countless roles in the cell.

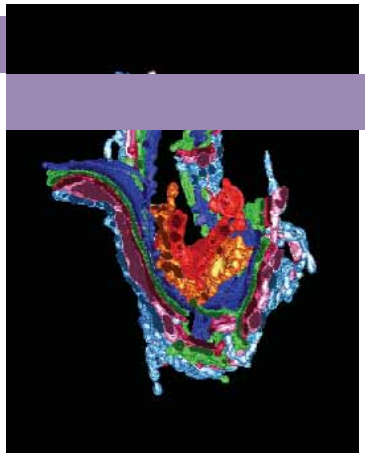
Cytoskeleton: The Cell's Skeleton...and More

Now, about all those pipes, ropes, and rods you've been bumping into. Together, they are called the **cytoskeleton**—the cell's skeleton. Like the bony skeletons that give us stability, the cytoskeleton gives our cells shape, strength, and the ability to move, but it does much more than that.

Think about your own cells for a moment. Right now, some of your cells are splitting in half, moving, or changing shape. If you are a man, your sperm use long tails called **flagella** to swim. If you are a woman, hairlike fibers called **cilia** sweep newly released eggs from your ovaries into your uterus. And all that is thanks to the cytoskeleton.

As you can see, the cytoskeleton is incredibly versatile. It is made up of three types of fibers that constantly shrink and grow to meet the needs of the cell: **microtubules**, **intermediate filaments**, and **actin filaments**. Each type of fiber looks, feels, and functions differently.

The 3-inch-wide flexible pipes you just banged your head on are called microtubules. Made of the strong protein tubulin, microtubules are the heavy lifters of the cytoskeleton. They do the tough



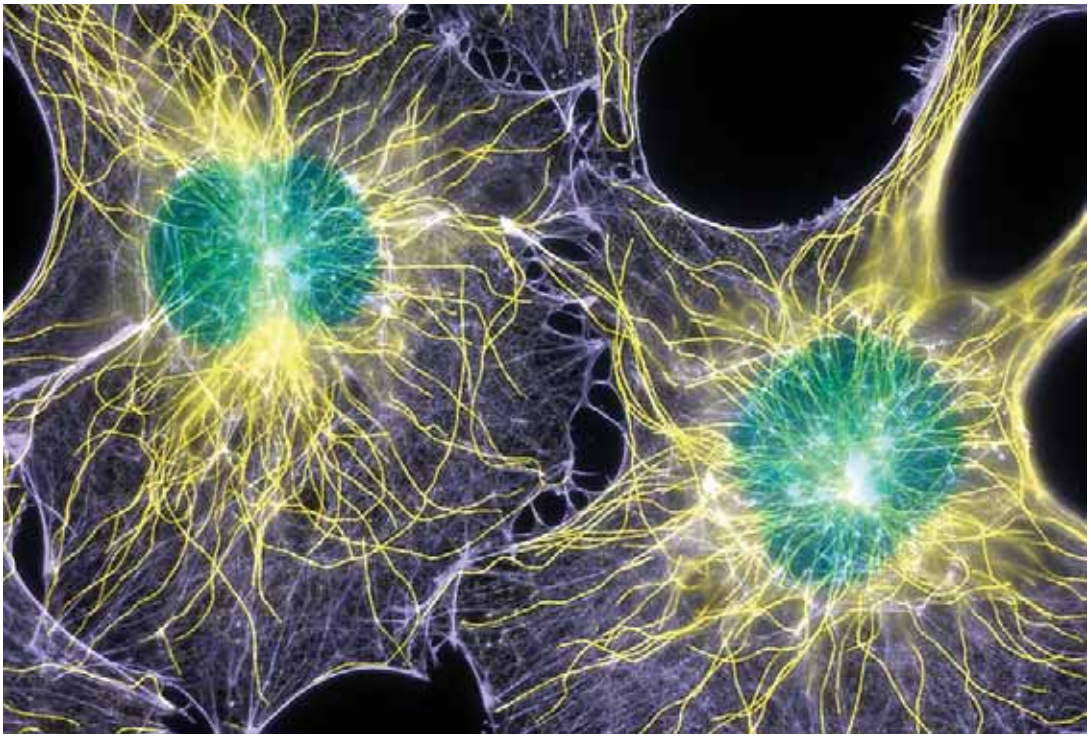
KATHRYN HOWELL

Golgi Spelunking: Exit Here, There, But Not Anywhere

Scientists use a variety of techniques to study organelles like the endoplasmic reticulum and Golgi, gaining ever more detailed understanding of these minute but very complicated structures. For example, Kathryn Howell of the University of Colorado School of Medicine in Denver uses a specialized high-voltage electron microscope, rapid freezing methods, and a computer modeling program to obtain a vivid three-dimensional view of the Golgi and the pathways that proteins use to exit it.

Howell begins by quick-freezing living cells, embedding them in plastic, and slicing the plastic-coated sample into thin sections. As she tilts the microscope stage, she can capture many images of the same region of the sample. A computer assembles these images to form a three-dimensional view, called a tomogram, of the Golgi and other organelles. Based on the tomogram, Howell's research team can produce a movie of a virtual journey through the cell. You can see one such movie at http://publications.nigms.nih.gov/insidethecell/extras.

Howell's research shows that there are several pathways for proteins and other molecules to exit the Golgi. The findings are revealing, as earlier studies using different methods had suggested that there was only one road out of this organelle. No doubt new chapters to this story will be written as biologists and computer scientists create even more sophisticated tools for imaging cells. —*A.D.*



TORSTEN WITTMANN

In these cells, actin filaments appear light purple, microtubules yellow, and nuclei greenish blue. This image, which has been digitally colored, won first place in the 2003 Nikon Small World Competition.

physical labor of separating duplicate **chromosomes** when cells copy themselves and serve as sturdy railway tracks on which countless molecules and materials shuttle to and fro. They also hold the ER and Golgi neatly in stacks and form the main component of flagella and cilia.

Grab one of those inch-thick ropes. Yeah, you can swing on it—it won't snap. These strands, called intermediate filaments, are unusual because they vary greatly according to their location and function in the body. For example, some intermediate filaments form tough coverings, such as in nails, hair, and the outer layer of skin (not to mention animal claws and scales). Others are found in nerve cells, muscle cells, the heart, and internal organs. In each of these **tissues**, the filaments are made of different proteins. So if doctors analyze intermediate filaments in tumors, they can determine the origin of—and possible treatments for—some kinds of cancer.

See that bundle of long rods near the edge of the cell? You can touch it, but don't try to bend the rods. They shatter easily. These rods, slightly thinner than intermediate filaments, are actin filaments. They are made up of two chains of the protein actin twisted together. Although actin filaments are the most brittle of the cytoskeletal fibers, they are also the most versatile in terms of the shapes they can take. They can gather together into bundles, weblike networks, or even three-dimensional gels. They shorten or lengthen to allow cells to move and change shape. Together with a protein partner called myosin, actin filaments make possible the muscle contractions necessary for everything from your action on a sports field to the automatic beating of your heart.

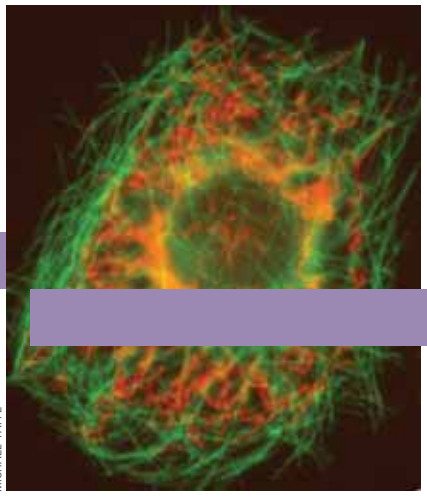
The Tour Ends Here

You've seen quite a bit of the cell in a short time. However, this tour covered only the highlights; there are many other fascinating processes that occur within cells. Every day, cell biologists learn more, but much remains unexplained.

You will now regain your normal size. There should be no lasting side effects of the miniaturization, except, I hope, a slight tingling sensation caused by new knowledge and a growing excitement about what scientists know—and still don't know—about cells.

Cool Tools for Studying Cells

Cell biologists would love to do what you just did—shrink down and actually see, touch, and hear the inner workings of cells. Because that's impossible, they've developed an ever-growing collection of approaches to study cellular innards from the outside. Among them are biochemistry, physical analysis, microscopy, computer analysis, and molecular genetics. Using these techniques, researchers can exhaustively inventory the individual molecular bits and pieces that make up cells, eavesdrop on cellular communication, and spy on cells as they adapt to changing environments. Together, the approaches provide vivid details about how cells work together in the body's organs and tissues. We'll start by discussing the traditional tools of the trade—microscopes—then touch on the new frontiers of quantum dots and **computational biology**.



MICHAEL YAFFE

In this fruit fly cell, mitochondria (in red) form a web throughout the cell. Microtubules are labeled in green.

Morphing Mitochondria

Scientists such as Michael P. Yaffe of the University of California, San Diego, study what mitochondria look like and how they change throughout a cell's life. To approach this research problem, Yaffe uses simple organisms—such as yeast or fruit fly cells—which, like your own cells, have membranes, a nucleus, and other organelles. This similarity makes these organisms important models for understanding human biology.

Yaffe's work helped change the textbook depiction of mitochondria as kidney bean-shaped organelles. Using advanced microscopy, Yaffe and others have unveiled many different shapes for mitochondria, ranging from the classic beans to long snakes and weblike structures, all of which are thought to change on a constant basis. Researchers are discovering that the different mitochondrial shapes accompany changes in cellular needs, such as when growing cells mature into specific types or when a cell responds to disease.

Many scientists believe that mitochondria—which divide on their own, have their own **genome** and protein-making machinery, and resemble prokaryotes in many ways—are descendents of oxygen-loving microorganisms that were taken in by primitive cells. This historical event set the stage for advanced life forms like plants and animals. —*A.D.*

Light Microscopes: The First Windows Into Cells

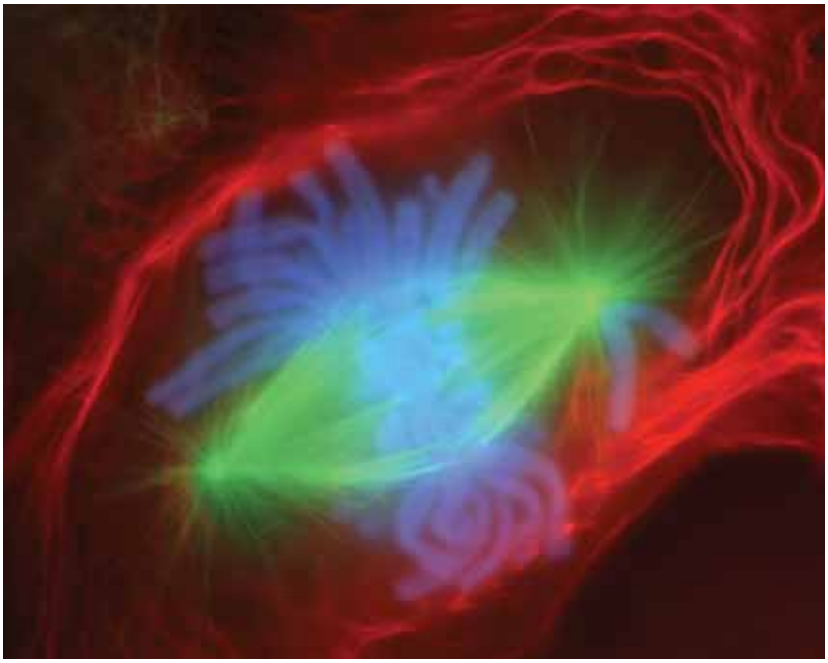
Scientists first saw cells by using traditional light microscopes. In fact, it was Robert Hooke (1635–1703), looking through a microscope at a thin slice of cork, who coined the word "cell." He chose the word to describe the boxlike holes in the plant cells because they reminded him of the cells of a monastery.

Scientists gradually got better at grinding glass into lenses and at whipping up chemicals to selectively stain cellular parts so they could see them better. By the late 1800s, biologists already had identified some of the largest organelles (the nucleus, mitochondria, and Golgi).

Researchers using high-tech light microscopes and glowing molecular labels can now watch biological processes in real time. The scientists start by chemically attaching a fluorescent dye or protein to a molecule that interests them. The colored glow then allows the scientists to locate the molecules in living cells and to track processes—such as cell movement, division, or infection—that involve the molecules.

Robert Hooke, the British scientist who coined the word "cell," probably used this microscope when he prepared *Micrographia*. Published in 1665, *Micrographia* was the first book describing observations made through a microscope. It was a best-seller.

IMAGE COURTESY OF THE NATIONAL MUSEUM OF HEALTH AND MEDICINE, ARMED FORCES INSTITUTE OF PATHOLOGY, WASHINGTON, DC



CONLY RIEDER

This fireworks explosion of color is a dividing newt lung cell seen under a light microscope and colored using fluorescent dyes: chromosomes in blue, intermediate filaments in red, and spindle fibers (bundled microtubules assembled for cell division) in green.

Fluorescent labels come in many colors, including brilliant red, magenta, yellow, green, and blue. By using a collection of them at the same time, researchers can label multiple structures inside a cell and can track several processes at once. The technicolor result provides great insight into living cells—and is stunning cellular art.

Electron Microscopes: The Most Powerful of All

In the 1930s, scientists developed a new type of microscope, an **electron microscope** that allowed them to see beyond what some ever dreamed possible. The revolutionary concept behind the machine grew out of physicists' insights into the nature of electrons.

As its name implies, the electron microscope depends not on light, but on electrons. The microscopes accelerate electrons in a vacuum, shoot them out of an electron gun, and focus them

with doughnut-shaped magnets. As the electrons bombard the sample, they are absorbed or scattered by different cell parts, forming an image on a detection plate.

Although electron microscopes enable scientists to see things hundreds of times smaller than anything visible through light microscopes, they have a serious drawback: They can't be used to study living cells. Biological tissues don't survive the technique's harsh chemicals, deadly vacuum, and powerful blast of electrons.

TINA CARVALHO

Scanning electron microscopes allow scientists to see the three-dimensional surface of their samples.

Electron microscopes come in two main flavors: transmission and scanning. Some transmission electron microscopes can magnify objects up to 1 million times, enabling scientists to see **viruses** and even some large molecules. To obtain this level of detail, however, the samples usually must be sliced so thin that they yield only flat, two-dimensional images. Photos from transmission electron microscopes are typically viewed in black and white.

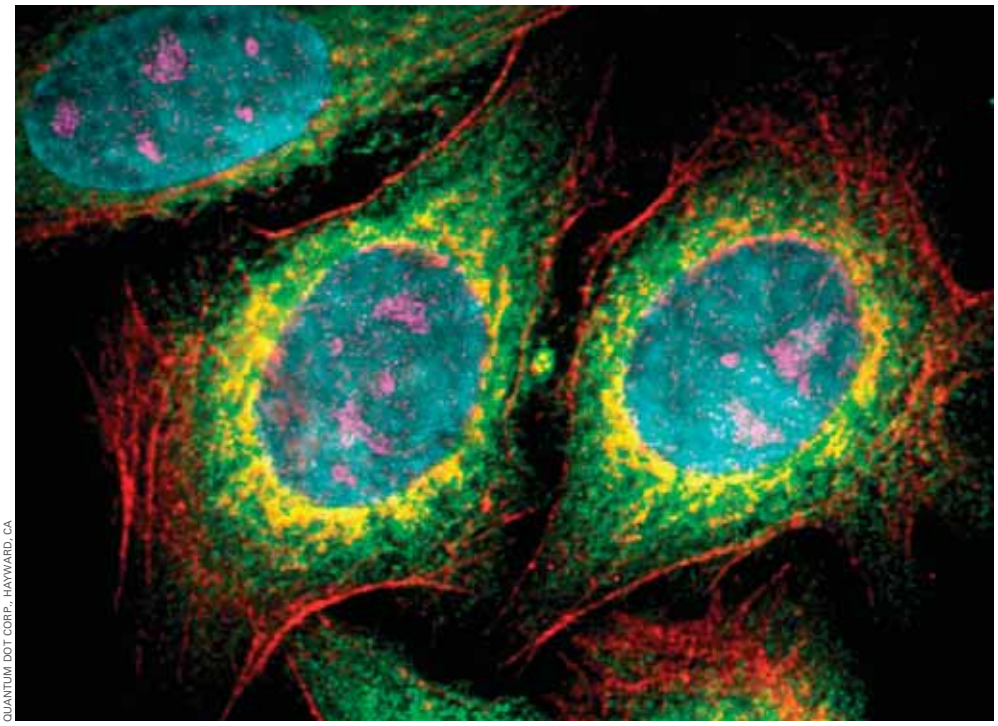
Scanning electron microscopes cannot magnify samples as powerfully as transmission scopes, but they allow scientists to study the often intricate surface features of larger samples. This provides a window to see up close the three-dimensional terrain of intact cells, material surfaces, microscopic organisms, and insects. Scientists sometimes use computer drawing programs to highlight parts of these images with color.

Studying Single Molecules: Connecting the Quantum Dots

Whether they use microscopes, genetic methods, or any other technique to observe specific molecules, scientists typically flag every molecule of a certain type, then study these molecules as a group. It's rather like trying to understand a profession—say, teaching, architecture, or medicine—by tagging and observing all the workers in that profession simultaneously. Although these global approaches have taught us a lot, many scientists long to examine individual molecules in real time—the equivalent of following individual teachers as they go about their daily routines.

Now, new techniques are beginning to allow scientists to do just that. One technology, called quantum dots, uses microscopic semiconductor crystals to label specific proteins and genes. The crystals, each far less than a millionth of an inch in diameter, radiate brilliant colors when exposed to ultraviolet light. Dots of slightly different sizes glow in different fluorescent colors—larger dots shine red, while smaller dots shine blue, with a rainbow of colors in between. Researchers can create up to 40,000 different labels by mixing quantum dots of different colors and intensities as an artist would mix paint. In addition to coming in a vast array of colors, the dots also are brighter and more versatile than more traditional fluorescent dyes: They can be used to visualize individual molecules or, like the older labeling techniques, to visualize every molecule of a given type.

Quantum dots promise to advance not only cell biology but also a host of other areas. Someday, the



QUANTUM DOT CORP., HAYWARD, CA

Dyes called quantum dots can simultaneously reveal the fine details of many cell structures. Here, the nucleus is blue, a specific protein within the nucleus is pink, mitochondria look yellow, microtubules are green, and actin filaments are red. Someday, the technique may be used for speedy disease diagnosis, DNA testing, or analysis of biological samples.

technology may allow doctors to rapidly analyze thousands of genes and proteins from cancer patients and tailor treatments to each person's molecular profile. These bright dots also could help improve the speed, accuracy, and affordability of diagnostic tests for everything from HIV infection to allergies. And, when hitched to medicines, quantum dots might deliver a specific dose of a drug directly to a certain type of cell.

Computers Clarify Complexity

Say you're hungry and stranded in a blizzard: If you eat before you seek shelter, you might freeze to death, but if you don't eat first, you might not have the strength to get yourself out of the storm. That's analogous to the decisions cells have to make every day to survive.

For years, scientists have examined cell behaviors—like the response to cold or hunger—one at a time. And even that they did bit by bit, laboriously hammering out the specific roles of certain molecules. This approach made it difficult or impossible to study the relative contributions of—and the interplay between—genes that share responsibility for cell behaviors, such as the 100 or so genes involved in the control of blood pressure.

Now, computers are allowing scientists to examine many factors involved in cellular behaviors and decisions all at the same time. The field of computational biology blossomed with the advent of high-end computers. For example, sequencing the 3.2 billion base pairs of the human genome, which was completed in 2003, depended on computers advanced enough to tackle the challenge. Now, state-of-the-art equipment and a wealth of biological data from genome projects and other technologies are opening up many new research opportunities in computer analysis and modeling. So, much as microscopes and biochemical techniques revolutionized cell biology centuries ago, computers promise to advance the field just as dramatically in this new century.

Science Schisms

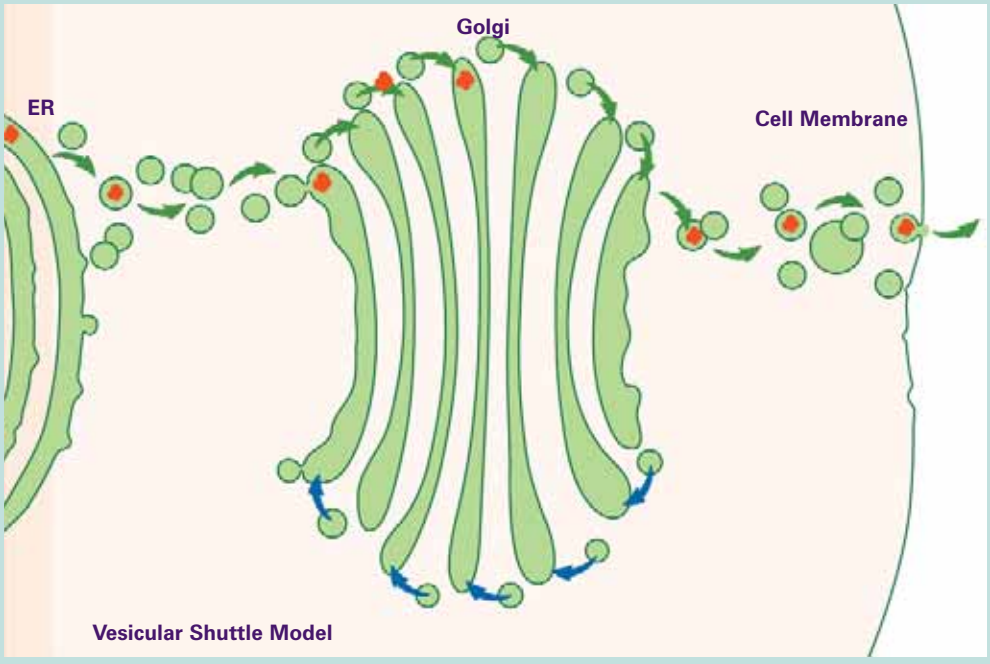
One great thing about science is that you're allowed to argue about your work.

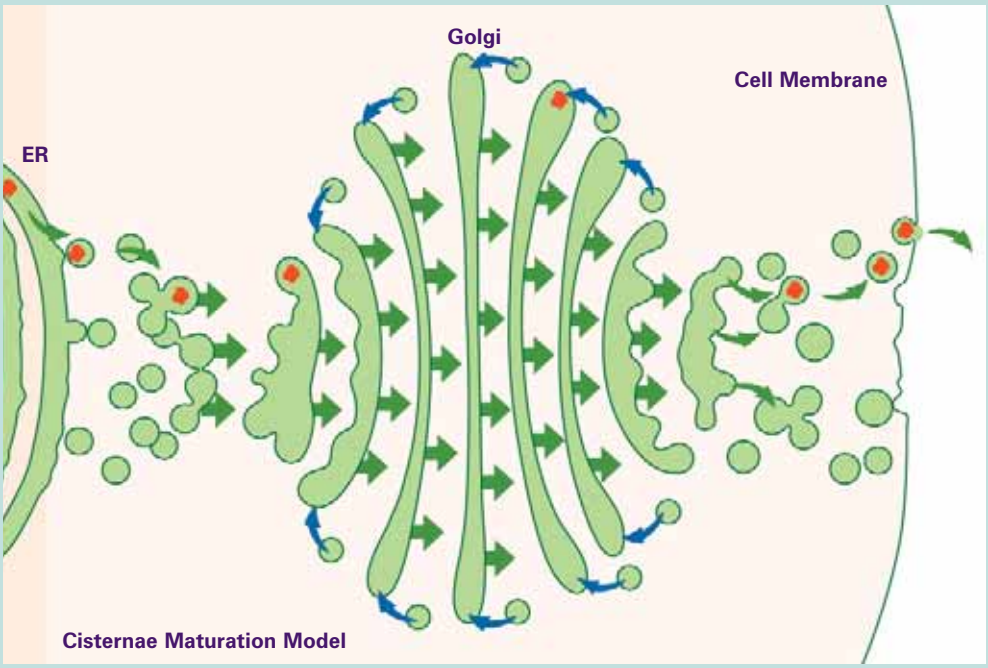
To gain new information, scientists ask a lot of questions. Often, the answers spur more questions. The never-ending circle not only feeds curiosity; it also can lead to important and sometimes unexpected breakthroughs. Sometimes, scientists studying the same topic but using different experimental approaches come up with different conclusions.

Take the Golgi, for example. Think it's noncontroversial? The details of how this organelle forms inside your cells have kept two camps of researchers in a lively battle.

On one side of the debate is Graham Warren of Yale University School of Medicine in New Haven, Connecticut, who argues that the Golgi is an architectural structure that cannot be made from scratch. He believes that newly made proteins are packaged in the rough ER and are sent for further processing to a pre-existing structure (the Golgi) that is made up of different compartments. This is called the vesicular shuttle model.

In living cells, material moves both forward (green arrows) and backward (blue arrows) from each tip of the Golgi. For simplicity, we have illustrated forward movement only on the top and backward movement only on the bottom of the Golgi cartoon.

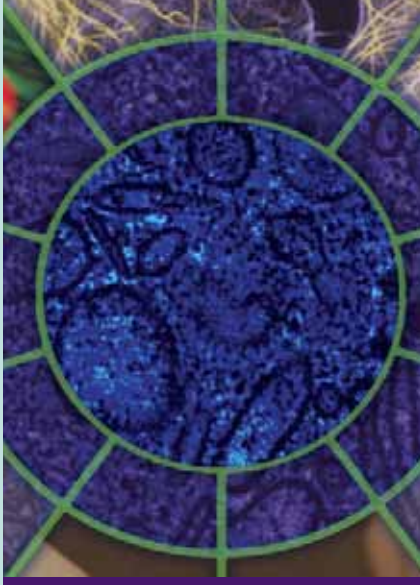




Cisternae Maturation Model

On the other side is Jennifer Lippincott-Schwartz of the National Institute of Child Health and Human Development (part of the National Institutes of Health) in Bethesda, Maryland. She says that the Golgi makes itself from scratch. According to her theory, packages of processing enzymes and newly made proteins that originate in the ER fuse together to form the Golgi. As the proteins are processed and mature, they create the next Golgi compartment. This is called the cisternae maturation model. You can see animations of the two different models at http://publications.nigms.gov/insidethecell.

Intriguing new data suggest that perhaps neither model is completely correct. This will likely lead to yet another model. You may not see what all the fuss is about, but the differing Golgi theories say very different things about how cells function. Understanding basic cellular processes, such as how the Golgi works, ultimately can have a profound impact on the development of methods to diagnose, treat, and prevent diseases that involve those processes.



Got It?

What are cells, and why is it important to study them?

List five different organelles and describe what they do.

Name three techniques that scientists use to study cells.

What are the differences between prokaryotic and eukaryotic cells?

Cells 101: Business Basics

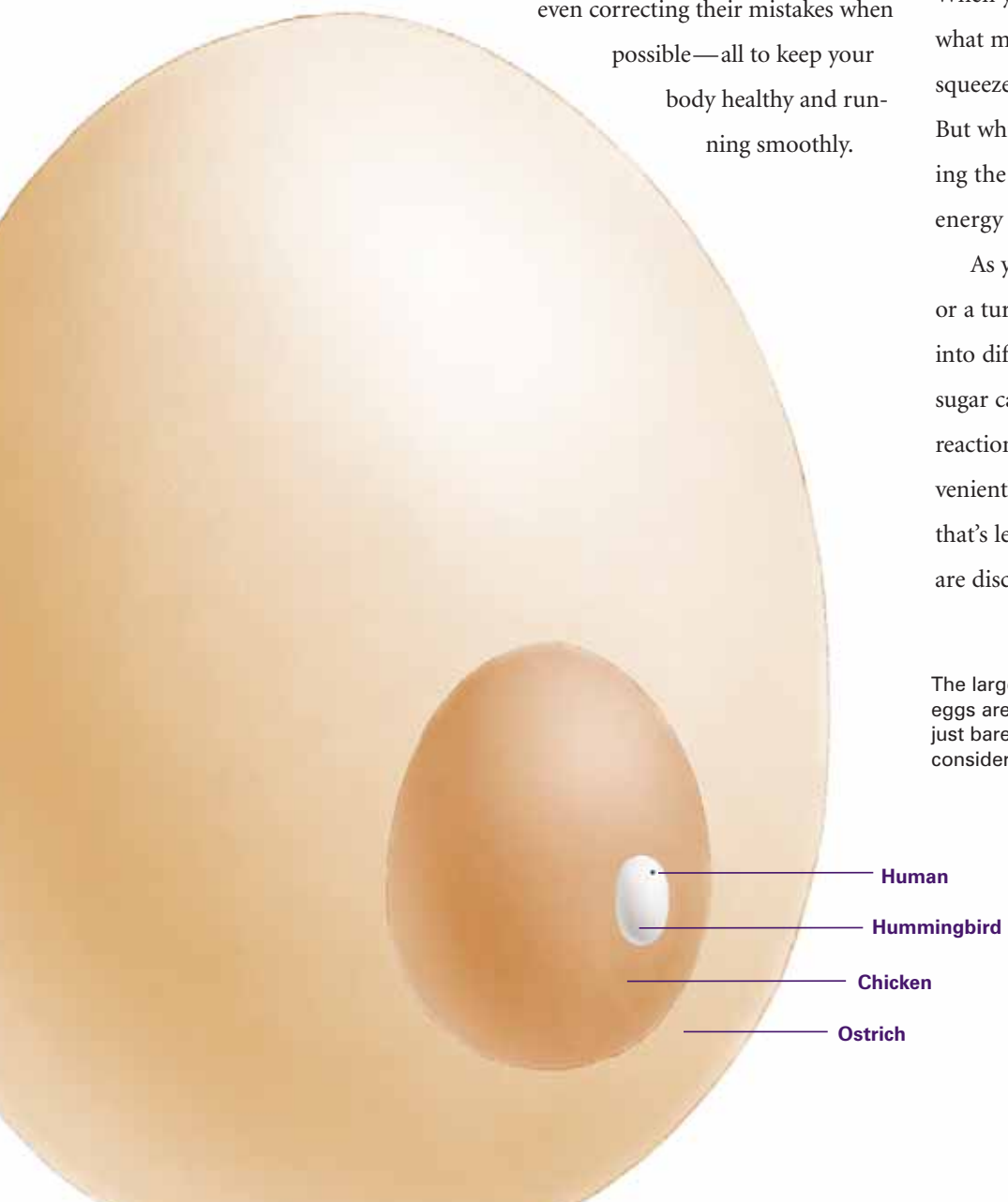
Performing as key actors in all living things, cells play an essential set of roles in your body. They roam around in your blood, come together to make organs and tissues, help you adjust to changes in your environment, and do any number of other important jobs. Far from being static structures, cells are constantly working, changing, sending and responding to chemical cues, even correcting their mistakes when possible—all to keep your body healthy and running smoothly.

This frenzied activity takes place with an intricacy and accuracy that nearly defies imagination. In this chapter, we'll focus on several of the basic functions that cells have in common: creating fuel, manufacturing proteins, transporting materials, and disposing of wastes.

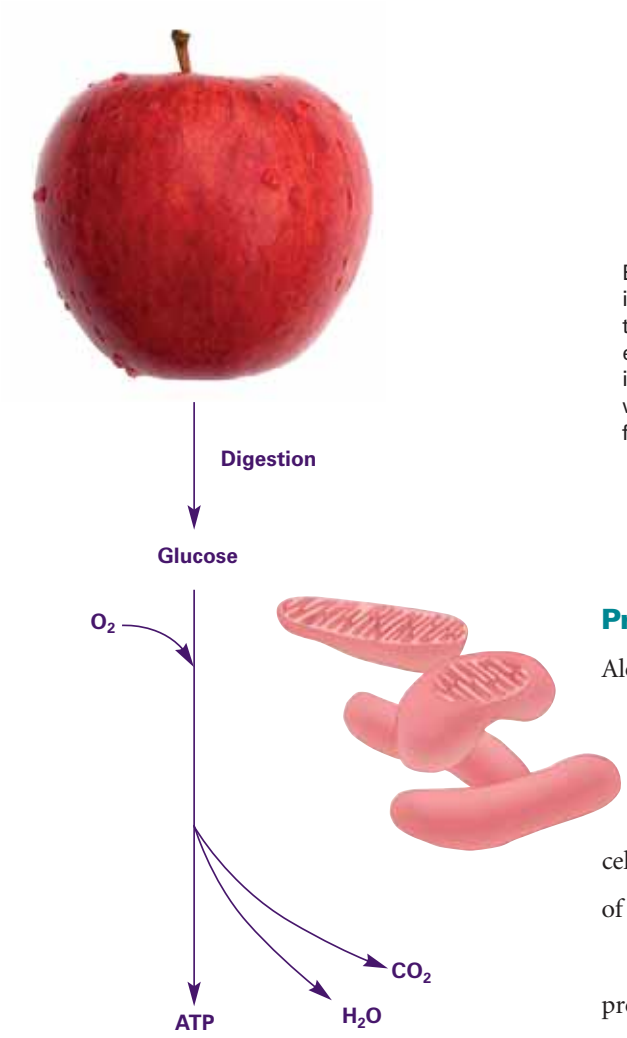
Got Energy?

When you think about food, protein, and energy, what may come to mind is the quick meal you squeeze in before racing off to your next activity. But while you move on, your cells are transforming the food into fuel (ATP in this case) for energy and growth.

As your digestive system works on an apple or a turkey sandwich, it breaks the food down into different parts, including molecules of a sugar called glucose. Through a series of chemical reactions, mitochondria transfer energy in conveniently sized packets from glucose into ATP. All that's left are carbon dioxide and water, which are discarded as wastes.



The largest human cell (by volume) is the egg. Human eggs are 150 micrometers in diameter and you can just barely see one with a naked eye. In comparison, consider the eggs of chickens…or ostriches!



Energy from the food you eat is converted in mitochondria into ATP. Cells use ATP to power their chemical reactions. For example, muscle cells convert ATP energy into physical work, allowing you to lift weights, jog, or simply move your eyeballs from side to side.

This process is extremely efficient. Cells convert nearly 50 percent of the energy stored in glucose into ATP. The remaining energy is released and used to keep our bodies warm. In contrast, a typical car converts no more than 20 percent of its fuel energy into useful work.

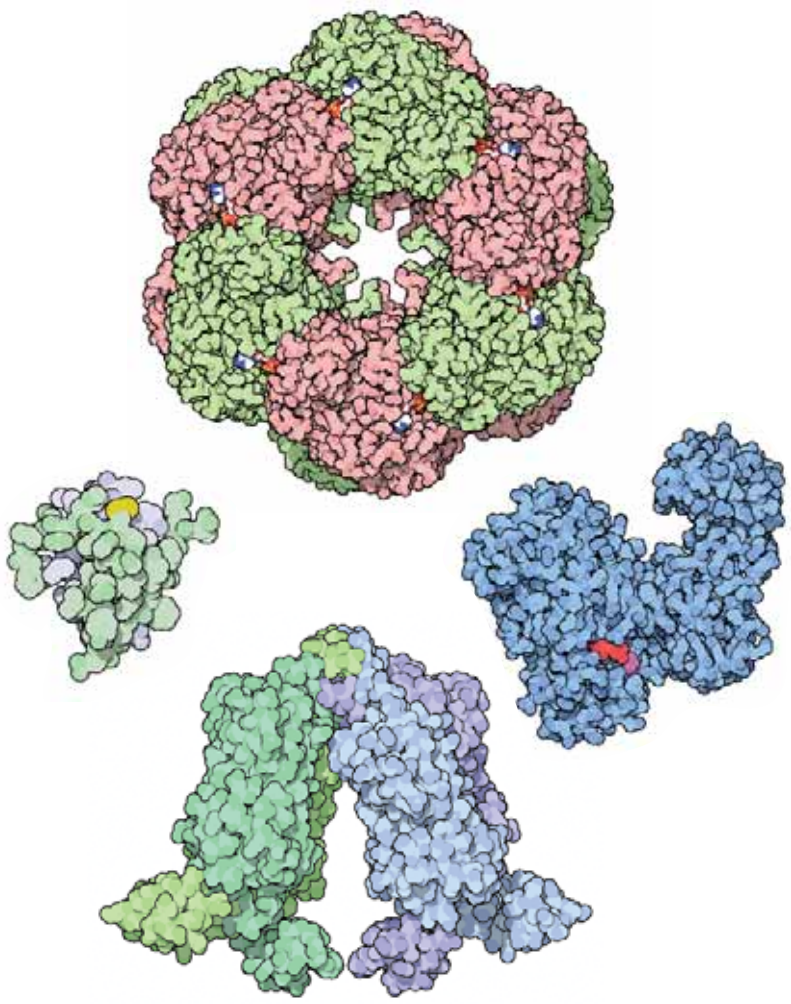
Your body uses ATP by breaking it apart. ATP stores energy in its chemical bonds. When one of these bonds is broken, loosing a chemical group called a phosphate, energy is released.

ATP is plentifully produced and used in virtually every type of cell. A typical cell contains about 1 billion molecules of ATP at any given time. In many cells, all of this ATP is used up and replaced every 1 to 2 minutes!

Priority: Proteins

Along with the fuel you need to keep moving, eating, thinking, and even sleeping, cells make other important products, including proteins. Scientists estimate that each of your cells contains about 10 billion protein molecules of approximately 10,000 different varieties.

The workhorse molecules of your cells, proteins are responsible for a wide range of tasks, including carrying oxygen in your blood (a protein called hemoglobin), digesting your food (enzymes like amylase, pepsin, and lactase), defending your body from invading microorganisms (antibodies), and speeding up chemical reactions inside your body (enzymes again—they're not all for digesting food). Specially designed proteins even give elasticity to your skin (elastin) and strength to your hair and fingernails (keratin).



▲ Because proteins have diverse roles in the body, they come in many shapes and sizes.

IMAGE COURTESY OF DAVID S. GOODSELL

Protein production starts in the cell's command center, the nucleus. Your genes, which are made of DNA, contain the instructions for making proteins in your body, although many other factors—such as your diet, activity level, and environment—also can affect when and how your body will use these genes.

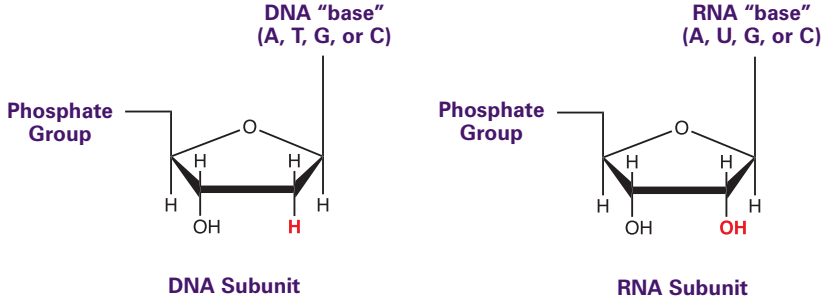
Code Reading

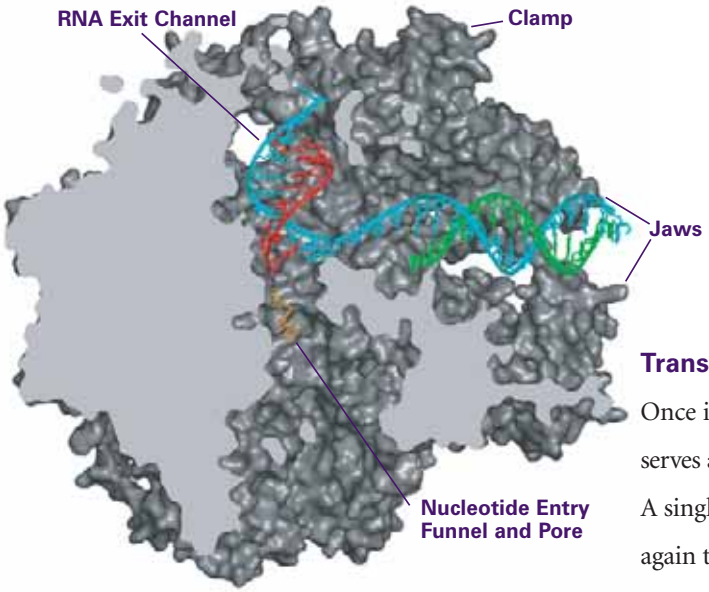
The first step in building proteins is reading the genetic code contained in your DNA. This process is called **transcription**. Inside the cell nucleus, where your DNA is safely packaged in chromosomes, are miniature protein machines called **RNA polymerases**. Composed of a dozen different small proteins, these molecular machines first pull apart the two strands of stringy DNA, then transcribe the DNA into a closely related molecule called RNA.

Researchers have used a technique called X-ray crystallography to help unravel just how transcription occurs. As one example, Roger Kornberg of the Stanford University School of Medicine in California, used this tool to obtain a detailed, three-dimensional image of RNA polymerase. The image suggests that the RNA polymerase enzyme uses a pair of jaws to grip DNA, a clamp to hold it in place, a pore through which RNA components enter, and grooves for the completed RNA strand to thread out of the enzyme.

Helper molecules may then cut and fuse together pieces of RNA and make a few chemical modifications to yield the finished products—correctly sized and processed strands of messenger

The units that make up DNA and RNA differ only slightly.





▲ The structure of RNA polymerase suggests, at the molecular level, how it reads DNA (blue and green) and makes a complementary strand of RNA (red, with the next building block in orange).

IMAGE COURTESY OF ROGER KORNBERG

RNA (mRNA). Completed mRNA molecules carry genetic messages to the cytoplasm, where they are used as instructions to make proteins.

Specialized proteins and small RNA molecules escort the mRNA out of the nucleus through pores in the nuclear envelope. A sequence of chemical reactions that burn ATP drives this export process.

Translation, Please

Once in the cell's cytoplasm, each mRNA molecule serves as a template to make a single type of protein. A single mRNA message can be used over and over again to create thousands of identical proteins.

This process, called **translation**, is carried out by ribosomes, which move along the mRNA and follow its instructions. The mRNA instructions are a string of units that, in groups of three, code for specific protein building blocks called **amino acids**. Ribosomes read the mRNA units in sequence and string together the corresponding amino acids in the proper order.

Where do ribosomes get the amino acids? From matchmaker molecules called transfer RNAs (tRNAs) that bring amino acids from the cytosol to the

RNA's Many Talents

RNA—it's not just for making proteins anymore. In the last few years, scientists have unearthed several previously unknown functions for the molecule that was regarded mostly as the molecular go-between in the synthesis of proteins from genes. It's not that RNA suddenly has developed any new talents. All of these tasks probably have been going on for millions of years, but researchers are just now discovering them.

In particular, certain types of small RNAs seem to be critical for carrying out important work inside cells. In addition to helping make proteins, small RNA molecules help cells grow and divide, guide developing organ and tissue formation, edit the "spellings" of genes, and control gene activity. This last ability, more generally referred to as gene expression, is key to how cells mature into so many different cell types throughout the body.

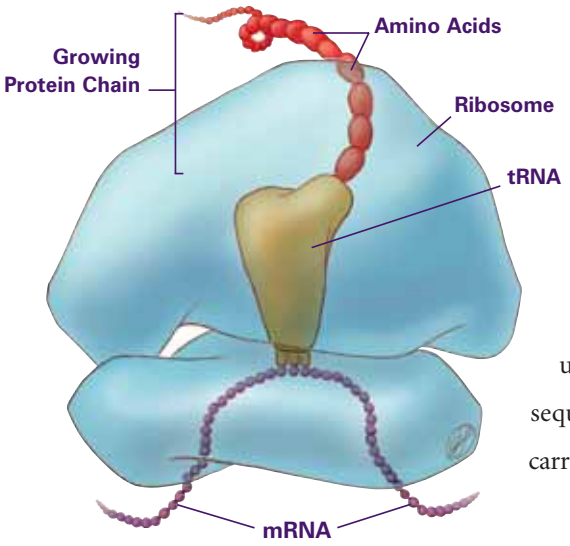
One of the most intriguing discoveries is RNA interference (**RNAi**), a mechanism that organisms use to silence genes when their protein products are no longer needed. The silencing happens when short RNA molecules bind to stretches of mRNA, preventing translation of the mRNA (see main text).

Scientists have found RNAi at work in almost every living thing examined, from worms to people. Researchers are learning that RNAi gone wrong may even contribute to certain diseases. Using experimental fruit flies, Gregory Hannon of Cold Spring Harbor Laboratory on Long Island, New York, has uncovered a link between RNAi and a disorder called Fragile X syndrome, which is one of the most common inherited forms of mental retardation.

Researchers also believe RNAi holds promise for future molecule-based therapies. For example, in lab tests, scientists have recently succeeded in killing HIV, the virus that causes AIDS, by wielding an RNAi-based molecular weapon. If the technique works equally well in people, it could lead to an entirely new class of anti-AIDS drugs.

ALISA Z. MACHALEK

▲ Scientists first discovered RNA interference while puzzling over an unexpected color in petunia petals. Now they know that this process, which may eventually be used to help treat certain diseases, occurs in almost all living organisms.



▲ Ribosomes manufacture proteins based on mRNA instructions. Each ribosome reads mRNA, recruits tRNA molecules to fetch amino acids, and assembles the amino acids in the proper order.

ribosome. One end of the L-shaped tRNA matches up with a three-unit mRNA sequence while the other end carries the appropriate amino acid.

One at a time, the tRNAs clip onto the mRNA in a cavern deep within the ribosome, allowing the ribosome to stitch together the amino acids in the right order. A finished amino acid chain can range in length from a few dozen to several thousand amino acids. Some proteins are made up of only one amino acid chain. Others, especially large proteins, contain two or more chains.

Translation consumes lots of energy, but it happens very fast. In bacteria, for example, ribosomes can stitch together 20 amino acids in 1 second.

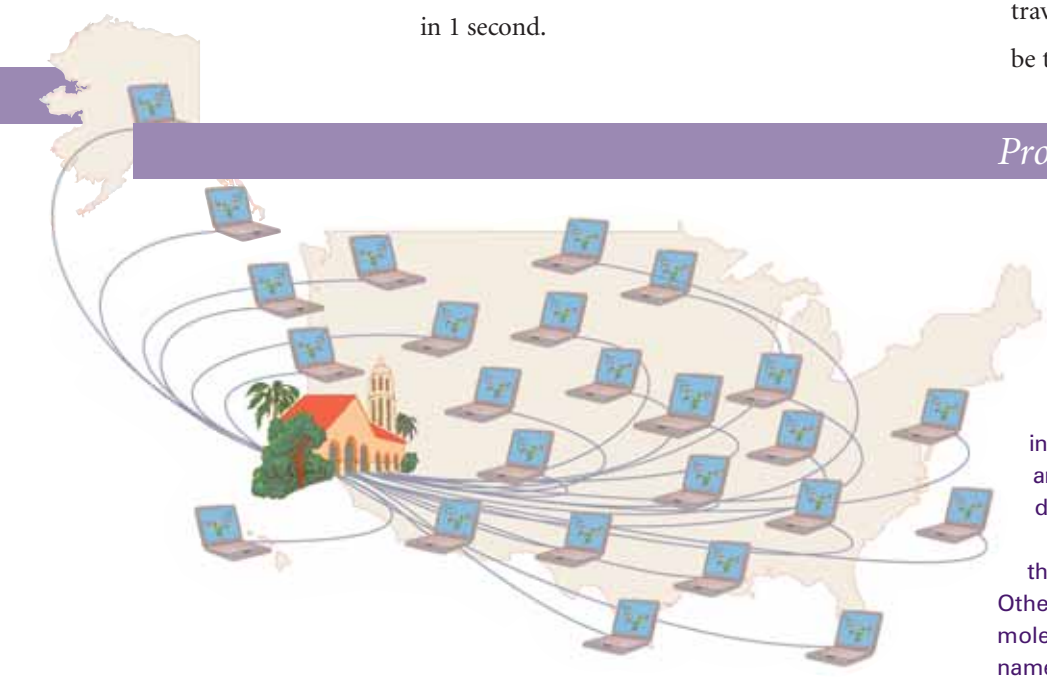
Some three-unit sequences in the mRNA message can immediately halt protein production. Reading one of these mRNA stop signs indicates to the ribosome that the new protein has all the amino acids it needs, and translation ends.

At this point, most proteins made by free-floating ribosomes are essentially complete. They will remain in the cytosol, where they conduct business—such as passing chemical messages in the cell.

A Sweet Finish

The story is different for proteins made by ribosomes on the rough ER. Inside the rough ER, enzymes add specialized chains of sugar molecules (**carbohydrates**) to proteins in a process called **glycosylation**. Next, the proteins traverse the Golgi, where the sugar groups may be trimmed or modified in other ways to create

Protein Origami



Proteins come in virtually every imaginable shape, each containing a sophisticated array of bends and folds that allow them to do their jobs. Further proving that a protein's proper three-dimensional shape is critical to its function, scientists have linked misfolded proteins to several diseases, including Alzheimer's, Huntington's, Parkinson's, amyotrophic lateral sclerosis (Lou Gehrig's disease), and cystic fibrosis.

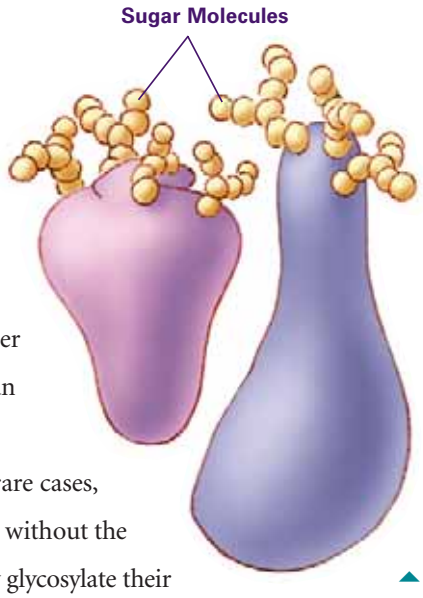
But proteins don't always accomplish their acrobatic folding feats by themselves. Other molecules often help them along. These molecules, which are also proteins, are aptly named chaperones. Like their human namesakes, chaperone proteins work around the clock to prevent inappropriate interactions (molecular ones, in this case) and to foster appropriate bonding.

the final protein. Unlike genes and proteins, carbohydrates are not based on a genetic template. As a result, they are more difficult to study because researchers cannot easily determine the sequence or arrangement of their components. Scientists are only just beginning to learn about the critical roles carbohydrates play in many life processes.

For example, without the carbohydrates on its outer surface, a fertilized egg would never implant into a woman's uterus, meaning it would never develop into a baby. Also, without sticky sugar molecules to slow down your immune cells, they would fly right by the cut on your hand without stopping to help fight infection. Sugars attached to lipids on the surface of red blood cells define a person's blood type (A, B, AB, or O). Carbohydrates even help proteins fold up into their proper shape and dictate where proteins go and which other molecules they can interact with.

In extremely rare cases, children are born without the ability to properly glycosylate their proteins, a disorder called carbohydrate deficiency glycoprotein syndrome. As you might imagine, this disease affects virtually every part of the body, causing symptoms like mental retardation, neurological defects, and digestive problems.

Glycosylation, then, does more than just add a sugar coating. It's an essential process that gets proteins ready for action.



▲ About half of all human proteins include chains of sugar molecules that are critical for the proteins to function properly.

Chaperones are so important in protein folding that some researchers believe that supplying them to cells may someday help treat devastating health problems caused by misfolded proteins.

Of course, it would help if scientists also could understand just how protein folding takes place. But it can happen so fast—small proteins can fold in a few millionths of a second—that researchers have had a difficult time understanding the process in detail.

Enter Stanford University scientist Vijay Pande, who decided to couple the power of computers with the help of the public. Computers are adept at simulating biological processes, but it would take a single personal computer a century to simulate the entire folding pathway of a single protein. Pande initiated a project called Folding@Home, a so-called distributed computing project in which anyone who wants to can download a screensaver that performs protein-folding calculations when a computer is not in use. Folding@Home is modeled on a similar project called SETI@Home, which is used to search for extraterrestrial intelligence.

Pande recruited tens of thousands of personal-computer owners who have Internet connectivity. Each idle computer was assigned a different job to help simulate the folding process of a test protein at several different temperatures. With so many computers employed, the simulation was complete in a matter of days. The scientists used data gathered from the screensavers to come up with a folding-time prediction, which was confirmed by lab tests to be correct. You can learn more about this project at http://folding.stanford.edu.

Cellular Rush Hour

To reach its destination, a newly created protein must toil through the cytosol, moving past obstacles, such as organelles, cytoskeletal fibers, and countless molecules. Luckily, the cell has well-organized systems to shepherd proteins to the places where they are needed.

Vesicle Taxis

Perhaps the most challenging obstacle is membranes. It's essentially an oil-and-water problem. The cell's cytosol, the insides of organelles, and many proteins are water-soluble, but the insides of membranes are fat-soluble (oily). As you know, oil and water don't mix. So how do water-loving proteins headed for lysosomes, the ER, or the Golgi cross the fatty membranes surrounding those organelles to get inside them? The cell chauffeurs them around in **vesicles**, membrane bubbles that essentially solve the problem by eliminating it. Proteins carried in these protective bubbles never really have to "cross" any membranes.

Take, for example, the journey of proteins from the ER to the Golgi. A small portion of the ER membrane pinches off, enveloping exiting proteins in a vesicle that has a special molecular

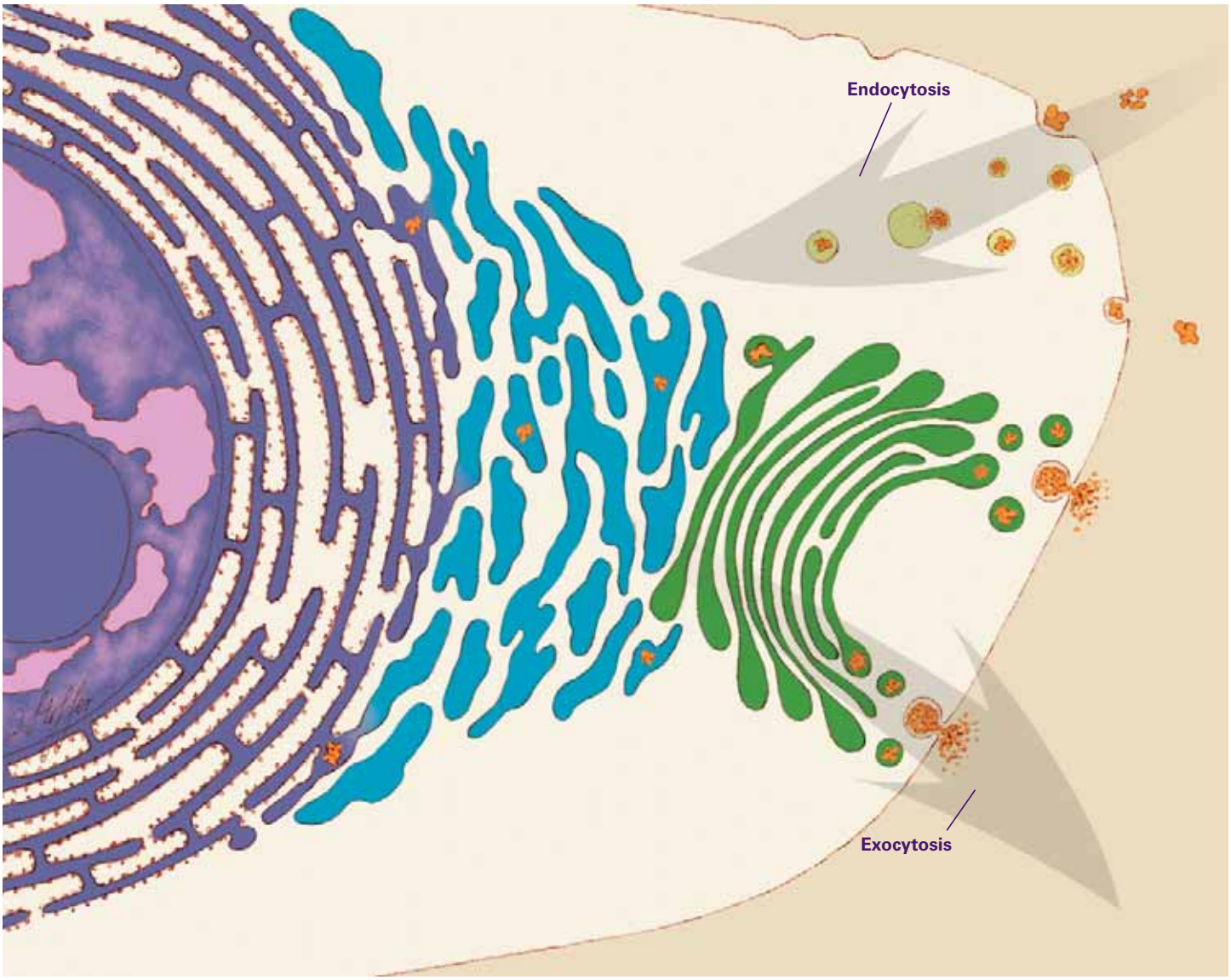
Vesicle Research Venerated

A technique devised by basic researchers to study cell secretion is now used to produce many medications.

The discovery of specialized vesicles called secretory vesicles earned two cell biologists a prestigious prize, the 2002 Albert Lasker Award for Basic Medical Research, an award often known as "America's Nobel Prize." James Rothman of Memorial Sloan-Kettering Cancer Center in New York City, and Randy Schekman of the University of California, Berkeley, shared the prize for figuring out that cells use secretory vesicles to organize their activities and communicate with their environment.

How these two scientists made their discovery is an interesting story itself. Despite skepticism from their peers, Rothman and Schekman pursued an unproven research method: using genetically altered yeast cells to study cell secretion. Working independently, the two discovered, in great detail, how cells use vesicles to direct proteins and other molecules to their proper destinations.

The fundamental research of Rothman and Schekman taught scientists that vesicles are vital to the livelihood of cells. Vesicle transport underlies countless processes, such as the secretion of insulin to control blood sugar, nerve cell communication, and the proper development of organs. The work also helped scientists learn to use yeast cells as protein factories. As a result, genetically altered yeast cells now pump out many important products, including approximately one-quarter of the world's insulin supply and a key ingredient in hepatitis B vaccines.



coat. This vesicle then travels to the Golgi. Strategically located docking sites on the Golgi permit vesicles to latch onto and fuse with its outer membrane to release their contents inside. The same process takes proteins in vesicles from the Golgi to lysosomes or to the cell's surface.

Cells also use vesicles to carry nutrients and other materials into the cell in a process called **endocytosis**. White blood cells use endocytosis to fight infection. They swallow bacteria whole, engulfing them in large vesicles. The vesicles then fuse with lysosomes, which break down the bacteria into molecular bits and pieces the cell can use.

Endocytosis occurs continuously, and cells essentially eat their entire skin every 30 minutes. So why don't cells continually shrink? Because there is a mirror-image process, called **exocytosis**, that counterbalances endocytosis. Cells use this process to dump wastes out of the cell and to replace membrane lost at the cell surface through endocytosis.

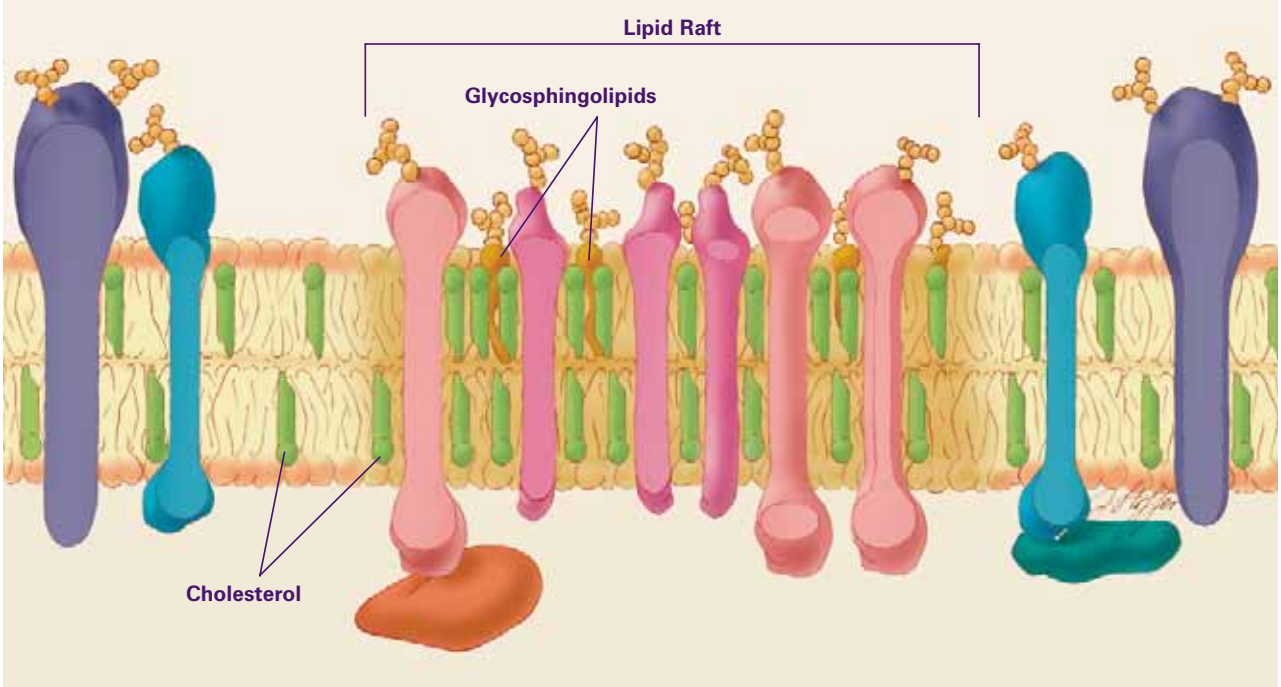
Molecular Motors

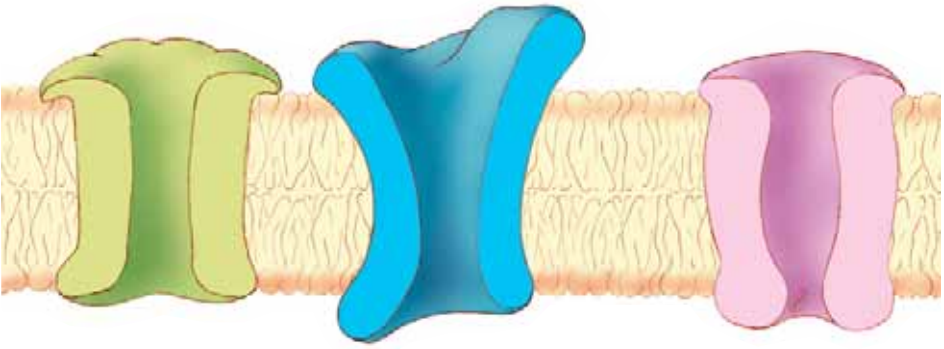
Vesicles don't just wander around aimlessly. Like many other materials inside the cell, including some organelles, they often are carried by small molecular motors along tracks formed by the cytoskeleton. Your body uses motors to get all sorts of things done—copying DNA (and fixing it when a "typo" slips in), making ATP and proteins, and putting molecules in the correct places during development to make sure the body is assembled correctly.

In recent years, scientists have discovered that the workings of every motor they examined hinge on the same two ingredients: an energy source (usually ATP) and chemical reactions. Ronald Vale of the University of California, San Francisco, has found that molecular motors function sort of like a falling row of dominoes. Chemical reactions driven by ATP cause small shape changes in parts of the motor proteins, which then alter the shape of other parts of the proteins, eventually causing a forward (or sometimes backward) movement of the motor along its track.

Tiny Tunnels

While vesicles are ideal for handling large molecules and bulky material, cells have a different way to transport smaller molecules, like water and charged particles (ions), across membranes. These molecules travel through hollow or gated proteins that form channels through membranes.





The body uses a variety of ion channels to transport small molecules across cell membranes.

Channel proteins are just one family of proteins that function within the cell's surface membrane. They transport ions like sodium and potassium that are critical to many biological processes, such as the beating of the heart, nerve impulses, digestion, and insulin release. Unfortunately, channel proteins are tough to study because they cannot easily be isolated from the membrane in either their natural or active states.

Yet with new and improved laboratory techniques and good old-fashioned tenacity, researchers are learning fascinating new things about membrane proteins. One example is work by Roderick MacKinnon of Rockefeller University in New York City, that showed what potassium channel proteins look like at the atomic level. This revealed how these channels precisely control which ions they transmit, why they sometimes conduct ions only in one direction, and how they open and close under different conditions. Just 5 years later, in 2003, MacKinnon received science's highest honor, the Nobel Prize.

Mystery Membrane Rafts

Cellular membranes are sort of like a layer of half-gelled Jell-O® studded with fruit. The Jell-O® portion is made up of lipids, and the pieces of fruit are proteins that float around within it. Of course, cell membranes are much more complex than that. Depending on which organelle a membrane encases and where in the body it is located, its proteins (and to a lesser extent, its lipids) can vary widely in type and amount. This allows different processes to be performed in each membrane.

Until recently, scientists thought that individual lipids and proteins floated around independently. New data indicate that certain proteins tend to group together, as if, in the Jell-O® analogy, all the peaches and pears clustered together while the pineapple floated around by itself.

Researchers have learned much of what they know about membranes by constructing artificial membranes in the laboratory. In artificial membranes, different lipids separate from each other based on their physical properties, forming small islands called lipid rafts. These rafts have a higher concentration of certain specialized lipids, called glycosphingolipids, and cholesterol than do non-raft parts of the membrane. Rafts also are distinguished by a different assortment of proteins. Certain types of proteins cluster together in rafts, while others remain mostly outside of rafts. The big question is, to what extent do these rafts, seen readily in artificial membranes, actually exist in living cells?

Using advanced laboratory methods and imaging techniques, some researchers found evidence that rafts, indeed, do form in living cellular membranes, but these rafts may be small and transitory. Although the existence of lipid rafts in cellular membranes remains controversial, many scientists believe they serve as communication hubs by recruiting proteins that need to come together in order to transmit a signal. Researchers are beginning to link lipid rafts with a variety of diseases, including AIDS, Alzheimer's, anthrax, and atherosclerosis. —*A.Z.M.*

The Mark of Death

As cells acquire and make the things they need, including nutrients, RNA, proteins, and energy, it's clear that something's got to give when it comes to space management.

One way cells clear out waste is by attaching a "death tag" to proteins they no longer need. Recognizing this tag, called **ubiquitin**, a cellular disposal machine called the **proteasome** begins digesting the proteins.

Researchers have known about the existence of ubiquitin for a long time. However, in recent years, they have come to appreciate the fact that cells use ubiquitin-targeted destruction for much more than simply getting rid of debris. As it turns out, cells fine-tune many critical processes by using ubiquitin and the proteasome disposal system.

One example is the **cell cycle**, the recurring sequence of phases the cell goes through that culminates in cell division. Specific enzymes control the cell's entry into each phase of the cell cycle. After a phase is complete, its associated enzymes are tagged with ubiquitin and chewed up by the proteasome. Once that happens, the cell knows to move on to the next phase of the cycle. (For more information about the cell cycle, see *The Cycling Cell* in Chapter 4.)

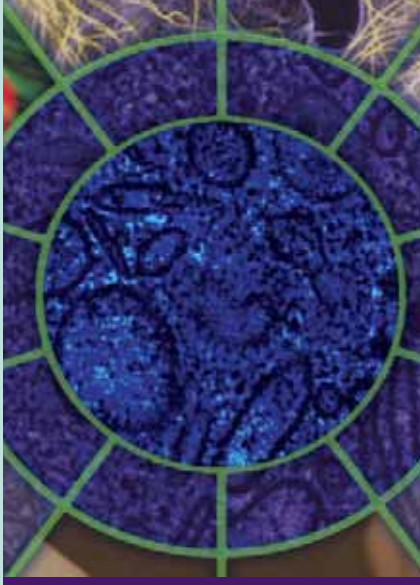
Researchers also are discovering that ubiquitin appears to participate in numerous other cell processes, including protein traffic control, DNA repair, organelle synthesis, cellular responses to stress, regulation of the immune system, and long-term memory. Originally, ubiquitin was so named because it is found in all higher organisms, making it ubiquitous, or everywhere. As scientists continue to learn of its myriad roles in cells, ubiquitin's name is taking on a new shade of meaning.

▲ Basic research on the proteasome led to the discovery of a drug to treat multiple myeloma, a deadly form of blood cancer that originates in bone marrow.

The significance of ubiquitin and the proteasome was recognized with the 2004 Nobel Prize in chemistry. Three researchers, Irwin Rose of the University of California, Irvine; and Aaron

Ciechanover and Avram Hershko of Technion-Israel Institute of Technology in Haifa, shared the award for discovering ubiquitin-mediated protein degradation. In announcing the prize, the Royal Swedish Academy of Sciences pointed out that cervical cancer and cystic fibrosis are two examples of diseases caused by faulty protein degradation. Deeper knowledge of ubiquitin-mediated protein degradation may advance the development of drugs against these diseases and others.

Basic research on the proteasome already has led to an important new anticancer drug. Scientists led by Alfred Goldberg of Harvard Medical School in Boston, Massachusetts, discovered the proteasome in the 1970s as they tried to figure out how and why the body sometimes destroys its own proteins. They created compounds to clog proteasomes, thinking that these substances might curb the excessive protein breakdown and subsequent muscle wasting associated with diseases like kidney and liver failure, AIDS, and cancer. To their surprise, they noticed that one of their substances had anticancer properties. This substance, later dubbed Velcade®, was approved by the U.S. Food and Drug Administration in 2003 and is used to treat multiple myeloma, the second most common blood cancer.



Got It?

What is cellular fuel called?

What is the name of the cell's transcription machine?

Describe the process of translating messenger RNA into a protein.

What is glycosylation, and why is it important?

What do cells use vesicles for?

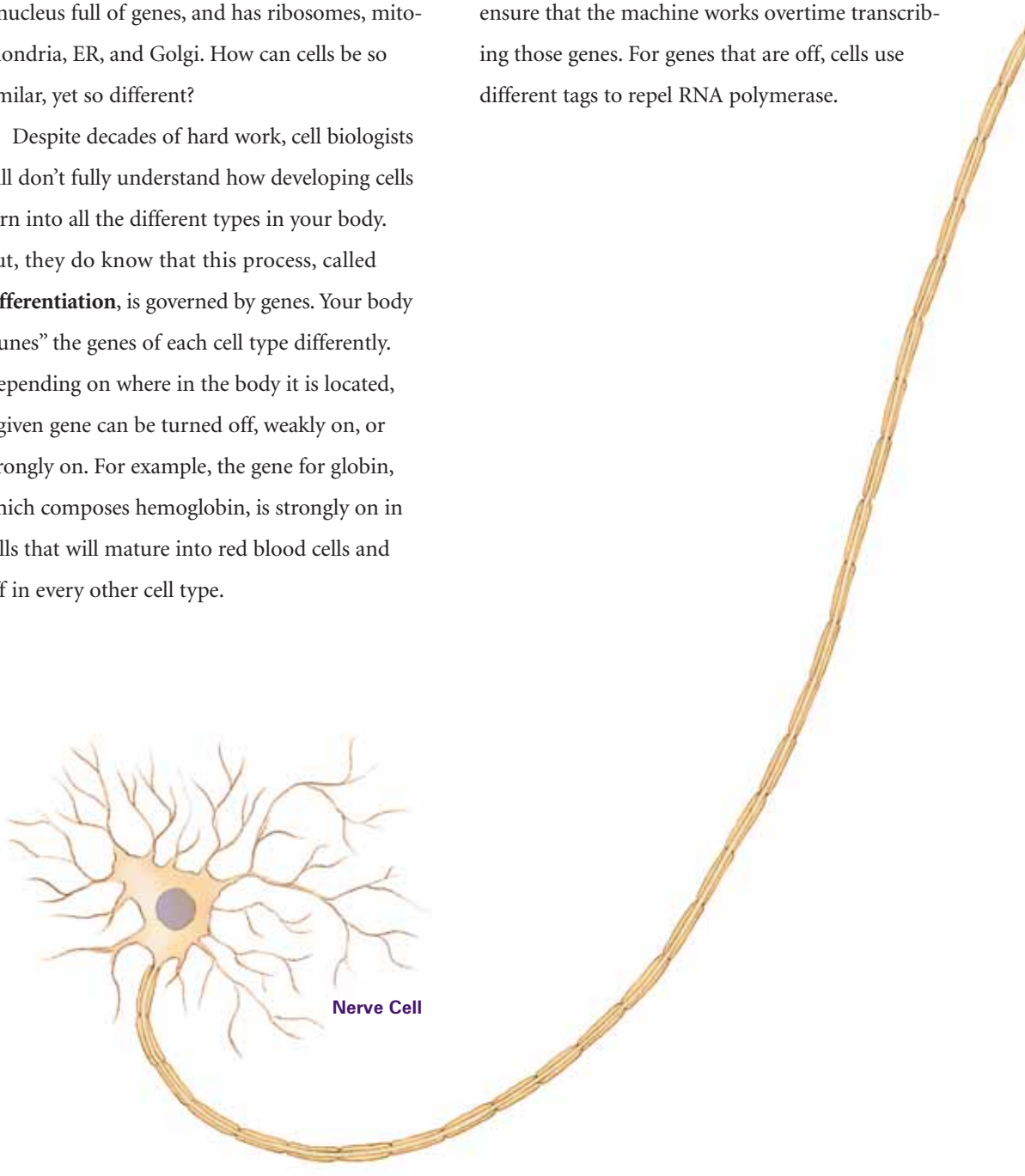
List three functions of ubiquitin.

On the Job: Cellular Specialties

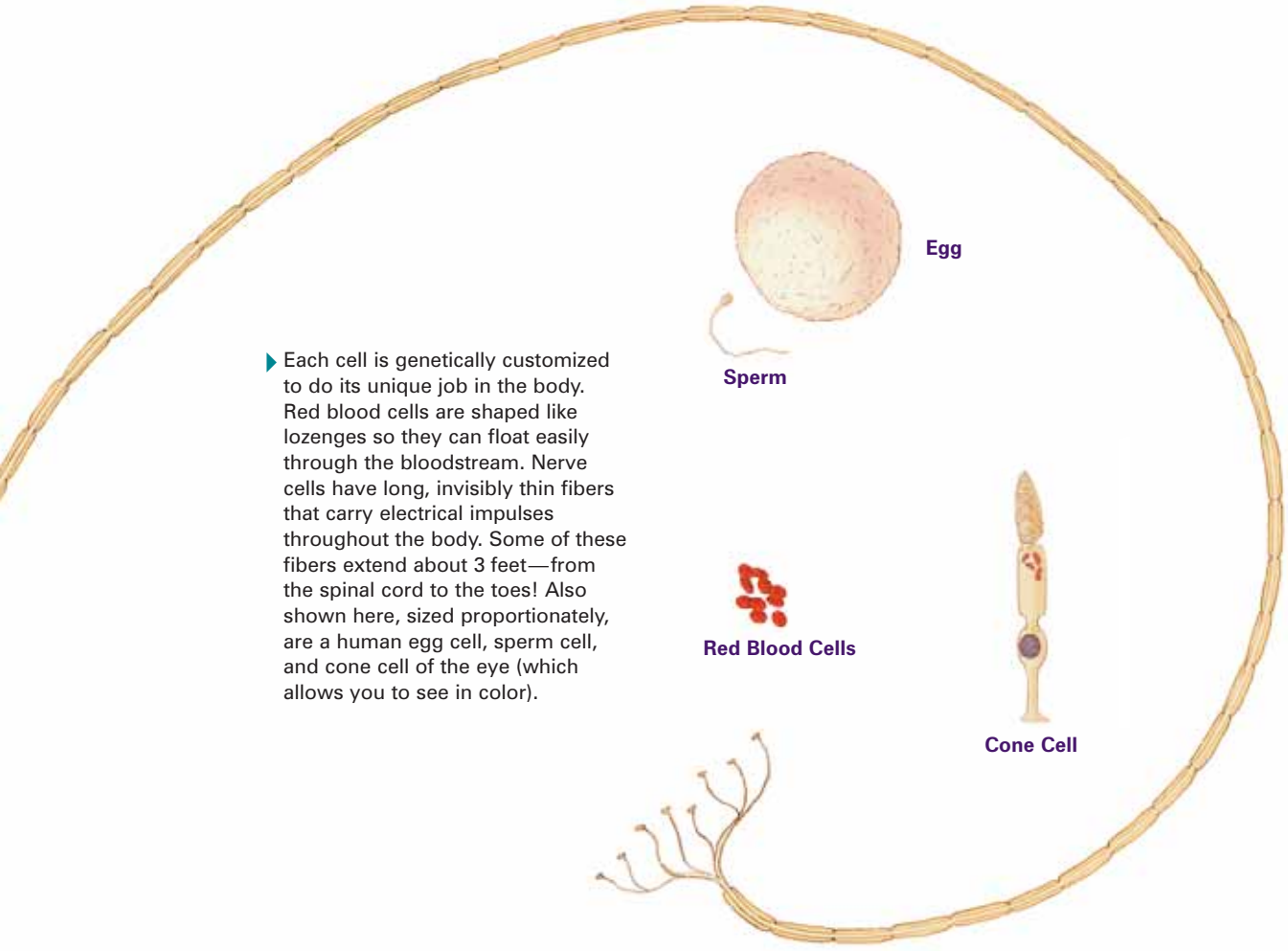
Liver cells look almost nothing like nerve cells. Muscle cells bear little physical resemblance to white blood cells. Yet every cell (with just a few exceptions) is encased in a membrane, contains a nucleus full of genes, and has ribosomes, mitochondria, ER, and Golgi. How can cells be so similar, yet so different?

Despite decades of hard work, cell biologists still don't fully understand how developing cells turn into all the different types in your body. But, they do know that this process, called **differentiation**, is governed by genes. Your body "tunes" the genes of each cell type differently. Depending on where in the body it is located, a given gene can be turned off, weakly on, or strongly on. For example, the gene for globin, which composes hemoglobin, is strongly on in cells that will mature into red blood cells and off in every other cell type.

Cells control the tuning, or expression, of genes by keeping a tight rein on RNA polymerase. For genes that are strongly on, cells use special molecular tags to lure in RNA polymerase and to ensure that the machine works overtime transcribing those genes. For genes that are off, cells use different tags to repel RNA polymerase.



Nerve Cell



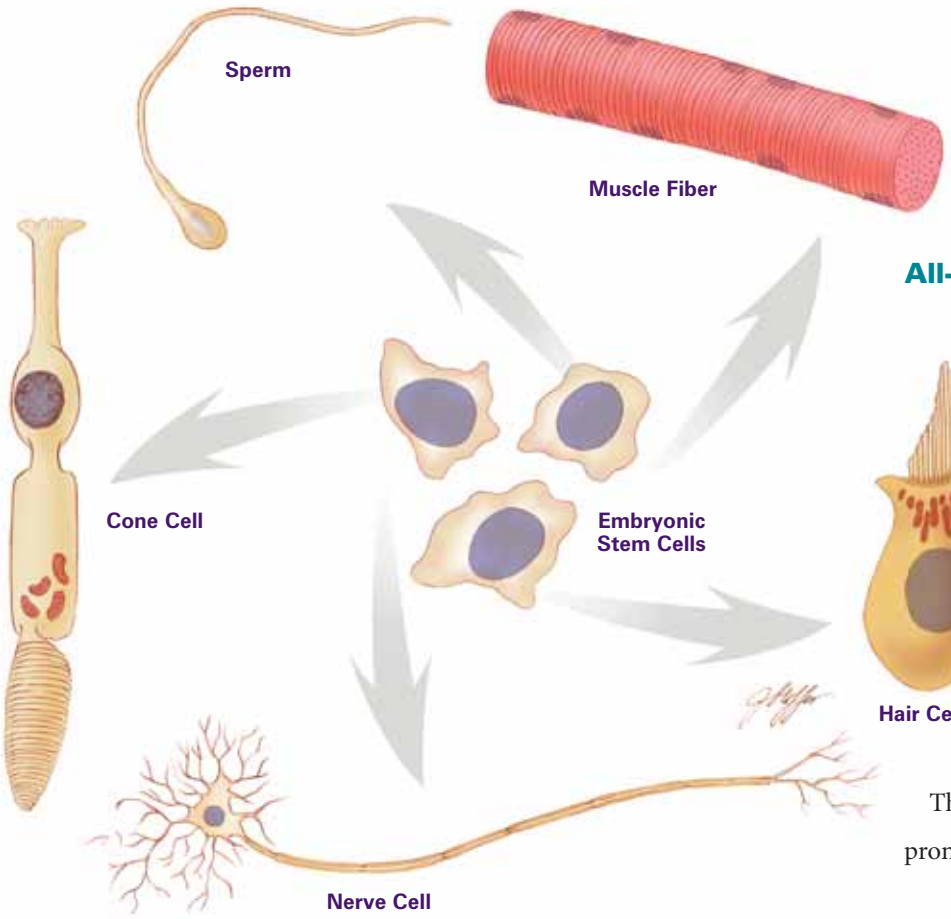
Each cell is genetically customized to do its unique job in the body. Red blood cells are shaped like lozenges so they can float easily through the bloodstream. Nerve cells have long, invisibly thin fibers that carry electrical impulses throughout the body. Some of these fibers extend about 3 feet—from the spinal cord to the toes! Also shown here, sized proportionately, are a human egg cell, sperm cell, and cone cell of the eye (which allows you to see in color).

Fit for the Job

The tuning of a cell's genes determines which products it can make. Liver cells make loads of enzymes to break down drugs and toxins. Certain immune cells produce antibodies to help fight infections. Cells in a variety of organs—including the pancreas, brain, ovary, and testes—whip up hormones that are secreted into the bloodstream. Many of these substances are produced throughout life in response to the body's need for them. Others are made only at specific times, like the milk proteins produced in a woman's breasts after she gives birth.

The pattern of gene expression also determines a cell's shape, allowing it to perform its job. For example, cells lining your small intestine express genes needed to form hundreds of miniature extensions (microvilli) used to absorb nutrients. Each sperm cell turns on genes needed to develop its wagging flagellum. Rod and cone cells in your eye express genes needed to form their characteristic shapes (cylindrical and cone-shaped respectively).

The body even alters the balance of organelles in different tissues. Take your heart, for example. This incredibly durable machine is designed to produce the extraordinary amount of ATP energy required for nonstop pumping—it pumps 100,000 times a day, every day, for your whole life. To do this, it is made up of specialized muscle cells jam-packed with mitochondria. A human heart cell contains several thousand mitochondria—around 25 percent of the cell's volume. Cells that don't need much energy, like skin cells, contain only a few hundred mitochondria.



All-In-One Stem Cells

There is only one type of cell that is completely generic—its gene expression is tuned so broadly that it has unlimited career potential to become any kind of cell in the body. These undifferentiated cells cease to exist a few days after conception. They are **embryonic stem cells**.

Each of us was once a hollow ball of 100 or so identical embryonic stem cells. Then, as dozens of hormones, sugars, growth-promoting substances, and other unknown

Tissues From Scratch

Within cells, much of the action takes place in organelles. Similarly, but on a larger scale, most bodily functions occur in compartments—our organs and tissues. Each compartment contains a number of different cell types that work together to accomplish a unique function.

Despite years of effort, scientists have had a frustrating time making tissues and organs in the lab from scratch. Researchers desperately want to succeed in this endeavor to develop more natural replacements for body parts that are destroyed or damaged by disease or injury. Lab-made tissues also might be useful as research tools and in developing and testing new medicines.

So, how do scientists make a tissue? Many are going about it by thinking like engineers. Just as a civil engineer designs and builds a bridge, bioengineers figure out how to combine biological molecules into three-dimensional structures. After all, that's what a tissue is: a sophisticated "apartment building" of cells joined together, nourished by fluid byways, and wired with nerves.

As you already know, the cytoskeleton serves as internal scaffolding to give cells their shape and to provide railways for molecules and organelles. Cells also have building materials on their outsides, coatings of special proteins that make up what's called the **extracellular matrix**. The molecular arrangement of the extracellular matrix is extremely complex, and scientists are still struggling to understand exactly how it is put together and how it works. They do know, however, that the matrix not only helps cells stick together, but also contributes to the overall texture and physical properties of tissues. It is firm in bones to give rigidity and elastic in ligaments so you can move your joints.

Mechanical engineer Andrés García of the Georgia Institute of Technology in Atlanta, is working toward building new tissues by measuring the forces that cells use to stick to the extracellular matrix. García does this by growing living cells in arrays of tiny wells coated with extracellular matrix components. He then spins the arrays at a high speed to see how many cells fly off. This shows

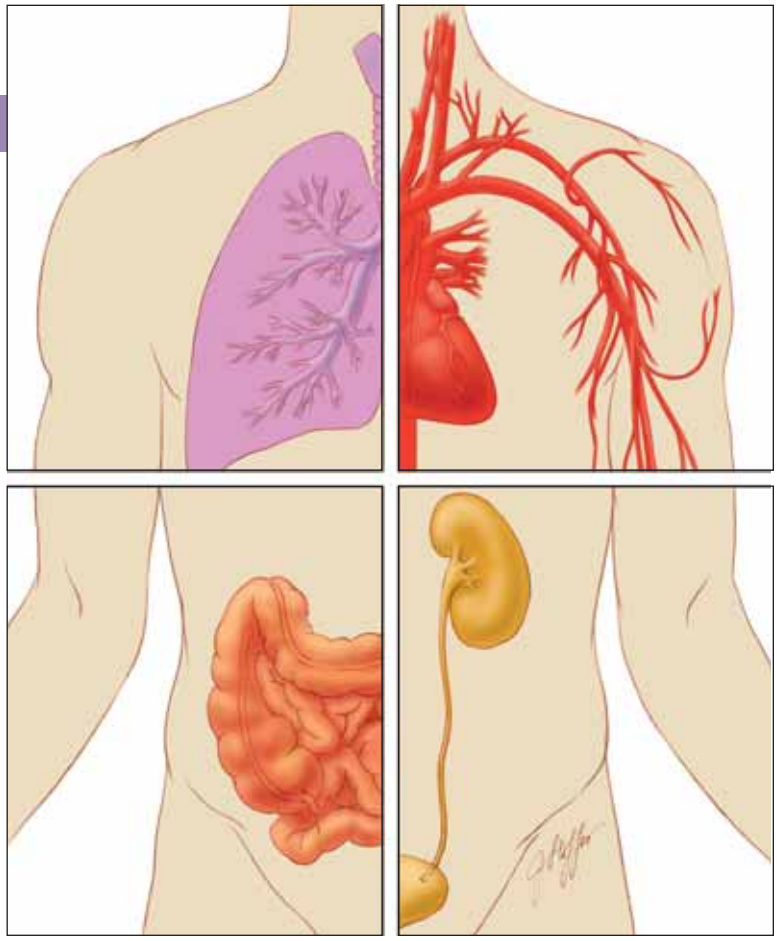
chemical cues washed over us, we began to change. Certain cells grew long and thin, forming nerve cells. Others flattened into skin cells. Still others balled up into blood cells or bunched together to create internal organs.

Now, long after our embryonic stem cells have differentiated, we all still harbor other types of multitalented cells, called **adult stem cells**. These cells are found throughout the body, including in bone marrow, brain, muscle, skin, and liver. They are a source of new cells that replace tissue damaged by disease, injury, or age. Researchers believe that adult stem cells lie dormant and largely undifferentiated until the body sends signals that they are needed. Then selected cells morph into just the type of cells required. Pretty cool, huh?

Like embryonic stem cells, adult stem cells have the capacity to make identical copies of themselves, a property known as self-renewal. But they differ from embryonic stem cells in a few important ways. For one, adult stem cells are quite rare. For example, only 1 in 10,000 to 15,000 cells in bone marrow is capable of

him how much force is required to dislodge cells from the extracellular matrix—in other words, how tightly the cells are stuck to the matrix. García also studies how cells change when they are grown on different surfaces. Based on his findings, he is tailoring artificial surfaces to be ideal materials on which to grow tissues.

The work of García and other researchers studying the extracellular matrix may have important and unforeseen applications, as the extracellular matrix influences almost every aspect of a cell's life, including its development, function, shape, and survival.



Your cells function within organs and tissues, such as the lungs, heart, intestines, and kidney. Scientists seek to create artificial tissues to use for research and, in the future, for transplantation.

becoming a new blood cell. In addition, adult stem cells appear to be slightly more "educated" than their embryonic predecessors, and as such, they do not appear to be quite as flexible in their fate. However, adult stem cells already play a key role in therapies for certain cancers of the blood, such as lymphoma and leukemia. Doctors can isolate from a patient's blood the stem cells that will mature into immune cells and can grow these to maturity in a laboratory. After the patient undergoes high-dose chemotherapy, doctors can transplant the new infection-fighting white blood cells back into the patient, helping to replace those wiped out by the treatment.

Although researchers have been studying stem cells from mouse embryos for more than 20 years, only recently have they been able to isolate stem cells from human embryos and grow them in a laboratory. In 1998, James A. Thomson of the University of Wisconsin, Madison, became the first scientist to do this. He is now at the forefront of stem cell research, searching for answers to the most basic questions about what makes these remarkable cells so versatile. Although scientists envision many possible future uses of stem cells for treating Parkinson's disease, heart disease, and many other disorders affected by damaged or dying cells, Thomson predicts that the earliest fruits of stem cell research will be the development of powerful **model systems** for finding and testing new medicines, as well as for unlocking the deepest secrets of what keeps us healthy and makes us sick.

Growing It Back

ALISA Z. MACHALEK

If scientists could figure out how salamanders regrow their legs and tails, they might be a step closer to helping people who have lost limbs.

If a salamander or newt loses a limb, the creature can simply grow a new one. The process is complicated—cells must multiply, morph into all the different cell types present in a mature limb (such as skin, muscle, bone, blood vessel, and nerve), and migrate to the right location. Scientists know that special growth factors and hormones are involved, but no one knows exactly how regeneration happens. Some believe that understanding how amphibians regenerate their tissues might one day enable doctors to restore human limbs that have been amputated or seriously injured.

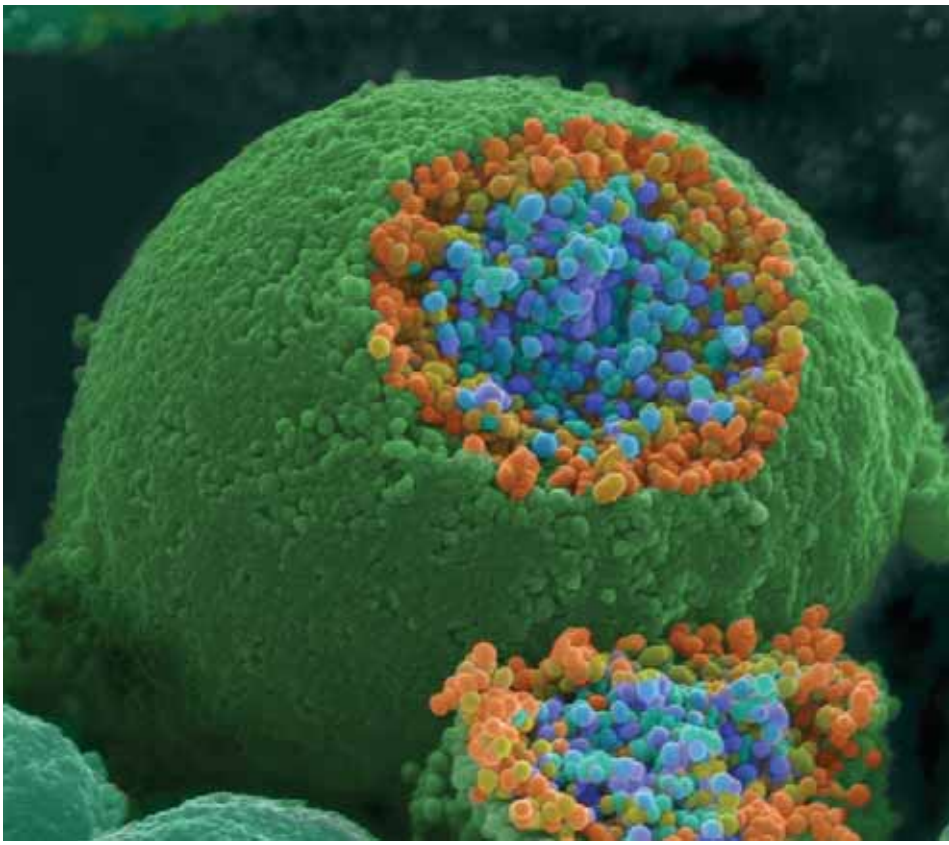
It may seem a distant goal, but researchers like Alejandro Sánchez Alvarado are fascinated with this challenge. Several years ago, Sánchez Alvarado, a biologist at the University of Utah School of Medicine in Salt Lake City, set out to

You've Got Nerve(s)!

What happens when you walk barefoot from the swimming pool onto a section of sun-baked pavement? Ouch! The soles of your feet burn, and you might start to hop up and down and then quickly scamper away to a cooler, shaded spot of ground. What happened?

Thank specialized cells again. Networks of connected cells called **neurons** make up your body's electrical, or nervous, system. This system works to communicate messages, such as, "Quick, move off the hot pavement!" Cells of the nervous system (specifically neurons) possess special features and a unique shape, both of which suit them for their job in communication. Or, as scientists like to put it, structure determines function.

Neurons have long, spindly extensions called axons that carry electrical and chemical messages.



TINA CARVALHO

A scanning electron microscope picture of a nerve ending. It has been broken open to reveal vesicles (orange and blue) containing chemicals used to pass messages in the nervous system.

find a way to help solve the regeneration mystery. After reading scientific texts about this centuries-old biological riddle, Sánchez Alvarado chose to study the problem using a type of flatworm called a planarian. This animal, the size of toenail clippings, is truly amazing. You can slice off a piece only 1/300th the size of the original animal, and it will grow into a whole new worm.

To understand the molecular signals that can make this feat possible, Sánchez Alvarado is reading the worm's genetic code. So far, he and his coworkers have used DNA sequencing machines and computers to read the spellings of over 4,000 of the worm's genes.

To focus in on the genes that enable planarians to regenerate, Sánchez Alvarado and his coworkers are using RNA interference (RNAi). As we discussed in the previous chapter (*RNA's Many Talents* section), RNAi is a natural process that organisms use to silence certain genes. Sánchez Alvarado's group harnesses RNAi to intentionally interfere with the function of selected genes. The researchers hope that by shutting down genes in a systematic way, they'll be able to identify which genes are responsible for regeneration.

The researchers are hoping that their work in planarians will provide genetic clues to help explain how amphibians regenerate limbs after an injury. Finding the crucial genes and understanding how they allow regeneration in planarians and amphibians could take us closer to potentially promoting regeneration in humans.

These messages convey information to your brain—"The ground is burning hot!"—and responses back from the brain—"Pick up your foot!"

To transmit these messages, charged particles (primarily sodium ions) jet across a nerve cell membrane, creating an electrical impulse that speeds down the axon. When the electrical impulse reaches the end of the axon, it triggers the neuron to release a chemical messenger (called a **neurotransmitter**) that passes the signal to a neighboring nerve cell. This continues until the message reaches its destination, usually in the brain, spinal cord, or muscle.

Most neurons can convey messages very fast because they are electrically insulated with a fatty covering called **myelin**. Myelin is formed by Schwann cells—one of the many types of **glial cells** that supply support and nutrition to nerve cells.

Nerves coated with myelin transmit messages at a speed of about 250 miles per hour, plenty of time for the message to get to your brain to warn you to lift your foot before it burns.

One reason young children are at a higher risk for burning themselves is because the neurons in children's bodies do not become fully coated with myelin until they are about 10 years old. That

Hitching a Ride

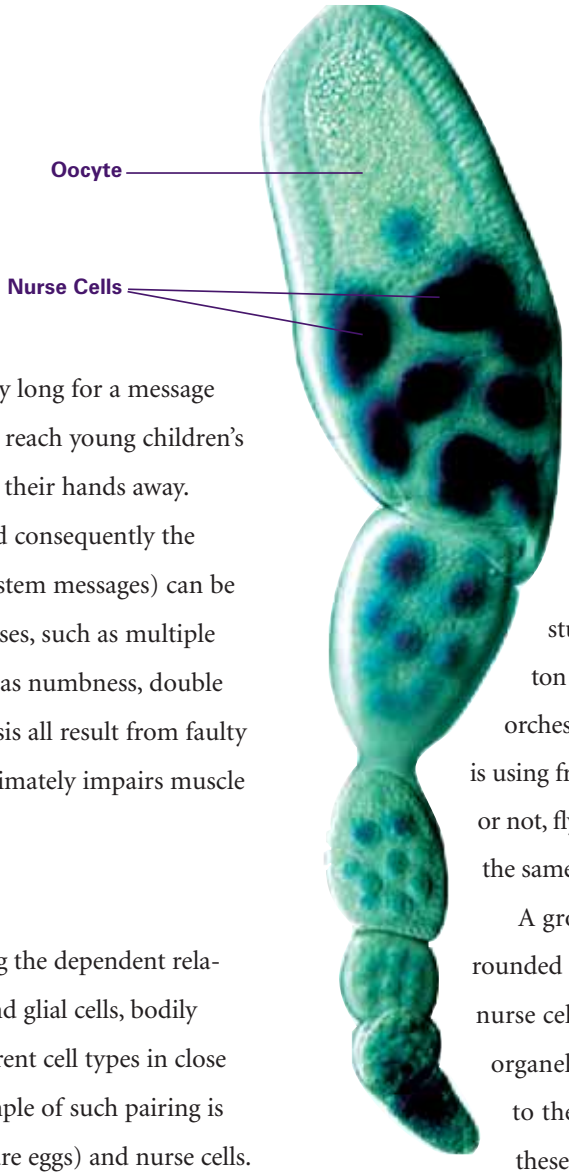
JOE DIGIORGIS

Squid nerve cells often are used in research because they are large and easy to work with. About the size of small, straightened-out paperclips, squid nerve cells are a thousand times fatter than human nerve cells.

Although many of our nerve cells are designed to convey electrical messages to and from our brains, they also can be co-opted for more nefarious purposes. For example, the herpes virus enters through the mucous lining of the lip, eye, or nose, then hitches a ride in a nerve cell to the brain. There, the virus copies itself and takes up long-term residence, often undetected for years.

Researchers had thought that herpes made its way toward the brain by successively infecting other nerve cells along the way. However, Elaine Bearer of Brown University in Providence, Rhode Island, recently learned something different. Bearer recreated the virus transport process in nerve axons from squid found off the coast of Massachusetts. While human nerve cells are difficult to grow in the lab and their axons are too small to inject with test transport proteins, squid axons are long and fat.

Bearer and her coworkers at the Marine Biological Laboratory in Woods Hole, Massachusetts, injected the huge squid axons with a modified form of the human herpes virus. The researchers were amazed to measure its travel speed at 2.2 micrometers per second. This speed can only be achieved, Bearer concluded, by a virus particle powered by a protein motor whipping down a cytoskeletal track. Apparently, the virus exploits the cytoskeleton and molecular motors in our nerve cells for its own use.



Studies of fruit fly oocytes, which are each served by 15 nurse cells, are shedding light on how human eggs mature.

IMAGE COURTESY OF LYNN COOLEY

means it takes dangerously long for a message like, "The stove is hot!" to reach young children's brains to tell them to pull their hands away.

Myelin formation (and consequently the conduction of nervous system messages) can be disrupted by certain diseases, such as multiple sclerosis. Symptoms such as numbness, double vision, and muscle paralysis all result from faulty nerve conduction that ultimately impairs muscle cell function.

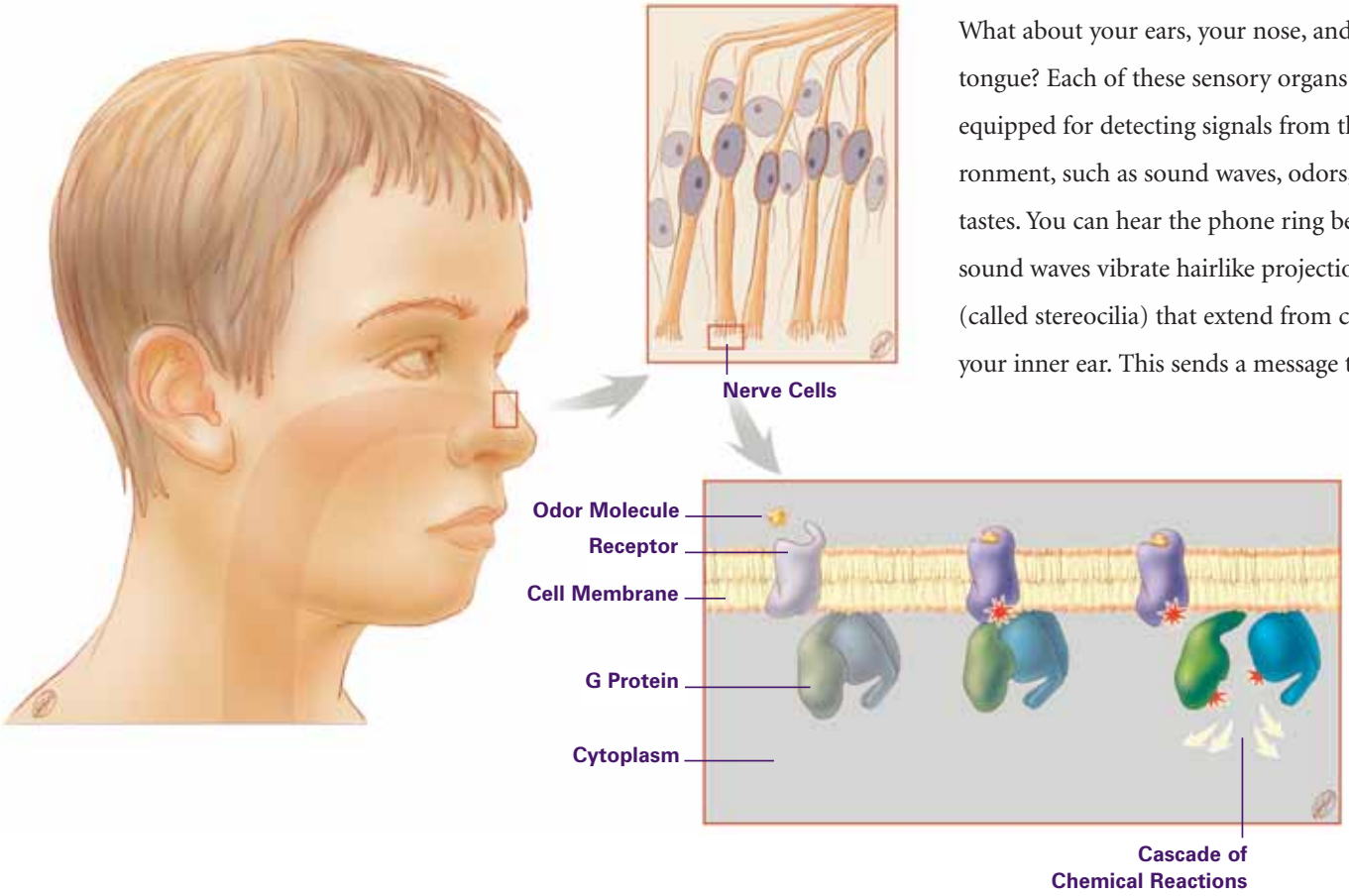
Nursing Baby Eggs

As we saw from examining the dependent relationship between nerve and glial cells, bodily tissues often contain different cell types in close association. Another example of such pairing is between **oocytes** (immature eggs) and nurse cells.

A distinguishing feature of being female is the ability to form eggs. Halfway through pregnancy, a baby girl growing inside her mother's uterus already contains an astonishing 6 to 7 million oocytes. By birth, however, 80 percent of these oocytes have died off naturally. By the time the girl reaches puberty, only a few hundred thousand are left, and over her lifetime, fewer than 1 percent of these oocytes will travel through her Fallopian tubes in a hormone-triggered process called ovulation. If an oocyte is then fertilized by a sperm cell, it becomes a **zygote**, the first cell of a new baby.

For the most part, scientists are baffled by how the body determines which oocytes make it to maturity and which don't. Researchers do know that one key to surviving and becoming a mature oocyte is getting the right molecular signal from your cellular neighbors. Lynn Cooley of Yale University is studying how the cytoskeleton in certain ovarian cells orchestrates this. To do so, she is using fruit flies, since, believe it or not, fly oocytes develop in much the same way as human oocytes.

A growing oocyte is surrounded and protected by several nurse cells, which deliver RNA, organelles, and other substances to their oocyte. To deliver these important materials, the nurse cells actually donate their own cytoplasm to oocytes. The cytoskeleton enables the giving of this gift. As Cooley's studies show, molecular signals prod the cytoskeleton to form specialized structures called ring canals that serve as nozzles to connect oocytes directly to their nurse cells. In a final act of self-sacrifice, the nurse cells contract their cytoskeletons to squeeze their cytoplasm into the oocyte, then die. Cooley's research in this area should help scientists better understand some of the mysteries of how oocytes mature—knowledge that may unravel fertility problems and the root causes of some birth defects.



The Science of Senses

What about your ears, your nose, and your tongue? Each of these sensory organs has cells equipped for detecting signals from the environment, such as sound waves, odors, and tastes. You can hear the phone ring because sound waves vibrate hairlike projections (called stereocilia) that extend from cells in your inner ear. This sends a message to your

Cell Connections

The human body operates by many of the same molecular mechanisms as a mouse, a frog, or a worm. For example, human and mouse genes are about 86 percent identical. That may be humbling to us, but researchers are thrilled about the similarities because it means they can use these simpler creatures as experimental, "model" organisms to help them understand human health. Often, scientists choose model organisms that will make their experiments easier or more revealing. Some of the most popular model organisms in biology include bacteria, yeast cells, roundworms, fruit flies, frogs, rats, and mice.

Barry Gumbiner of the University of Virginia in Charlottesville, performs experiments with frogs to help clarify how body tissues form during development. Gumbiner studies proteins called cadherins that help cells stick together (adhere) and a protein (beta-catenin) that works alongside cadherins.

Scientists know that beta-catenin is critical for establishing the physical structure of a tadpole as it matures from a spherical fertilized egg. Specifically, beta-catenin helps cadherin proteins act as molecular tethers to grip onto cell partners. This function is critical because cell movement

brain that says, "The phone is ringing." Researchers have discovered that what's sending that signal is a channel protein jutting through a cell membrane, through which charged particles (primarily potassium ions) pass, triggering the release of neurotransmitters. The message is then communicated through the nervous system.

Similarly, for you to see and smell the world around you and taste its variety of flavors, your body must convey molecular signals from the environment into your sensory cells. Highly specialized molecules called **G proteins** are key players in this transmission process.

Imagine yourself walking down a sidewalk and catching the whiff of something delicious. When odor molecules hit the inside of your nose, they are received by receptor molecules on the surfaces of nerve cells. The odor message fits into a specially shaped site on the receptors, nudging the receptors to interact with G proteins on the inner surface of the nerve cell membrane. The G proteins then change their own shape and split in two, which sets off a cascade of chemical reactions inside the cell. This results in an electrical message that travels from your nose to your brain, and evokes your response—"Yummm…fresh baked bread," in this case.

Figuring out the molecular details of this process led to the 2004 Nobel Prize in physiology or medicine for two researchers, Richard Axel of Columbia University in New York, and Linda B. Buck of the University of Washington and Fred Hutchinson Cancer Research Center in Seattle.

and adhesion must be carefully choreographed and controlled for the organism to achieve a proper three-dimensional form.

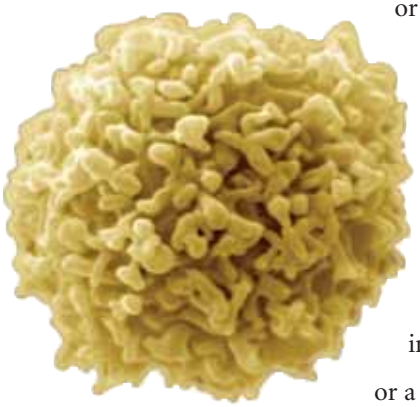
While cell adhesion is a fundamental aspect of development, the process also can be a double-edged sword. Cell attraction is critical for forming tissues in developing humans and frogs, but improper contacts can lead to disaster.

Cells on the Move

Although many types of cells move in some way, the most well-traveled ones are blood cells. Every drop of blood contains millions of cells—red blood cells, which carry oxygen to your tissues; platelets, which are cell fragments that control clotting; and a variety of different types of white blood cells. Red blood cells, which get their deep color from rich stores of iron-containing hemoglobin protein, are carried along passively by—and normally retained within—the bloodstream. In contrast, other blood cells can move quickly out of the bloodstream when they're needed to help heal an injury or fight an infection.

Infection Protectors

White blood cells serve many functions, but their primary job is protecting the body from infection. Therefore, they need to move quickly to an injury or infection site. These soldiers of the immune system fight infection in many ways: producing antibodies, engulfing bacteria, or waging chemical warfare on invaders. In fact, feeling sick is often the result of chemicals spilt by white blood cells as they are defending you. Likewise, the pain of inflammation, like that caused by sunburn or a sprained ankle, is a consequence of white cells moving into injured tissue.



White blood cells protect us from viruses, bacteria, and other invaders.

IMAGE COURTESY OF JIM EHRMAN, DIGITAL MICROSCOPY FACILITY, MOUNT ALLISON UNIVERSITY

How do white blood cells rush to heal a wound? Remarkably, they use the same basic process that primitive organisms, such as ameobae, use to move around.

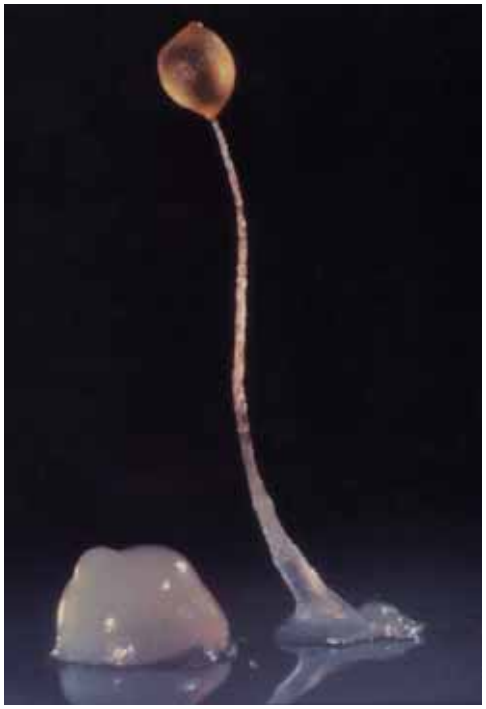
Shape-Shifting Amoebae

In a remarkable example of cell movement, single-celled organisms called amoebae inch toward a food source in a process called **chemotaxis**. Because they live, eat, and die so fast, amoebae are excellent model systems for studying cell movement. They are eukaryotic cells like the ones in your body, and they use many of the same message systems your own cells use.

Peter Devreotes of Johns Hopkins University School of Medicine in Baltimore, Maryland, studies the molecular triggers for chemotaxis using bacteria-eating amoebae named *Dictyostelia* that undergo dramatic changes over the course of their short lifespans.

Individual *Dictyostelia* gorge themselves on bacteria, and then, when the food is all eaten up, an amazing thing happens. Tens of thousands of them come together to build a tower called a fruiting body, which looks sort of like a bean sprout stuck in a small mound of clay.

Devreotes and other biologists have learned that *Dictyostelia* and white blood cells move by first stretching out a piece of themselves, sort of like a little foot. This "pseudopod" then senses its environment for the highest concentration of a local chemical attractant—for the amoebae, this is often food, and for the white blood cell, it is the scent of an invader. The pseudopod, followed by the entire cell, moves toward the attractant by alternately sticking and unsticking to the surface along which it moves. The whole process, Devreotes



REX L. CHISHOLM

Dictyostelia can completely transform themselves from individual cells into a multicellular organism. Studies of these unique creatures are teaching scientists important lessons about development, cell movement, and cell division.

has discovered, relies on the accumulation of very specific lipid molecules in the membrane at the leading edge of a roving cell. Devreotes is hopeful that by clarifying the basics of chemotaxis, he will uncover new ways to design treatments for many diseases in which cell movement is abnormal. Some of these health problems include asthma, arthritis, cancer, and artery-clogging atherosclerosis.

Healing Wounds

The coverings for all your body parts (your skin, the linings of your organs, and your mouth) are made up primarily of epithelial cells. You might think that of all the cell types, these would be the ones staying put. Actually, researchers are learning that epithelial cells are also good at snapping into action when the situation calls for them to get moving.

Say you get a nasty gash on your foot. Blood seeps out, and your flesh is exposed to air, dirt, and bacteria that could cause an infection. Platelets stick together, helping to form a clot that stops the bleeding. At the same time, your skin cells rapidly grow a new layer of healed skin over the wound.

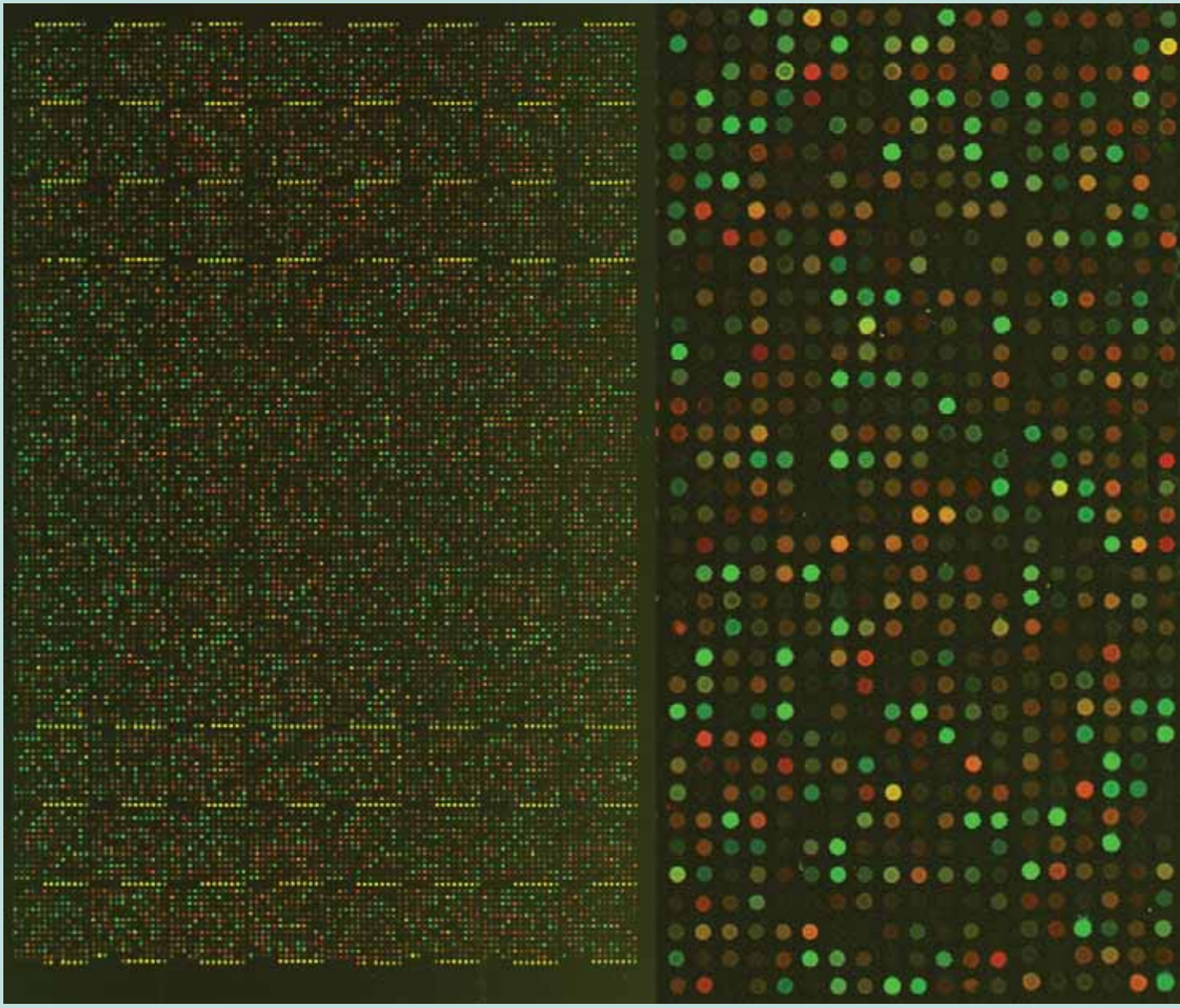
Researchers have learned that epithelial cells have the wondrous ability to move around in clumps. These clumped cells help clean up an injured area quickly by squeezing together and pushing away debris from dead cells.

All organisms get wounds, so some researchers are studying the wound-healing process using model systems. For example, William Bement of the University of Wisconsin, Madison, examines wounded membranes of frog oocytes. He chose these cells because they are large, easy to see into, and readily available. Looking through a specialized microscope, Bement watches what happens when wounds of different shapes and sizes start to heal.

Bement learned that just as with human epithelial cells, the wounds in frog oocytes gradually heal by forming structures called contractile rings, which surround the wound hole, coaxing it into a specific shape before gradually shrinking it. He is now identifying which molecules regulate this process. His research may help find better ways to treat injuries in people and animals.

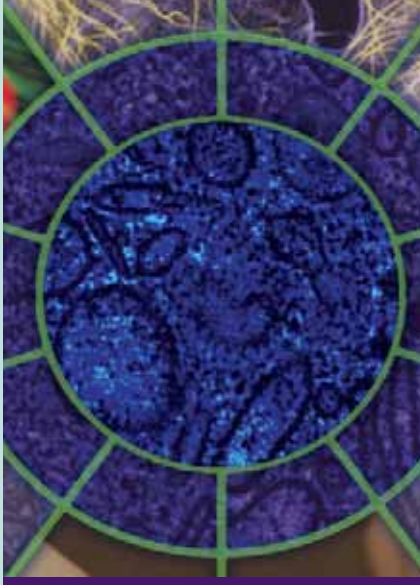
As you can see, all of your 200-plus cell types work in harmony, each playing its own role to keep you alive and healthy. Next, we'll cover how cells replenish themselves and how certain cells enable us to pass on some—but not all—of our genes through sexual reproduction.

Big Science



BRIAN OLIVER

Gene chips let scientists visualize the activity of thousands of molecules.



"-Omics." You probably won't see this suffix in the dictionary just yet, but chances are you've heard it in words like genomics and proteomics. A new scientific catchphrase of the 21st century, -omics tagged on to the end of a word means a systematic survey of an entire class of molecules. For example, genomics is the study of all of the genes of a particular organism (rather than one gene or just a few). Scientists interested in metabolomics study how metabolism (the body's breakdown of certain molecules and the synthesis of others) is governed by thousands of enzymes and signaling networks in an organism.

Name just about any branch of life science, and chances are researchers are working on its -omics in an attempt to figure out how the zillions of separate pieces of biological information can explain the whole of biology. You can probably figure out what lipidomics is. You're right! It relates to lipids, the oily molecules in cell membranes. Researchers in this field try to identify, determine the function of, and analyze how all the lipids in a cell respond to cellular stimuli (like hormones). Do they shift around? Break apart? Change the texture of the membrane?

Because this sort of blanket approach means evaluating millions of molecules, it requires and generates a landslide of data. Only extremely sophisticated computer programs can process the amount of data typical of -omics experiments. Consequently, information management is becoming a big challenge in biology. Many years from now, scientists hope to be able to construct computer models of how organisms as simple as bacteria and as complex as people do all the incredible things they do. Such models will have great practical use in testing medicines and in understanding and predicting many aspects of health and disease.

Many scientists doing -omics experiments collect their data using microarrays. These high-tech grids contain tiny samples of hundreds or even thousands of types of molecules. Using microarrays, scientists can observe and compare molecules under carefully controlled conditions.

For example, a kind of microarray known as a gene chip lets genome scientists track the activity of many genes simultaneously. This allows researchers to compare the activities of genes in healthy and diseased cells and, in that way, pinpoint the genes and cell processes that are involved in the development of a disease.

Got It?

How do cells specialize (differentiate), and why is this important?

Give three examples of different specialized cells and explain how they are customized to accomplish their cellular duties.

How are adult stem cells different from embryonic stem cells?

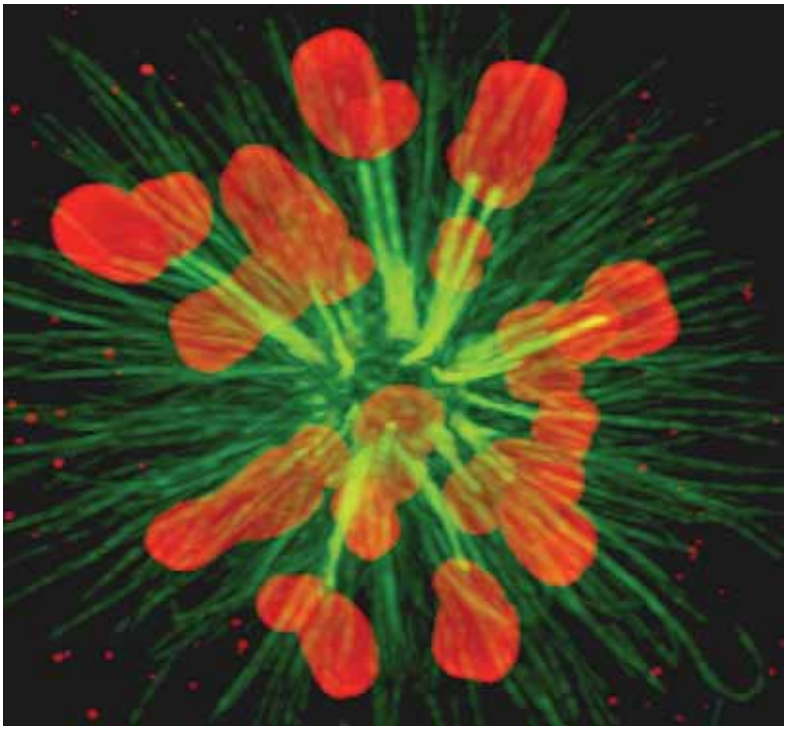
Name four model organisms scientists use to study basic biological processes.

Give two examples of why a cell's shape is important.

Give two examples of why the ability to move is important to cells.

Cellular Reproduction: Multiplication by Division

Each of us began as a single cell. This cell couldn't move, think, see, or do things like laugh and talk. But the one thing it could do, and do very well, was divide—and divide it did. The lone cell became two, and then four, then eight and so on, in time becoming the amazing person that is you. Think of how far you've come. You can laugh at a joke, stand on your head, read a book, eat an ice cream cone, hear a symphony, and do countless other things.



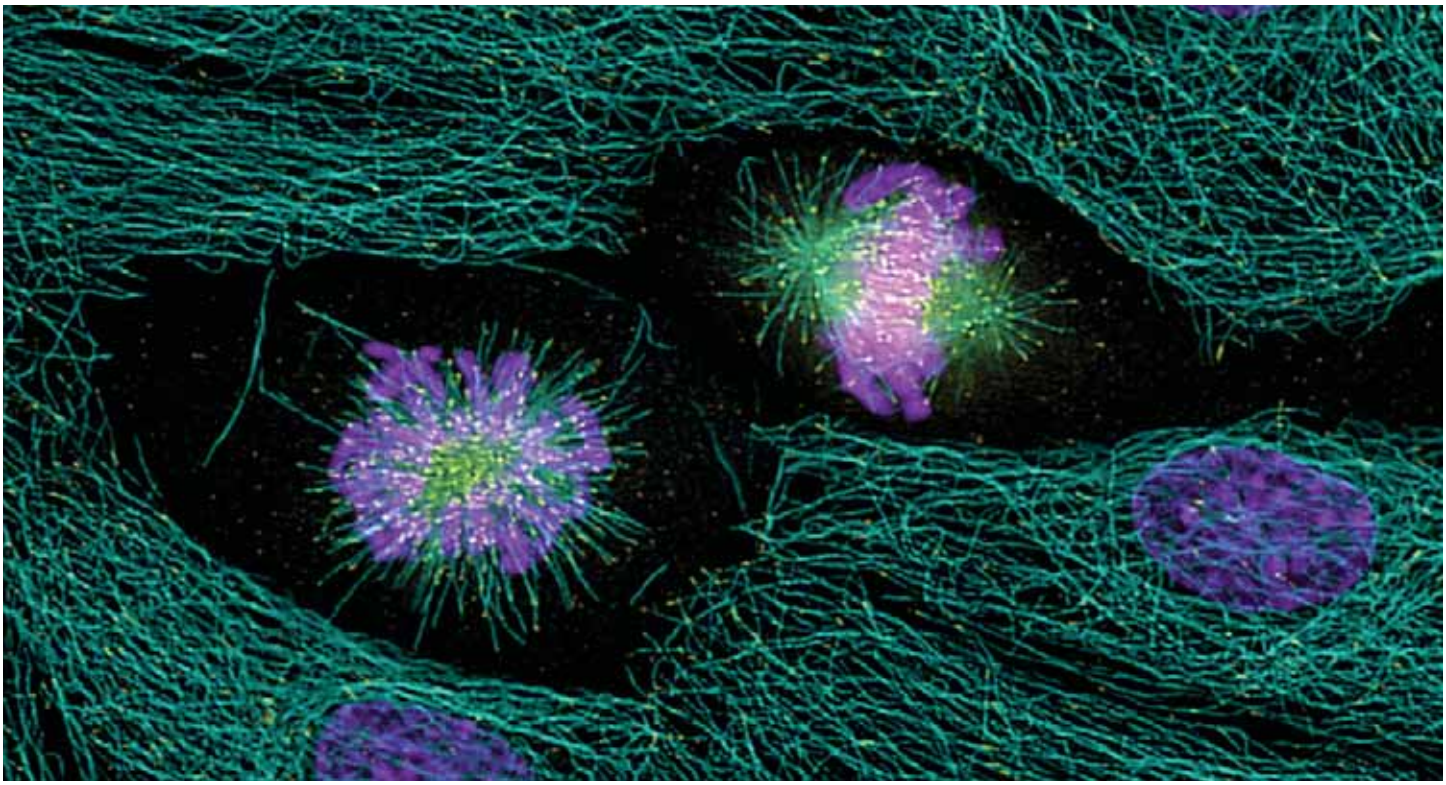
TED SALMON

In this chapter, we will discuss how cells divide, a topic that has fascinated scientists since they first observed it through a microscope more than 100 years ago. Scientists can actually watch cells divide under the microscope, and they have been able to figure out the rules of division by carefully observing the process, much as someone could gradually learn the rules of a game like football or chess by watching it played repeatedly.

But you don't need your own microscope to see cells dividing. By hooking up cameras to their microscopes, scientists have produced stunning images of the process, two of which we've reproduced here.

"It is not a simple life to be a single cell, although I have no right to say so, having been a single cell so long ago myself that I have no memory at all of that stage of my life."

—Lewis Thomas (1913–1993) author, biologist, physician

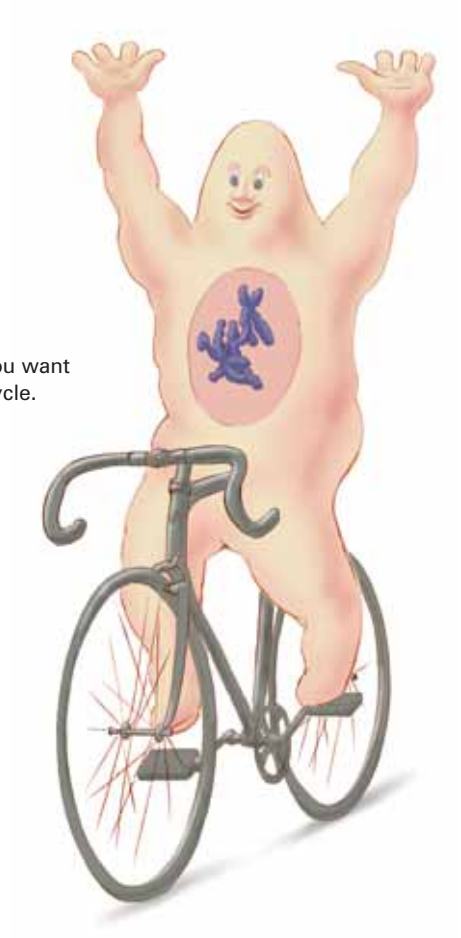


TORSTEN WITTMAN

The Two Faces of Cell Division

There are two kinds of cell division: **mitosis** and **meiosis**. Mitosis is essentially a duplication process: It produces two genetically identical "daughter" cells from a single "parent" cell. You grew from a single embryonic cell to the person you are now through mitosis. Even after you are grown, mitosis replaces cells lost through everyday wear and tear. The constant replenishment of your skin cells, for example, occurs through mitosis. Mitosis takes place in cells in all parts of your body, keeping your tissues and organs in good working order.

Meiosis, on the other hand, is quite different. It shuffles the genetic deck, generating daughter cells that are distinct from one another and from the original parent cell. Although virtually all of your cells can undergo mitosis, only a few special cells are capable of meiosis: those that will become eggs in females and sperm in males. So, basically, mitosis is for growth and maintenance, while meiosis is for sexual reproduction.



Look here if you want to see a cell cycle.

The Cycling Cell

Before focusing on mitosis, let's take a step back and look at the big picture. The illustration on the right shows the cell cycle of a eukaryotic plant or animal cell. This cycle begins when the cell is produced by mitosis and runs until the cell undergoes its own mitosis and splits in two. The cycle is divided into distinct phases: G_1 (gap 1), S (synthesis), G_2 (gap 2), and M (mitosis and cytokinesis). As you can see, mitosis only occupies a fraction of the cycle. The rest of the time—phases G_1 through G_2—is known as **interphase**.

Scientists used to think of interphase as a resting phase during which not much happened, but they now know that this is far from the truth.

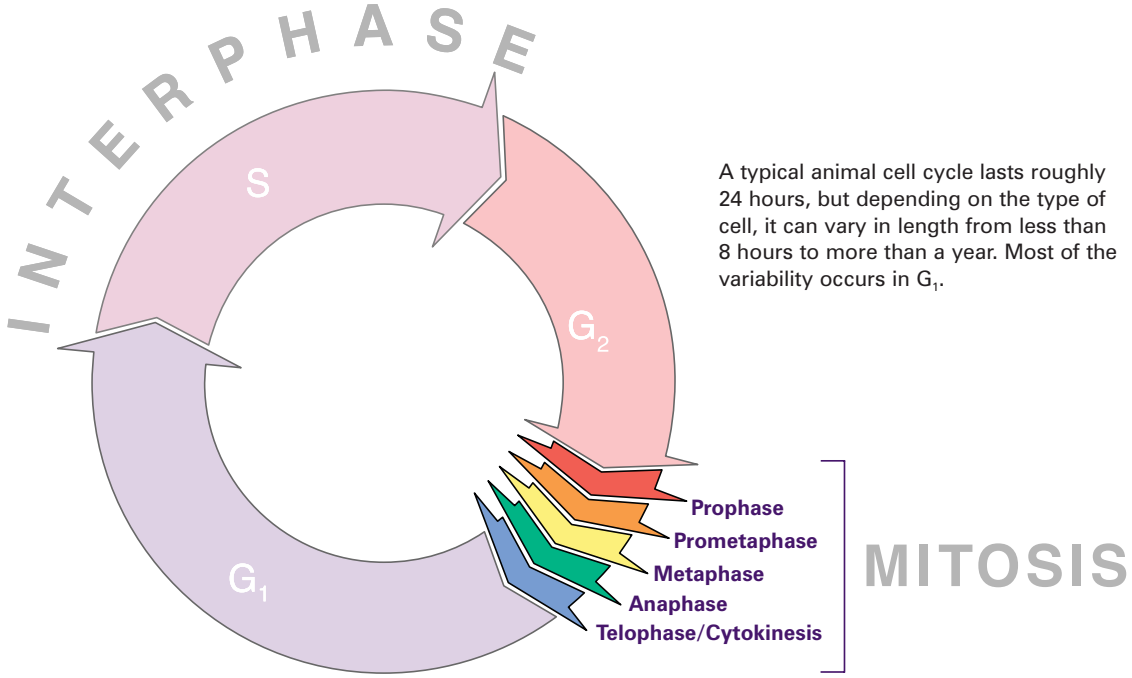
Checkpoints: Cellular Inspectors

At first glance, the orderly progression of the cell through the phases of the cell cycle may seem perfectly straightforward. When building a house, the walls aren't erected until after the foundation has been laid. Likewise, in the cell, mitosis doesn't begin until after the genetic material has been copied. Otherwise, the daughter cells would end up with less than a complete set of chromosomes and probably would die. So in the cell cycle, just as in housebuilding, certain steps need to precede others in an orderly fashion for the process to work.

How does the cell "know" when a step has been completed and it's time to move on to the next? The answer is that the cell has several molecular "inspectors" stationed at intervals—called **checkpoints**—throughout the cell cycle. These cellular

HANS MEHLIN, NOBEL PRIZE.ORG

It is during interphase that chromosomes—the genetic material—are copied, and cells typically double in size. While this is happening, cells continue to do their jobs: Your heart muscle cells contract and pump blood, your intestinal cells absorb the food you eat, your thyroid gland cells churn out hormones, and so on. In contrast, most of these activities cease during mitosis while the cell focuses on dividing. But as you have probably figured out, not all cells in an organ undergo mitosis at the same time. While one cell divides, its neighbors work to keep your body functioning.



A typical animal cell cycle lasts roughly 24 hours, but depending on the type of cell, it can vary in length from less than 8 hours to more than a year. Most of the variability occurs in G_1.

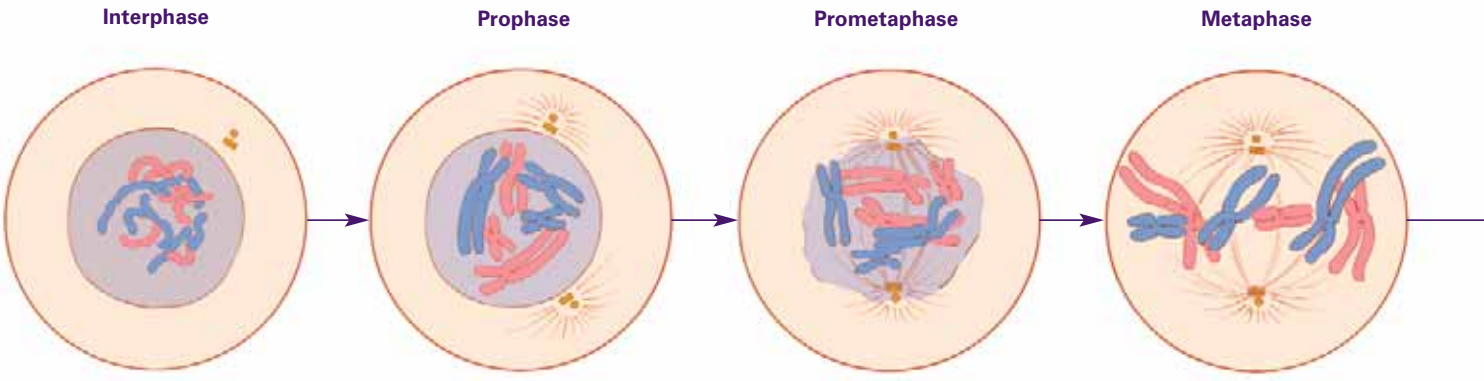
inspectors function much like building inspectors do: If a step has been completed to their satisfaction, they give the OK to move forward. If not, they halt progress until the cellular construction workers finish the task. There are three major checkpoints in the cell cycle: one between G_1 and S phase, one between G_2 and mitosis, and one during mitosis itself.

The concept of checkpoints in the cell cycle was first introduced by Ted Weinert of the University of Arizona in Tucson, and Leland Hartwell of the Fred Hutchinson Cancer Research Center in Seattle, Washington. In experiments with yeast cells, Weinert and Hartwell showed that a protein called Rad9 is part of a cell cycle checkpoint. Normal cells will stop and repair any damage to their DNA before embarking upon mitosis. Cells that lack Rad9, however, ignore the damage and proceed through mitosis, with catastrophic consequences—having inherited damaged DNA, the daughter cells invariably die. Since these discoveries were made, other checkpoint genes have been identified in many kinds of cells, including human cells.

Hartwell has identified more than 100 genes that help control the cell cycle, and in recognition of the importance of these discoveries, he shared the Nobel Prize in physiology or medicine in 2001.

Phases of Mitosis

Mitosis is responsible for growth and development, as well as for replacing injured or worn out cells throughout your body. For simplicity, we have illustrated cells with only six chromosomes.



Interphase
Chromosomes duplicate, and the copies remain attached to each other.

Prophase
▲ In the nucleus, chromosomes condense and become visible. In the cytoplasm, the spindle forms.

Prometaphase
▲ The nuclear membrane breaks apart, and the spindle starts to interact with the chromosomes.

Metaphase
The copied chromosomes align in the middle of the spindle.

Mitosis: Let's Split!

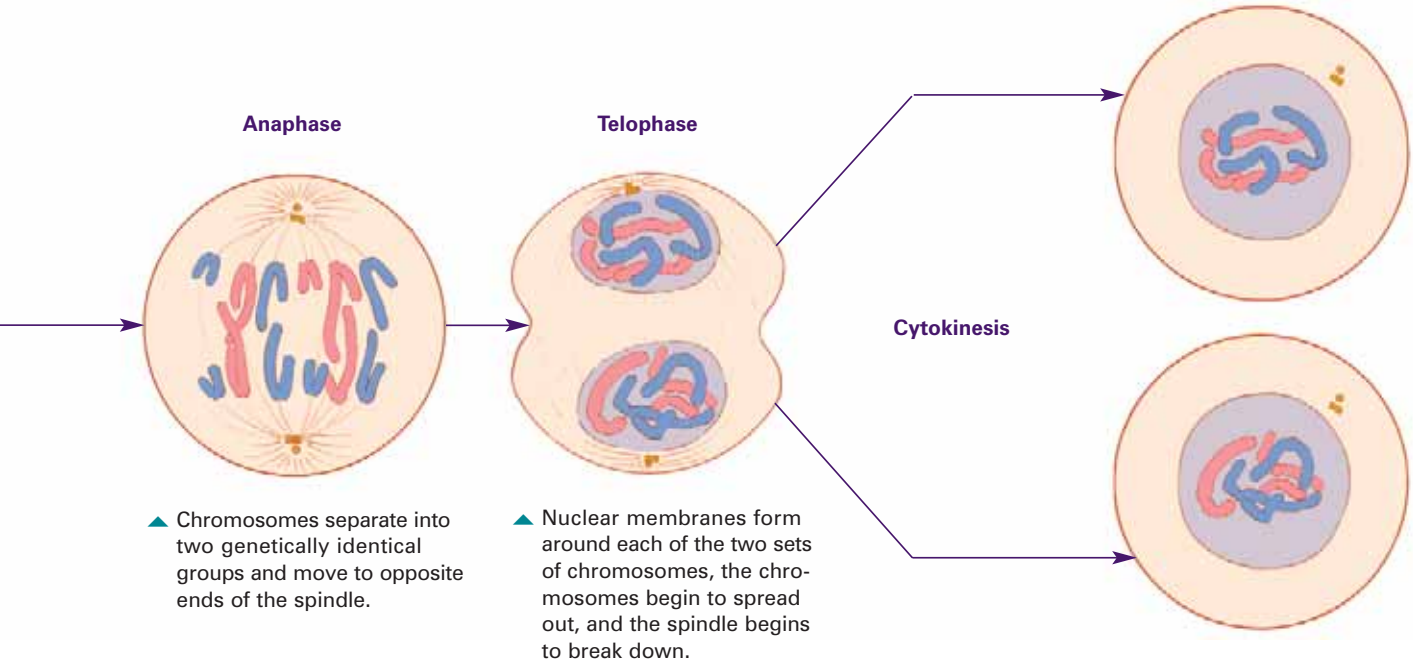
Mitosis is the most dramatic event in a cell's life. Cellular structures that have always been there suddenly disintegrate, new structures are constructed, and it all culminates in the cell splitting in half. Imagine quietly going about your business one day, when you suddenly feel the bones of your skeleton rearranging themselves. Then, you find yourself being pinched apart from your midline, and before you know it, someone who looks just like you is sitting beside you. That's akin to what happens to a cell during mitosis.

Mitosis is divided into six phases: **prophase**, **prometaphase**, **metaphase**, **anaphase**, **telophase**, and **cytokinesis**. The first five phases do the job of splitting the nucleus and its duplicated genetic information in two, while in the final step, the entire cell is split into two identical daughter cells.

The primary goal of mitosis is to make sure that each daughter cell gets one copy of each chromosome. Other cellular components, like ribosomes and mitochondria, also are divided between the two daughter cells, but their equal partitioning is less important.

ANDREW S. BAJER

The stages of mitosis are clear in these cells from the African globe lily (*Scadoxus katherinae*) whose enormous chromosomes are thicker in metaphase than the length of the longest human chromosome.



▲ Chromosomes separate into two genetically identical groups and move to opposite ends of the spindle.

▲ Nuclear membranes form around each of the two sets of chromosomes, the chromosomes begin to spread out, and the spindle begins to break down.

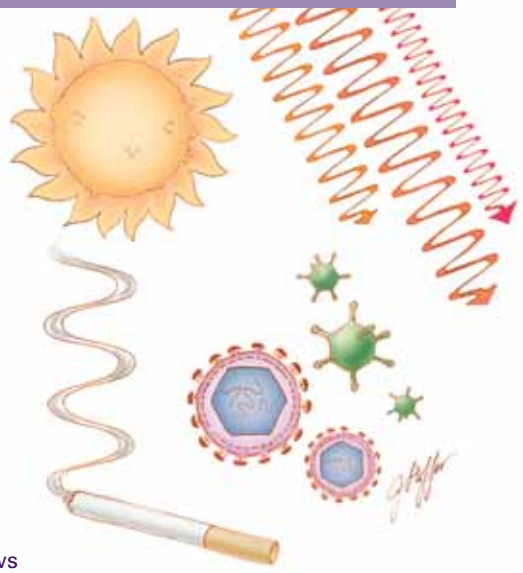
The cell splits into two daughter cells, each with the same number of chromosomes as the parent. In humans, such cells have two copies of 23 chromosomes and are called **diploid.**

Cancer: Careening Out of Control

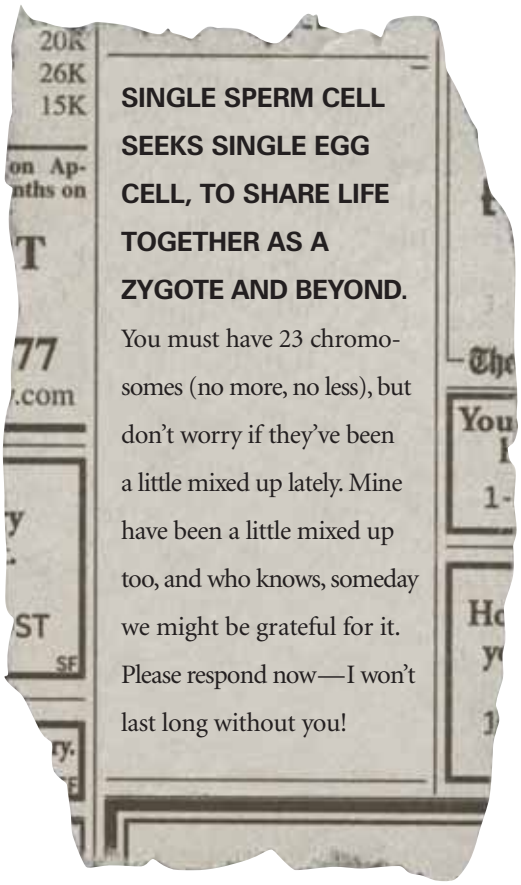
Your body carefully controls which cells divide and when they do so by using molecular stop and go signals. For example, injured cells at the site of a wound send go signals to the surrounding skin cells, which respond by growing and dividing and eventually sealing over the wound. Conversely, stop signals are generated when a cell finds itself in a nutrient-poor environment. Sometimes, however, go signals are produced when they shouldn't be, or stop signals aren't sent or heeded. Both scenarios can result in uncontrolled cell division and cancer. Mitosis then becomes a weapon turned against the body, spurring the growth of invasive tumors.

Fortunately, it takes more than one mistaken stop or go signal for a cell to become cancerous. Because our bodies are typically quite good at protecting their essential systems, it usually requires a one-two punch for healthy cells to turn malignant. The punches come in the form of errors, or **mutations**, in DNA that damage a gene and result in the production of a faulty protein. Sunlight, X rays and other radiation, toxins such as those found in cigarette smoke and air pollution, and some viruses can cause such mutations. People also can inherit mutations from their parents, which explains why some families have higher rates of certain cancers: The first punch is delivered at conception. Subsequent mutations can then push a cell down the path toward becoming cancerous.

Ironically, mitosis itself can cause mutations too, because each time a cell's DNA is copied, errors are made. (Fortunately, almost all of these errors are corrected by our extremely efficient DNA repair systems.) So there's an inherent trade off in mitosis: It allows us to grow to maturity and keeps us healthy, but it's also the source of potentially damaging DNA mutations. We'll come back to the link between cell division and DNA damage when we talk about aging in the next chapter.



A number of environmental factors cause DNA mutations that can lead to cancer: toxins in cigarette smoke, sunlight and other radiation, and some viruses.



Meiosis: Sex, Heredity, and Survival

Nearly all multicellular organisms reproduce sexually by the fusion of an egg and a sperm. Like almost every cell in your body, this new cell—a zygote—has a full contingent of 23 pairs of chromosomes. But what about its parent cells, the sperm and egg? If the egg and sperm each had 23 chromosome pairs, their union would result in a zygote with 46 pairs—double the usual number. Theoretically, this cell would then grow into a person with 46 pairs of chromosomes per cell (rather than the usual 23 pairs). Subsequent generations would have even more chromosomes per cell. Given the length of human history, can you imagine how many chromosomes our cells would have by now? Clearly, this is not what actually happens. Even early cell biologists realized that there must be a way to cut in half the number of chromosomes in egg and sperm cells.

Spindle Secrets

If mitosis is a show, then chromosomes are the stars. The main plot line is the even distribution of stars into two groups by the time the curtain goes down. But the stars play an unusually passive role. A director called the mitotic **spindle** moves them from here to there on the cellular stage. The mitotic spindle—a football-shaped array of fibers made of microtubules and associated proteins—forms at the beginning of mitosis between opposite ends, or poles, of the cell.

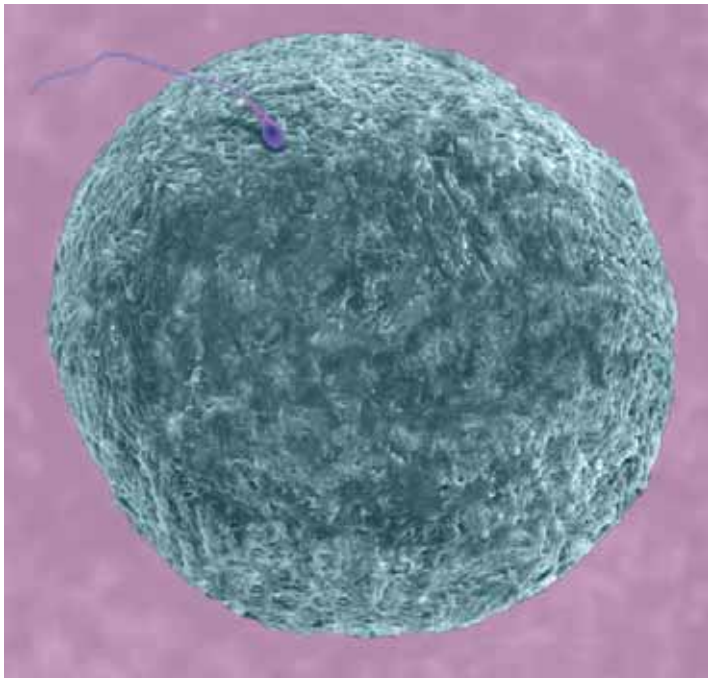
The chromosomes (blue) become attached to the spindle fibers (green) early in mitosis. The spindle is then able to move chromosomes through the various phases of mitosis.

How spindle fibers move chromosomes has captivated scientists for decades, and yet the answer remains elusive. Conly Rieder, a cell biologist at the Wadsworth Center in Albany, New York, is investigating this challenging question. Some scientists believe that motor proteins act like cellular buses, conveying chromosomes along the fibers. Others, including Rieder, favor the idea that microtubules shrink or grow at their ends to reel in or cast out chromosomes. Still other scientists believe that the answer will come from combining both views.

The potential applications of this molecular detective work are significant. When the spindle makes mistakes, chromosomes can end up in the wrong place, which may lead to cells with abnormal numbers of chromosomes. This, in turn, can cause serious problems, such as **Down syndrome**, cancer, or miscarriage, which, in 35 percent of cases is associated with cells carrying an atypical amount of genetic material.

To accomplish that task, nature devised a special kind of cell division called meiosis. In preparation for meiosis, the chromosomes are copied once, just as for mitosis, but instead of one cell division, there are two. The result is four daughter cells, each containing 23 individual chromosomes rather than 23 pairs.

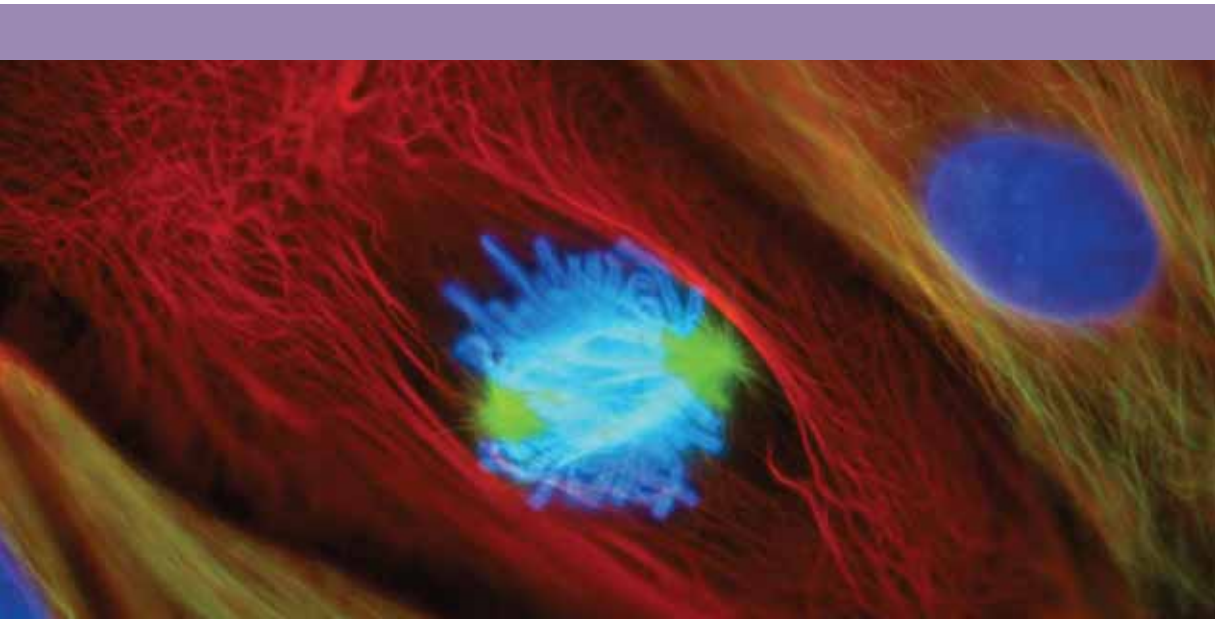
Meiosis is divided into chronological phases just like mitosis, and although the phases have the same names, there are some differences between them, especially in the early stages. Also, since there are two cell divisions in meiosis, each phase is followed by a I or II, indicating to which division it belongs.



Every one of us began with the fusion of a sperm and egg cell.

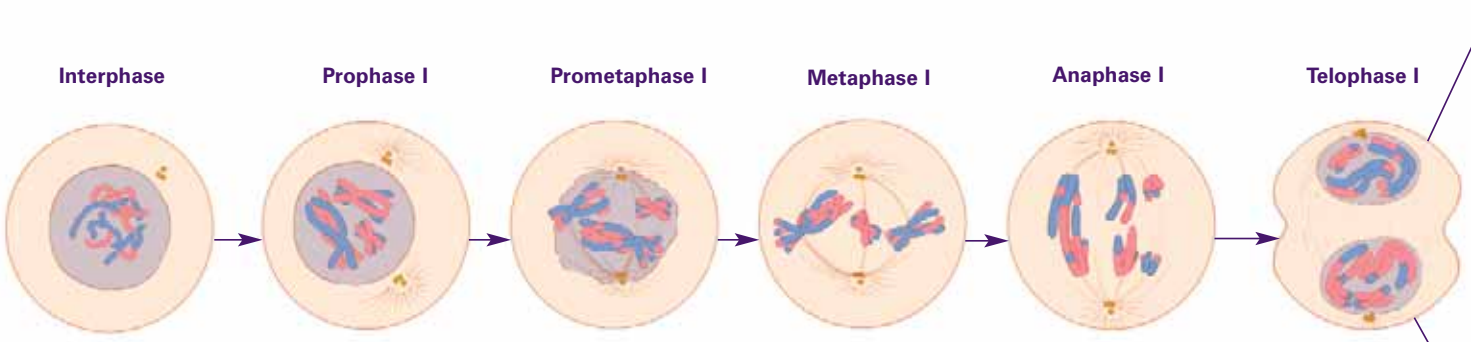
"The cell is always speaking—the secret is to learn its language."

—Andrew S. Bajer (1928–) cell biologist



Phases of Meiosis

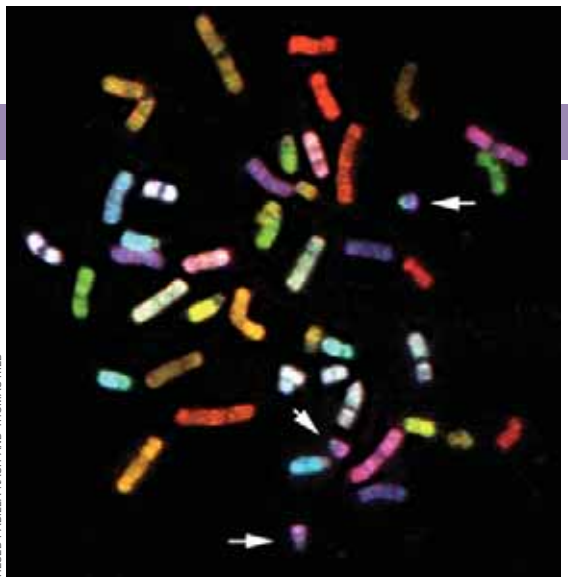
▼ Meiosis is used to make sperm and egg cells. During meiosis, a cell's chromosomes are copied once, but the cell divides twice. For simplicity, we have illustrated cells with only three pairs of chromosomes.



▲ In Prophase I, the matching chromosomes from your mother and father pair up.

▲ While paired up, maternal and paternal chromosomes can swap matching sections. This process, called **crossing over**, increases genetic diversity.

First Meiotic Division



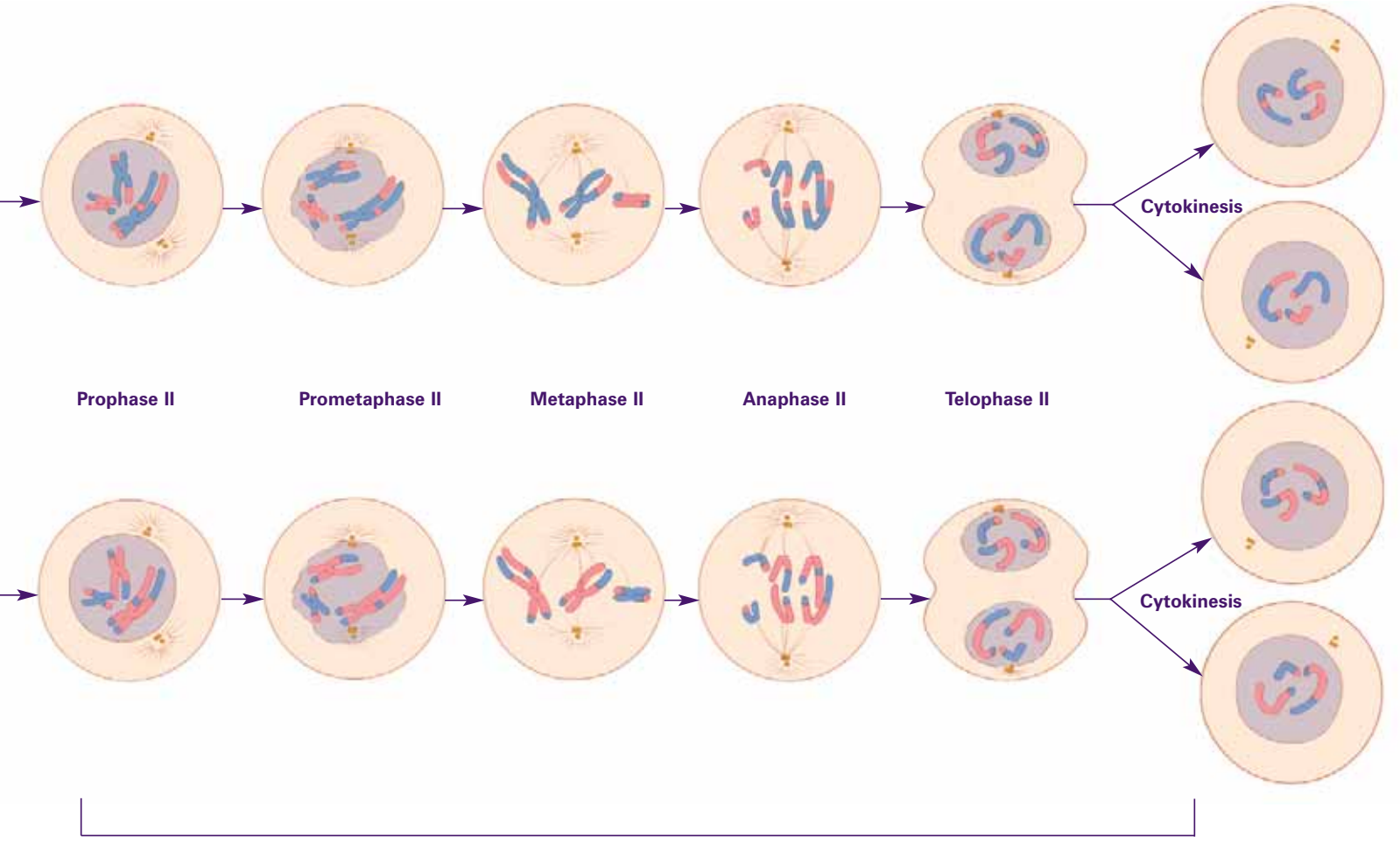
HESED PADILLA-NASH AND THOMAS RIED

This diagram (karyotype) of all the chromosomes in a single cell shows three—rather than the normal two—copies of chromosome 21 (arrows). This condition is commonly known as Down syndrome.

Errors in Aging Eggs

Men produce sperm continuously from puberty onward, and the formation of a sperm takes about a week. The situation is quite different in women. Baby girls are born with a certain number of "pre-egg" cells that are arrested at an early stage of meiosis. In fact, the pre-egg cell does not complete meiosis until after fertilization has occurred. Fertilization itself triggers the culmination of the process. This means that meiosis in women typically takes decades and can take as long as 40 to 50 years!

Scientists have long suspected that this extended meiosis in women is responsible for certain genetic disorders in their children. The pre-egg cells have years in which to accumulate damaging mutations that may cause errors in the remaining steps of meiosis. For example, the risk of Down syndrome, a common cause of mental retardation, increases in the babies of older mothers.



▲ The four daughter cells have half as many chromosomes as the parent cell and are called **haploid**.

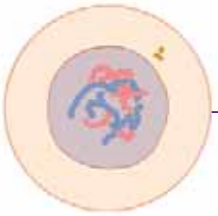
The syndrome occurs when the chromosome 21 pair fails to separate during meiosis and both copies of the chromosome end up in a single egg cell. Subsequent fertilization by a sperm means that the resulting cell has three copies of chromosome 21 rather than the standard two. No one knows exactly how or why the chromosomes fail to separate, and the question has been difficult to answer because of the lack of a suitable animal model in which to study the disorder.

Now, Sharon Bickel, a molecular biologist at Dartmouth College in Hanover, New Hampshire, has developed a method that uses fruit flies to gain insight into this human puzzle. Fruit flies normally produce eggs continuously, but Bickel manipulated their diet in such a way as to suspend egg maturation, allowing the eggs to age. This mimicked the aging of human eggs. Studying the aged fruit fly eggs, Bickel found that the incidence of problems in chromosome separation increased, just as it does in older women. Her work also indicated that a backup genetic system that helps to ensure proper chromosome separation and distribution deteriorates as fruit fly eggs age. No one yet knows if the same backup system exists in humans or if the same mistakes seen in the flies account for the increased risk of Down syndrome in the babies of older mothers. But the fruit fly model system will allow Bickel and others to investigate these important questions.

Comparison Between Mitosis and Meiosis

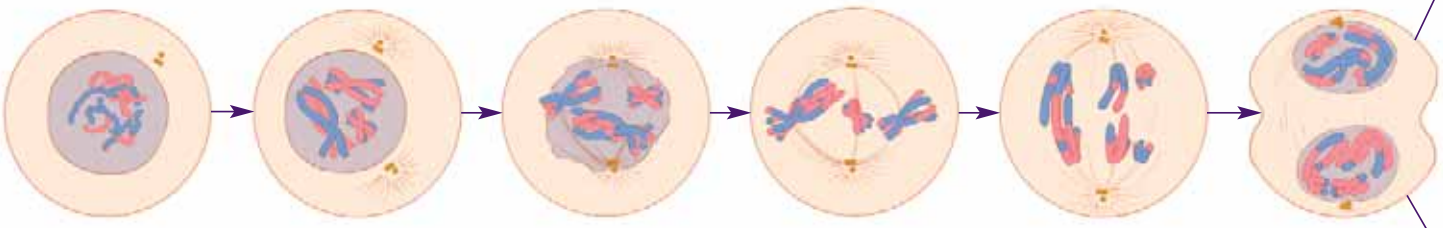
Mitosis

Interphase

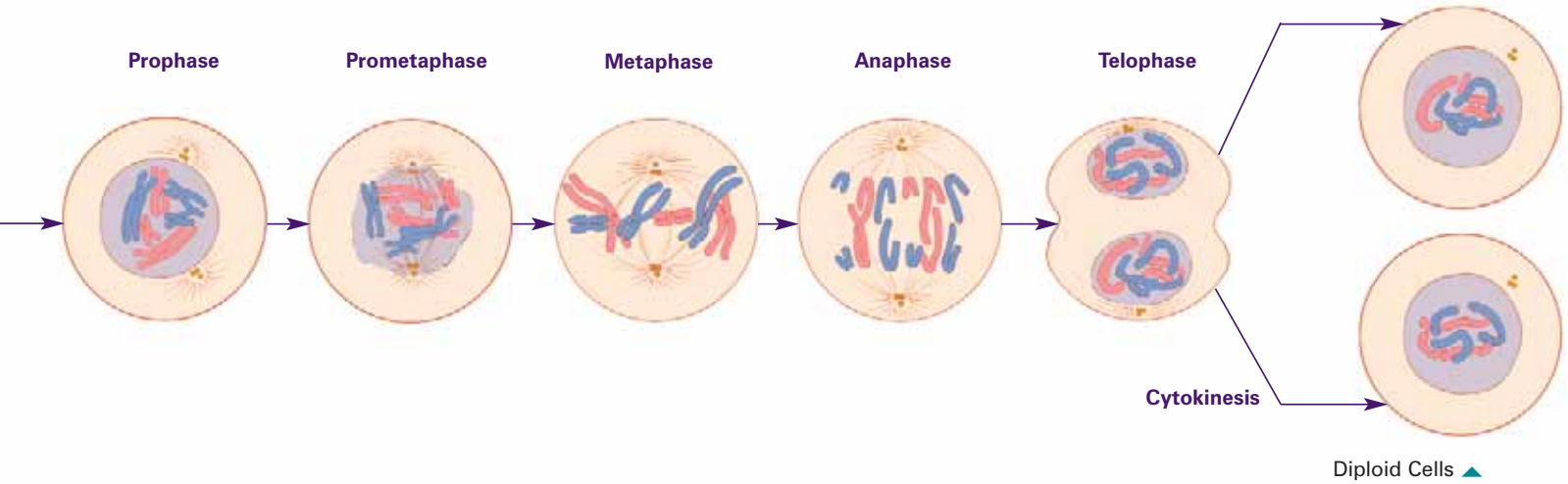


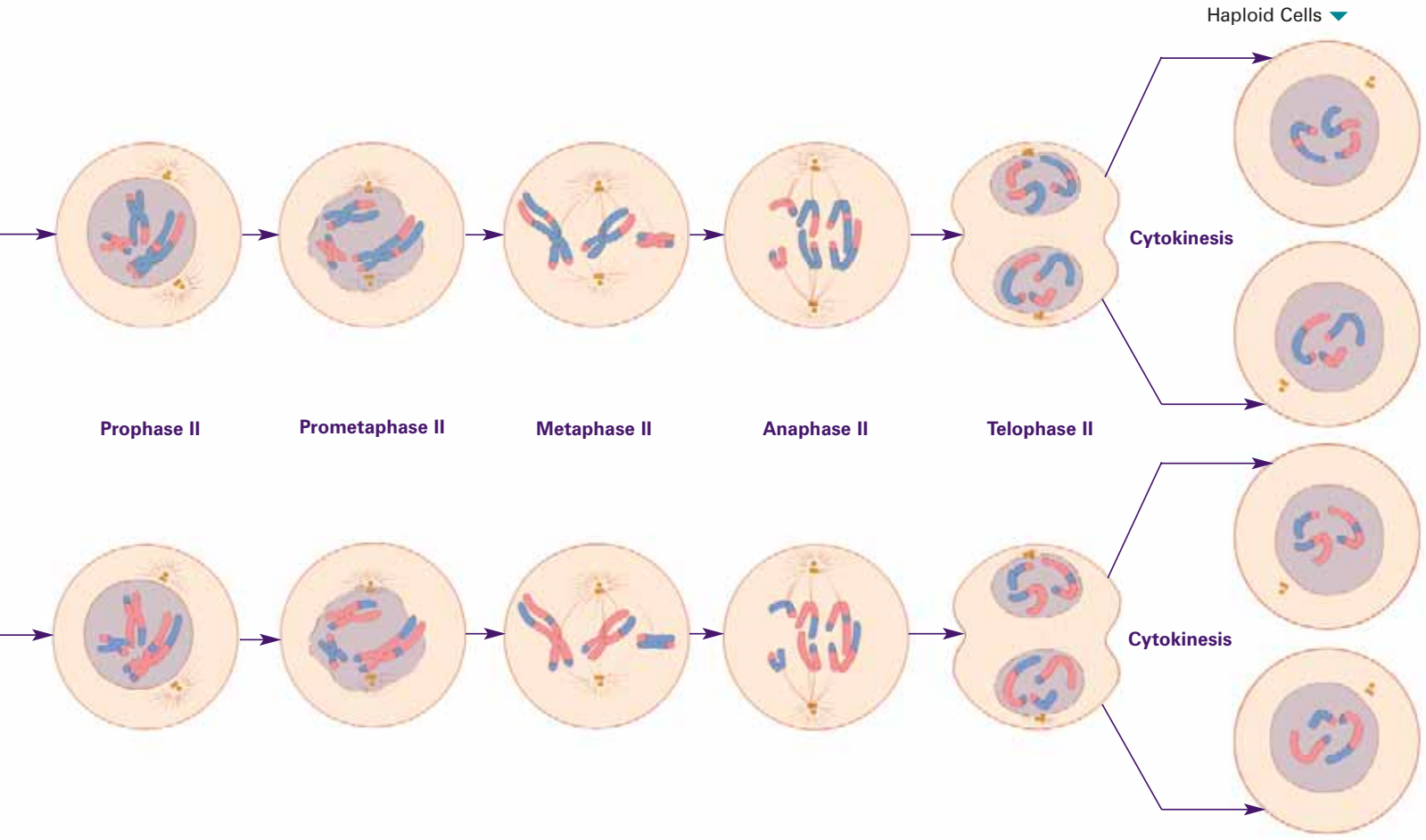
Meiosis

Interphase | Prophase I | Prometaphase I | Metaphase I | Anaphase I | Telophase I



Cytokinesis


Prophase
Prometaphase
Metaphase
Anaphase
Telophase
Cytokinesis
Diploid Cells

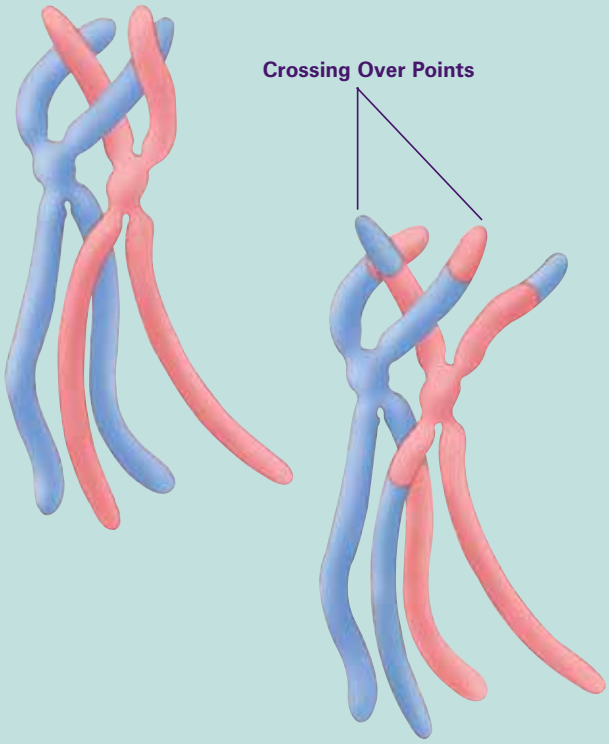

Haploid Cells
Cytokinesis
Prophase II
Prometaphase II
Metaphase II
Anaphase II
Telophase II
Cytokinesis

Why You're Not Just Like Your Relatives

Even members of the same family, who share much of their genetic material, can be dramatically different from one another. If you've ever been to a family reunion, you've seen living proof of this. How can the incredible diversity that we see in our own families, let alone in the world at large, be explained? Imagine 23 couples participating in a dance. The couples begin by lining up facing each other, forming two parallel lines. It doesn't matter which line the dancers stand in, as long as they're across from their partners. Because men and women can be in either line, the dancers can line up in millions of different ways. In fact, the number of possible arrangements is 2^{23}, or more than 8 million!

Some family members are exactly the same (genetically, at least): identical twins. Identical twins arise when the embryo splits early in development and creates two genetically identical babies. Fraternal twins, the more common type, are genetically no more similar than siblings. They develop from two different eggs, each fertilized by a different sperm.

Chromosome Dancers



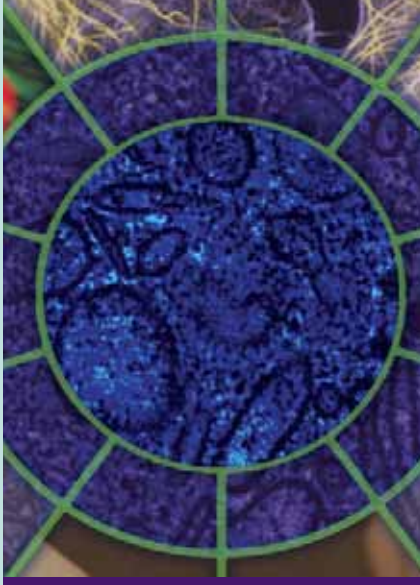
You can think of the partitioning of the 23 pairs of chromosomes between the two daughter cells during the first cell division in exactly the same way: Each daughter cell will get one chromosome from each pair, but which one it gets is completely random. As we saw with the dancers, this generates over 8 million different combinations. This means that a single set of parents can produce over 64 trillion different zygotes!

Meiosis can generate still more genetic variation through crossing over, during which chromosome partners physically swap sections with one another, generating hybrid chromosomes that are a patchwork of the original pair. This rearrangement of the genetic material expands the number of possible genetic configurations for the daughter cells, further increasing diversity.

So, thanks to the random splitting up of chromosome pairs and the genetic swapping that goes on during meiosis, you inherit a rather mixed bag of genes from your parents. This explains why family members can be so different from one another despite having a number of genes in common.

The genetic diversity brought to us courtesy of meiosis (and occasional genetic mutations) enhances the survival of our species. Having a widely varied pool of genes in a population boosts the odds that in the face of disease outbreaks or harsh environmental conditions, at least some individuals will have the genetic stuff it takes to survive—and pass on their genes. So in more ways than one, you have meiosis (and your parents) to thank for being here at all!

You share some genes, and hence some physical traits, with your parents and your other relatives. But thanks to meiosis, you are a unique individual.



Got It?

Compare mitosis and meiosis in terms of their purpose and the type of cell in which each takes place.

Do cells divide during interphase?

What are cell cycle checkpoints, and why are they important?

Do most of our cells have one or two copies of each chromosome?

Describe two genetic processes that make each person unique.

BY KIRSTIE SALTSMAN

The Last Chapter: Cell Aging and Death

Have you ever wondered why we age? What exactly is happening inside our bodies to bring on the wrinkles, gray hair, and the other changes seen in older people? Considering the universality of the process, you might be surprised to know that there remain many unanswered questions about how aging happens at the cellular level. However, theories abound, and the roles played by various suspects in the aging process are beginning to take shape.

UN/DPI PHOTOS

JENNA KARLSBERG

Beautiful. This image of a woman's eye was photographed and titled by her 15-year-old granddaughter.

Cell death, on the other hand, is an area in which scientists have made great leaps in understanding in recent years. Far from being strictly harmful, scientists have found that cell death, when carefully controlled, is critical to life as we know it. Without it, you wouldn't have your fingers and toes or the proper brain cell connections to be able to read the words on this page.

If you'd like to know more about these fascinating processes, read on. And thank cell death for it!

Aging: A World of Theories

Most scientists now agree that aging is, at least in part, the result of accumulating damage to the molecules—such as proteins, lipids, and nucleic acids (DNA and RNA)—that make up our cells. If enough molecules are damaged, our cells will function less well, our tissues and organs will begin to deteriorate, and eventually, our health will decline. So in many respects, we appear to age much like a car does: Our parts start to wear out, and we gradually lose the ability to function.

The question is, where does the damage come from? It turns out that damage can come from many different sources, both internal and external.

Thieving Oxygen

Take a deep breath. Oxygen in the air you just breathed entered your lungs, passed into the tiny blood vessels that line them, and then went on a wild ride through the creeks, rivers, and cascades of your bloodstream. Thanks to your rich network of blood vessels, oxygen gets carried to every cell in every corner of your body. Once delivered to a cell, oxygen heads for the mitochondria, where it slurps up the electrons coming off the end of the energy-production assembly line. Mitochondria need oxygen to generate cellular energy, and humans need a constant supply of that energy to survive. That's why people die within a few minutes if deprived of oxygen.

But oxygen has a darker side, and it has attracted the attention of scientists who study aging. Normally, an oxygen molecule (O_2) absorbs four electrons and is eventually safely converted into water. But if an oxygen molecule only takes up one or two electrons, the result is one of a group of highly unstable molecules called **reactive oxygen species** that can damage many kinds of biological molecules by stealing

Growing Old Is Fairly New

AP/WIDE WORLD PHOTOS

When she died at the verified age of 122, Jeanne Calment (1875–1997) had lived longer than any other human on record.

It's important to realize that growing old is a relatively new phenomenon in humans. For more than 99.9 percent of the time humans have roamed the Earth, average life expectancies have topped out at 30 or 40 years. The most dramatic leap in life expectancy occurred in the past century, with the advent of improved sanitation and medical care in developed countries. For example, in 1900, the average lifespan in the United States was 47 years, while just a century later, it had skyrocketed to 77 years.

In contrast to the average life expectancy, the maximum human life expectancy has always hovered around 115 to 120 years. This apparent inborn maximum intrigues scientists who study aging. Does there have to be a maximum? What determines it? Why is it about 120 years?

Studies of centenarians (people who live 100 years or more) have indicated that a positive and inquisitive outlook, healthy eating habits, moderate exercise, close ties to family and friends, and genetic factors are associated with long life. Some centenarians have their own theories. Jeanne Calment, a French woman who died at age 122, claimed olive oil, port wine, and chocolate were the keys to her long life!

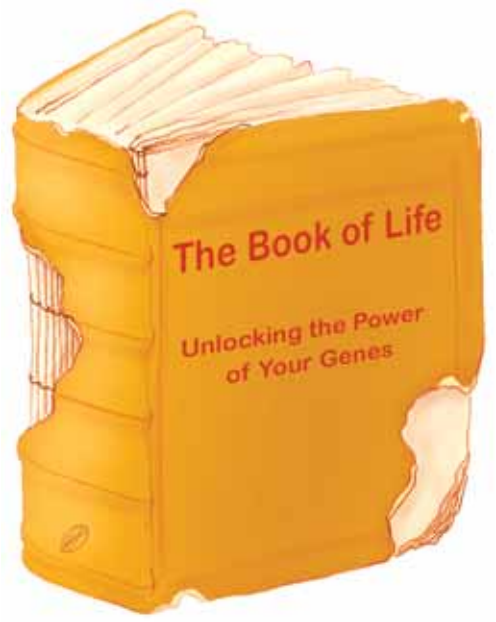
their electrons. These renegade oxygen-containing species can mutate your genes, damage the lipids that make up your cellular membranes, and break the proteins that do much of the cell's work, thereby causing cellular injury in multiple and overlapping ways.

Vividly colored fruits and vegetables such as these are rich in antioxidants. Although their role in the aging process is still unknown, antioxidants are believed to reduce the risk of certain cancers.

Damage, Yes. But Aging?

Scientists already have uncovered clear links between reactive oxygen compounds and aging. Fruit flies genetically engineered to produce high levels of enzymes that destroy reactive oxygen species lived almost 50 percent longer than normal flies. The same enzymes also made the microscopic roundworm *C. elegans* live significantly longer than normal.

Long-lived flies and worms are one thing, but are reactive oxygen species a factor in human aging as well? The answer is that we don't know yet. Large-scale clinical studies are under way to examine the link between aging and **antioxidants**—compounds, such as vitamins E and C, found in fruits and vegetables as well as within our own bodies. Antioxidants are less potent than the enzymes that quash reactive oxygen species, but like the enzymes, they can disarm dangerous reactive oxygen compounds.



Damage to each person's genome, often called the "Book of Life," accumulates with time. Such DNA mutations arise from errors in the DNA copying process, as well as from external sources, such as sunlight and cigarette smoke. DNA mutations are known to cause cancer and also may contribute to cellular aging.

Telomeres: Cellular Timekeepers

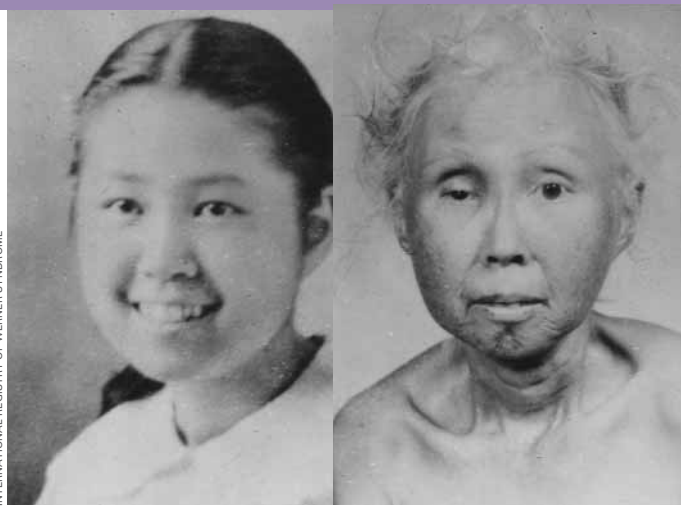
Many scientists speculate that another contributor to the aging process is the accumulation of cellular retirees. After cells divide about 50 times, they quit the hard work of dividing and enter a phase in which they no longer behave as they did in their youth.

How do our cells know when to retire? Do cellular clocks have a big hand and a little hand and go, "Tick, tock?" Not exactly. It turns out that each cell has 92 internal clocks—one at each end of its 46 chromosomes. Before a cell divides, it copies its chromosomes so that each daughter cell will get a complete set. But because of how the copying is done, the very ends of our long, slender chromosomes don't get copied. It's as if a photocopier cut off the first and last lines of each page.

As a result, our chromosomes shorten with each cell division. Fortunately, the regions at the

Aging in Fast-Forward: Werner Syndrome

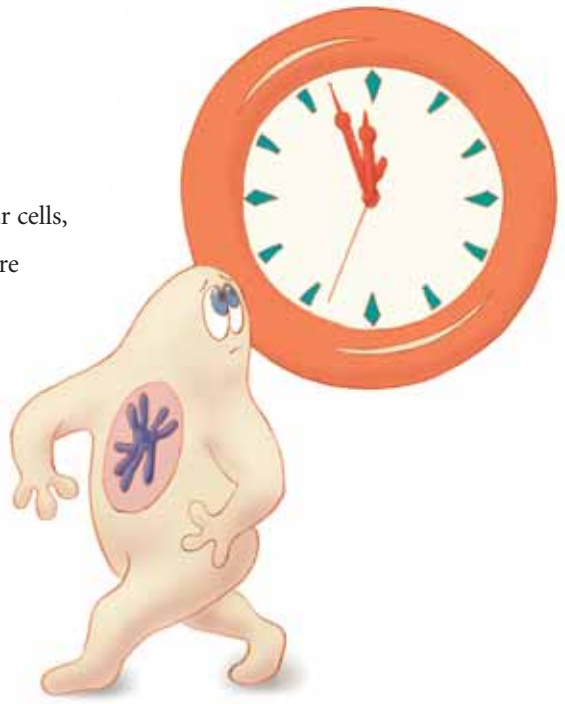
Mary was diagnosed with Werner syndrome at age 26, when she was referred to an ophthalmologist for cataracts in both eyes, a condition most commonly found in the elderly. She had developed normally until she'd reached her teens, at which point she failed to undergo the growth spurt typical of adolescents. She remembers being of normal height in elementary school, but reports having been the shortest person in her high school graduating class, and she had slender limbs relative to the size of her trunk. In her early 20s, she noticed her hair graying and falling out, and her skin became unusually wrinkled for someone her age. Soon after the diagnosis, she developed diabetes.

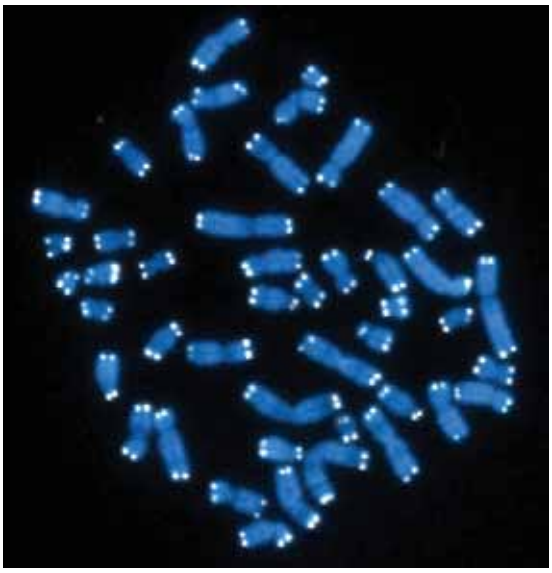


INTERNATIONAL REGISTRY OF WERNER SYNDROME

ends of our chromosomes—called **telomeres**—spell out the genetic equivalent of gibberish, so no harm comes from leaving parts of them behind. But once a cell's telomeres shrink to a critical minimum size, the cell takes notice and stops dividing.

In 1985, scientists discovered **telomerase**. This enzyme extends telomeres, rebuilding them to their former lengths. In most of our cells, the enzyme is turned off before we're born and stays inactive throughout our lives. But theoretically, if turned back on, telomerase could pull cellular retirees back into the workforce. Using genetic engineering, scientists reactivated the enzyme in human cells grown in the laboratory. As hoped, the cells multiplied with abandon, continuing well beyond the time when their telomerase-lacking counterparts had stopped.





HESED PADILLA-NASH AND THOMAS RIED

The 46 human chromosomes are shown in blue, with the telomeres appearing as white pinpoints. And, no you're not seeing double—the DNA has already been copied, so each chromosome is actually made up of two identical lengths of DNA, each with its own two telomeres.

Although hypothetical, Mary's case is a classic example of Werner syndrome, a rare inherited disease that in many respects resembles premature aging. People with Werner syndrome are particularly prone to cancer, cardiovascular disease, and diabetes, and they die at a young age—typically in their 40s. At a genetic level, their DNA is marked by many mutations. These characteristics support the theory that accumulating DNA mutations is a significant factor in normal human aging.

At age 15, this Japanese-American woman looked healthy, but by age 48, she had clearly developed symptoms of Werner syndrome.

The gene involved in Werner syndrome was identified in 1996 and was found to encode what appears to be an enzyme involved in DNA repair. This suggests that people with Werner syndrome accumulate excessive DNA mutations because this repair enzyme is either missing or not working properly.

A few years after the discovery of the human Werner syndrome gene, scientists identified a corresponding gene in yeast. Deleting the gene from yeast cells shortened their lifespan and led to other signs of accelerated aging. This supports a link between this gene and aging, and it provides scientists a model with which to study Werner syndrome and aging in general.

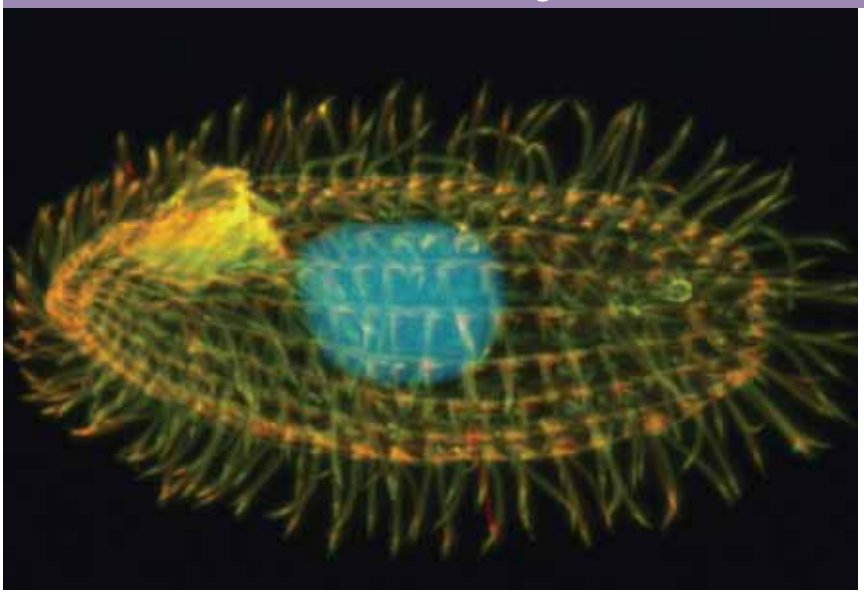
Cells That Never Die Can Kill You

Could reactivating telomerase in our cells extend the human lifespan? Unfortunately, the exact opposite—an untimely death from cancer—could occur. Cancer cells resurrect telomerase, and by maintaining the ends of the cell's chromosomes, the enzyme enables the runaway cell division that typifies cancer. It may, therefore, be a good thing that shrinking telomeres mark most of our cells for eventual retirement.

Nonetheless, scientists still have high hopes for harnessing telomerase. For instance, the enzyme could be used as a tool for diagnosing cancer, alerting doctors to the presence of a malignancy. Another possibility is to use chemicals that block telomerase to put the brakes on cell division in cancer cells. The search for such chemicals is on, and several candidates already have shown promise in preliminary studies.

According to most scientists, aging is caused by the interplay of many factors, such as reactive oxygen species, DNA mutations, and cellular retirement. Unfortunately, as a result, there is probably no such thing as a simple anti-aging remedy.

Pond-Dwelling Creature Led Scientists to Telomerase



RUPAL THAZHATH AND JACEK GAERTIG

Elizabeth Blackburn, a molecular biologist at the University of California, San Francisco, has been studying telomeres since the 1970s. She says that we can think of telomeres as the plastic caps at the ends of our shoelaces—the aglets of our genome. Her work has propelled our understanding of telomeres, in particular as they relate to aging and cancer.

Prior to her work, scientists knew telomeres existed but knew little else about them. Blackburn probed the genetic aglets through studies of a pond-dwelling microorganism called *Tetrahymena*. It may seem like a strange choice, but *Tetrahymena* has the distinct advantage of having roughly 20,000 chromosomes (humans have 46), so it's a rich source of telomeres.

Death of a Cell

As you read this, millions of your cells are dying. Don't panic—you won't miss them. Most of them are either superfluous or potentially harmful, so you're better off without them. In fact, your health depends on the judicious use of a certain kind of cell death—**apoptosis**.

Apoptosis is so carefully planned out that it is often called programmed cell death. During apoptosis, the cell shrinks and pulls away from its neighbors. Then, the surface of the cell appears to boil, with fragments breaking away and escaping like bubbles from a pot of boiling water. The DNA in the nucleus condenses and breaks into regular-sized fragments, and soon the nucleus itself, followed by the entire cell, disintegrates. A cellular cleanup crew rapidly mops up the remains.

Cells come primed for apoptosis, equipped with the instructions and instruments necessary for their own self-destruction. They keep these tools carefully tucked away, like a set of sheathed knives, until some signal—either from within or outside the cell—triggers their release. This initiates a cascade of carefully coordinated events that culminate in the efficient, pain-free excision of unneeded cells.

There is another kind of cell death, called **necrosis**, that is unplanned. Necrosis can result from a sudden traumatic injury, infection, or exposure to a toxic chemical. During necrosis, the cell's outer membrane loses its ability to control the flow of liquid into and out of the

In a 1978 paper, Blackburn described the structure of telomeres in detail for the first time.

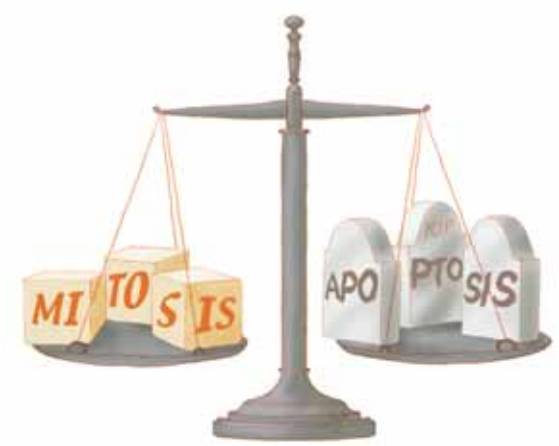
Seven years later, Blackburn and her then-graduate student, Carol Greider, discovered telomerase. Without it, single-celled organisms like *Tetrahymena* would die out after a limited number of generations, when their telomeres were worn down. Greider and her colleagues later observed that human telomeres become progressively shorter with each cell division, and the scientists suggested that this eventually could destabilize the chromosomes and lead to cell aging and death. Subsequent studies proved this prediction to be correct.

Since then, Blackburn has made inroads into understanding exactly how telomerase works—in particular, how the functions of the enzyme are split between its RNA and protein components. She currently is testing the application of her findings to anticancer strategies in human breast, prostate, and bladder cells.

Greider, now a molecular biologist at Johns Hopkins University School of Medicine, is studying another connection between telomerase and disease. Defects in telomerase have been linked to a rare genetic disorder called dyskeratosis congenita, in which limited telomerase activity causes progressive bone marrow failure, typically leading to death by the mid-teens. Greider has recently developed a mouse model of the disease, which should lead to a deeper understanding of the ailment and lay the foundation for the development of new treatments.

cell. The cell swells up and eventually bursts, releasing its contents into the surrounding tissue. A cleanup crew composed of immune cells then moves in and mops up the mess, but the chemicals the cells use cause the area to become inflamed and sensitive. Think of the redness and pain in your finger after you accidentally touch a hot stove.

Many different kinds of injuries can cause cells to die via necrosis. It's what happens to heart cells during a heart attack, to cells in severely frostbitten fingers and toes, and to lung cells during a bout of pneumonia.



Apoptosis and Mitosis: Life in Balance

Mitosis creates cells, and apoptosis kills them. Although these processes oppose one another, they often work together to keep us healthy. For example, our skin and hair cells are renewed via a continuous cycle of apoptosis and mitosis. So are the cells lining

Apoptosis: Nature's Sculptor

EWA M. DAVISON

C. elegans is a transparent, 1-millimeter-long roundworm commonly used to study the genetics of development, nerve function, behavior, and aging. In this developing *C. elegans* worm, cell nuclei appear pink. The green stain serves as a control to indicate that the staining procedure and microscope are working as they should.

Death is part of life. And at the cellular level, it's essential for life. Like a sculptor carving away unneeded pieces of stone, cell death—apoptosis—shapes our physical features and organs before we are born.

How do we know the way apoptosis works in embryos? In the 1970s, H. Robert Horvitz, a geneticist at Massachusetts Institute of Technology in Cambridge, began looking for a genetic program that controls apoptosis in the tiny roundworm *C. elegans*. During development of the worm, cell division generates 1,090 cells, and exactly 131 of those cells die before the worm becomes an adult.

In a landmark paper published in 1986, Horvitz and his then-graduate student Hilary Ellis unearthed two death genes in the worm that are necessary for apoptosis. He later helped identify a gene that protects against apoptosis, as well as genes that direct how the body removes dead cells. He also identified the human counterparts of the worm death genes. Other scientists confirmed the roles of the human genes in apoptosis. Horvitz's research, which won a Nobel Prize in physiology or medicine in 2002, proved that apoptosis is directed from within—by our very own genes.

The pioneering work of Horvitz and his collaborators touched off rapid advances in our understanding of apoptosis. Scientists are making fast-paced discoveries about the genes, proteins, and organelles involved in the process. Pharmaceutical scientists now are testing human apoptosis genes as potential drug targets for ailments as diverse as neurodegenerative diseases, liver diseases, and cancer.

our intestines. Because new cells replace old, worn-out ones, our tissues remain healthy.

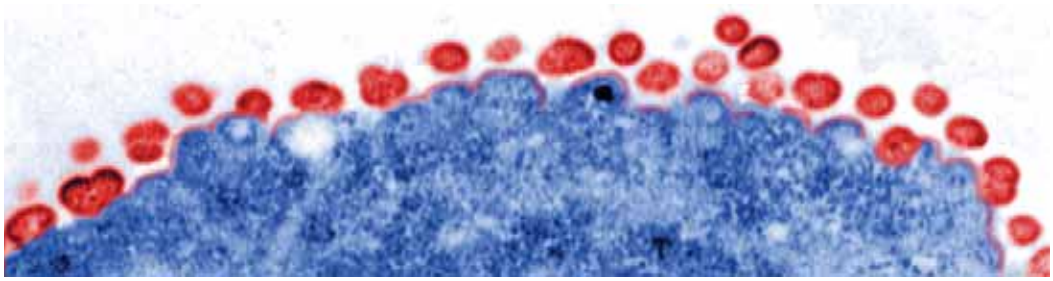
As you can well imagine, loss of the balance between apoptosis and mitosis can have hazardous consequences. If apoptosis is triggered when it shouldn't be, our bodies squander perfectly good cells. Scientists believe that too much apoptosis is at least partly to blame for some neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Lou Gehrig's. On the other hand, unchecked mitosis can lead to cancer.

WOODY MACHALEK

Apoptosis removes excess cells to help shape fingers and toes.

ESTATE OF LOU GEHRIG, C/O CMG WORLDWIDE

Before being diagnosed with an incurable muscle-wasting disease that now bears his name, Lou Gehrig proved himself to be one of the most talented baseball players of all time.



UTA VON SCHWEDLER AND WES SUNDQUIST

HIV particles (red) budding off an infected cell (blue).

Getting Rid of Troublemakers

During an infection, apoptosis can serve a protective function by killing off virus-contaminated cells before they spill over with virus particles. This act of self-sacrifice hampers the spread of infection and can save the whole organism.

Unfortunately, our viral assailants are not so easily done in. They come armed with a box full of tools designed to defuse the apoptotic response. Because viruses depend upon their cellular hosts for survival, it's in their best interest to keep cells alive until the viruses are ready to move on.

The tools viruses use to forestall the cell's suicide attempt are remarkable in their diversity and ingenuity. Some viruses, such as a type that causes common colds, make proteins that mimic

The SPITZ of Life

Nature has its harsh realities, even at the cellular level. Nowhere is this more true than in the developing nervous system, where the prevailing canon seems to be, "Make yourself useful or die." Scientists have found that some cells automatically die by apoptosis when they are poorly positioned and unlikely to play a useful role in the nervous system. So if the default is death, how do the survivors stay alive? Scientists have speculated about this for some time, but only recently have they identified the exact mechanisms.

Hermann Steller, a developmental biologist at Rockefeller University in New York City, investigates the signals that control cell death in the developing fruit fly embryo. He and his colleagues were the first to identify all of the molecular messengers that direct the survival of certain glial cells in the nervous system.

It turns out that the signal for glial cells to survive originates from nearby nerve cells. So glial cells have their neighbors to thank for their continued existence.

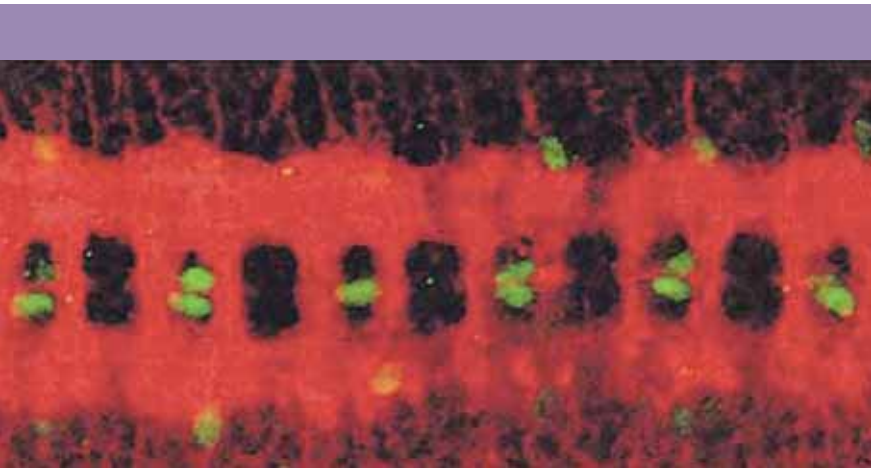
Physical contact between glial and nerve cells triggers nerve cells to release a chemical messenger called SPITZ, which sticks to and activates molecular receptors on the glial cell surface. The activated receptors then trigger a cascade of enzymatic reactions inside the glial cells that ultimately blocks apoptosis. This process ensures that the only glial cells to survive are those that come close enough to a nerve cell to compete for SPITZ. If a glial cell is close enough to a nerve cell to be SPITZed upon, it's probably also close enough to nurture the SPITZing nerve cell. Thus, like self-serving neighbors, nerve cells only extend a lifesaving hand to those in a position to return the favor.

These findings could help scientists better understand cell death and survival in the human brain and possibly in other parts of the body. The work also might point the way to new treatments for diseases resulting from the premature death of brain cells, such as Parkinson's and Alzheimer's.

"off" switches of the cellular apoptotic pathway, fooling cells into thinking their own sensors have put the brakes on suicide. Others, such as HIV, have an enzyme that can disable a key component of the pathway, bringing the death march to a screeching halt.

Still other viruses, such as smallpox, inhibit apoptosis by throwing up a smokescreen in front of external triggers of the pathway. Normally, immune cells recognize virally infected cells and release alarm chemicals that stick to receptors on the infected cell surface, triggering apoptosis. But smallpox and other related viruses release proteins that specifically recognize and capture the alarm chemicals before they can do their job. Other kinds of viruses target the executioners themselves, the enzymes that, once activated, shred the cell contents and lead to its demise.

Although these evasion tactics can allow viruses to gain the upper hand and make us sick, they've also guided scientists toward a deeper understanding of apoptosis. Key insights into the process have emerged from studies about how viruses evade apoptosis, and clinical benefits are likely not far behind.



ANDREAS BERGMANN AND HERMANN STELLER

Glial cells (stained green) in the developing fly embryo have survived thanks to chemical messages sent by neighboring nerve cells (stained red).

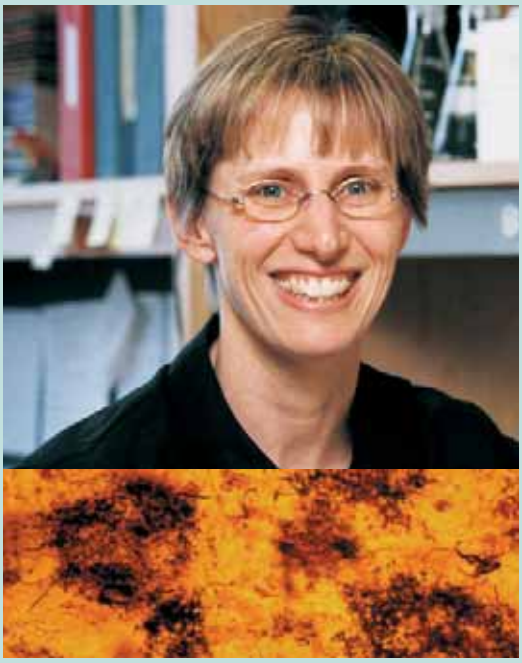
Cell Biology: The Science of Life

Have you picked a favorite topic in cell biology? Could you see yourself zooming through organelles using the powerful beams of an electron microscope? Or would you like to harness computers to understand the countless, intertwined factors that mold the behavior of your cells?

Have you been captivated by a certain type of cell—sensory cells that bring the world to us, or brain cells that hold the secrets of consciousness? Would you like to help solve the mysteries of how cells differentiate, communicate, or age?

While advances in cell biology have already led to many important applications from the development of vaccines to improved crops, there is still much more to explore.

Understanding basic cell biology propels our ability to treat virtually any disease—cancer, heart disease, Alzheimer's, malaria, tuberculosis, AIDS—and can help us prepare for new diseases. A career in cell biology provides the opportunity to unravel the mysteries of life and the reward of helping to save lives. —*A.Z.M.*



JEFF MILLER

Laura Kiessling of the University of Wisconsin, Madison, studies how cells stick to each other. Her research may lead to new ways to treat inflammation, Alzheimer's disease, and organ rejection. To learn more, go to http://publications.nigms.nih.gov/findings/feb01.pdf.

NICOLE CAPPELLO

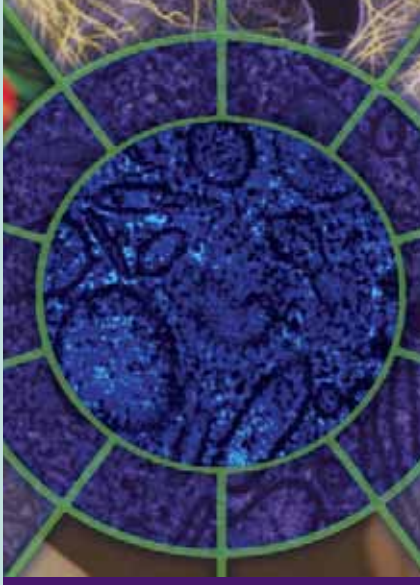
Andrés García of Georgia Institute of Technology, studies how cells adhere to surfaces. He aims to create new materials that can heal bones and other body tissues. To learn more, go to http://publications.nigms.nih.gov/findings/mar05/bind.html.

CHRIS T. ANDERSON

Hobart Harris of the University of California, San Francisco, grows liver cells in his laboratory to study sepsis, a sometimes fatal, body-wide infection that shuts down organs. His work may lead to new treatments for sepsis, which can quickly overwhelm people in critical condition. To learn more, go to http://publications.nigms.nih.gov/findings/mar02/harris.html.

DENISE APPLEWHITE

Bonnie Bassler of Princeton University, studies how cells talk to each other by focusing on bacteria that glow when they reach a certain population size. Bassler's research might help vanquish ailments that rely on similar bacterial chatter, including tuberculosis, pneumonia, and food poisoning. To learn more, go to http://publications.nigms.nih.gov/findings/oct04/bugging.html.



Got It!

How do reactive oxygen species damage cells?

What happens to our chromosomes in the absence of telomerase activity?

Why might your cells possess the tools for their own destruction?

Why can too much or too little apoptosis be a bad thing?

What are some differences between necrosis and apoptosis?

Glossary

Actin (AK-tin) **filament** | Part of the cytoskeleton. Actin filaments contract or lengthen to give cells the flexibility to move and change shape. Together with myosin, actin filaments are responsible for muscle contraction.

Adult stem cells | Cells that can renew themselves and differentiate into a limited number of specialized cell types. They replace and renew damaged tissues.

Amino (uh-MEE-no) **acid** | A chemical building block of proteins. There are 20 standard amino acids. A protein consists of a specific sequence of amino acids.

Anaphase (ANN-uh-faze) | The fourth of six phases of cell division, following metaphase and preceding telophase. In anaphase, the chromosomes separate into two genetically identical groups and move to opposite ends of the spindle.

Aneuploidy (ANN-yoo-PLOY-dee) | The condition of having an abnormal number of chromosomes. See *Down syndrome*.

Antibody | A protein produced by the immune system in response to a foreign substance such as a virus or bacterium.

Antioxidant (ANN-tee-AWK-si-dunt) | A substance that can neutralize dangerous compounds called reactive oxygen species. Antioxidants are found naturally in our bodies and in foods such as fruits and vegetables.

Apoptosis (ay-PAH-TOE-sis) | Programmed cell death, a normal process in which cells die in a controlled and predictable way. See *necrosis*.

ATP, adenosine triphosphate (ah-DEH-no-seen try-FOSS-fate) | The major source of energy for biochemical reactions in all organisms.

Bacterium (plural: bacteria) | A one-celled microorganism that contains no nucleus. Some bacteria are helpful, such as those in the intestines that help digest food, while others cause disease. Bacteria are frequently used as model organisms to study basic biological processes. See *prokaryotic cell* and *model organism*.

Carbohydrate | A molecule made up of one or more sugars. In the body, carbohydrates can exist independently or be attached to proteins or lipids.

Cell | The basic subunit of any living organism; the simplest unit capable of independent life. Although there are some single-celled organisms, such as bacteria, most organisms consist of many cells that are specialized for particular functions. See *prokaryotic cell* and *eukaryotic cell*.

Cell cycle | The sequence of events by which a cell duplicates its contents and divides in two.

Channel protein | A hollow or pore-containing protein that spans a cell membrane and acts as a conduit for small molecules, such as charged particles (ions).

Checkpoint | One of several points in the cell cycle where the cycle can pause if there is a problem such as incomplete DNA synthesis or damaged DNA. See *cell cycle*.

Chemotaxis (KEE-moh-TACK-sis) | The movement of a cell toward or away from the source of a chemical.

Cholesterol | A waxy lipid produced by animal cells that is a major component of cell membranes. Cholesterol is also used as a building block for some hormones.

Chromosome (KROH-muh-sohm) | A cellular structure containing genes. Excluding sperm and egg cells, humans have 46 chromosomes (23 pairs) in each cell.

Cilium (SILL-ee-um) (plural: cilia) | A hairlike projection from a cell surface. The rhythmic beating of cilia can move fluid or mucus over a cell or can propel single-celled organisms. Cilia are shorter than flagella.

Computational biology | A field of science that uses computers to study complex biological processes that involve many molecular interactions.

Crossing over | A process that occurs during meiosis in which chromosome partners, one inherited from each parent, physically swap sections with one another. This creates hybrid chromosomes that are a patchwork of the original pair. Crossing over occurs in species that reproduce sexually and increases the genetic variety of offspring.

Cytokinesis (SYE-toe-kin-EE-sis) | The last of six phases of cell division. It occurs after the duplicated genetic material has segregated to opposite sides of the cell. During cytokinesis, the cell splits into two daughter cells.

Cytoplasm (SYE-toe-PLAZ-um) | The material found between the cell membrane and the nuclear envelope. It includes the cytosol and all organelles except the nucleus. See *cytosol*.

Cytoskeleton (SYE-toe-SKEL-uh-tun) | A collection of fibers that gives a cell shape and support and allows movement within the cell and, in some cases, by the cell as a whole. The three main types of cytoskeletal fibers are microtubules, actin filaments, and intermediate filaments.

Cytosol (SYE-tuh-sol) | The semi-fluid portion of the cytoplasm, excluding the organelles. The cytosol is a concentrated solution of proteins, salts, and other molecules. See *cytoplasm*.

Differentiation | The series of biochemical and structural changes by which an unspecialized cell becomes a specialized cell with a specific function. During development, embryonic stem cells differentiate into the many cell types that make up the human body.

Diploid (DIP-loyd) | Having two sets of chromosomes, one inherited from each parent. All human cells except eggs and sperm are diploid and have 46 chromosomes, 23 from each parent.

DNA, deoxyribonucleic (dee-AW-ksee-RYE-bo-new-CLAY-ick) **acid** | The substance of heredity. A long, helical, double-stranded molecule that carries the cell's genetic information. See *chromosome*.

Down syndrome | An inherited condition caused by having an extra copy of chromosome 21. See *aneuploidy*.

Electron microscope | A powerful microscope that uses beams of fast-moving electrons instead of light to magnify samples. Powerful magnets focus the electrons into an image.

Embryonic stem cell | A cell found in early embryos that can renew itself and differentiate into the many cell types that are found in the human body.

Endocytosis (EN-doe-sye-TOE-sis) | A process cells use to engulf particles or liquid from their surroundings. It occurs when the cell surface membrane puckers inward, encircling the material, then pinches off, producing a vesicle inside the cell.

Endoplasmic reticulum (ER) (EN-doe-PLAZ-mik reh-TIK-yoo-lum) | An organelle made up of interconnected tubes and flattened sacs. There are two kinds of ER: rough (because it is dotted with ribosomes) ER, which processes newly made proteins, and smooth ER, which helps make lipid and neutralizes toxins.

Enzyme | A protein that speeds up a specific chemical reaction without being permanently altered or consumed.

Eukaryotic (YOO-kare-ee-AW-tick) **cell** | A cell that has a nucleus and other organelles not found in prokaryotes; includes all animal and most plant cells.

Exocytosis (EK-so-sye-TOE-sis) | A process cells use to send substances outside their surface membrane via vesicles.

Extracellular matrix | The material that surrounds and supports cells. It includes structural proteins such as collagen and elastin.

Flagellum (fluh-JELL-um) (plural: flagella) | A long, taillike structure extending from a cell. Sperm and many microorganisms move using flagella.

G protein | A protein located on the inside of the cell membrane that helps transmit molecular signals into cells.

Gene | A unit of heredity; a segment of DNA that contains the code for making a specific protein or RNA molecule.

Genome (JEE-nome) | All of an organism's genetic material.

Glial (GLEE-uhl) **cell** | A kind of cell in the nervous system that provides nutrition and support to a nerve cell.

Glycosylation (glye-KAW-sil-AY-shun) | The process of adding specialized chains of sugar molecules to proteins or lipids; occurs in the ER and Golgi.

Golgi (GOLE-jee) | Also called the Golgi apparatus or Golgi complex; an organelle composed of membranous sacs in which many newly made proteins mature and become functional.

Haploid (HAP-loyd) | Having a single set of chromosomes, as in egg or sperm cells. Haploid human cells have 23 chromosomes.

Hormone | A molecule that stimulates specific cellular activity; made in one part of the body and transported via the bloodstream to tissues and organs. Examples include insulin, estrogen, and testosterone.

Intermediate filament | Part of the cytoskeleton that provides strength. Some intermediate filaments form nails, hair, and the outer layer of skin. Others are found in nerves or other organs.

Interphase (IN-tur-faze) | A period in a cell's life cycle when it is not undergoing mitosis.

Lipid (LIP-id) | A fatty, waxy, or oily compound that will not dissolve in water. Lipids are a major part of biological membranes.

Lysosome (LYE-so-sohm) | A bubble-like organelle that contains powerful enzymes that can digest a variety of biological materials.

Meiosis (my-OH-sis) | The type of cell division that makes egg and sperm cells. Meiosis generates cells that are genetically different from one another and contain half the total number of chromosomes in the parent cell. See *haploid*.

Membrane | A semi-fluid layer of lipids and proteins. Biological membranes enclose cells and organelles and control the passage of materials into and out of them.

Metaphase (MET-uh-faze) | The third phase of cell division, following prometaphase and preceding anaphase. In metaphase, the copied chromosomes align in the middle of the spindle.

Micrometer (MY-kroh-MEE-tur) | One micrometer is one millionth (10^{-6}) of a meter or one thousandth of a millimeter. The micrometer is frequently used to measure cells and organelles.

Microtubule (MY-kroh-TOO-byool) | Part of the cytoskeleton; a strong, hollow fiber that acts as a structural support for the cell. During cell division, microtubules form the spindle that directs chromosomes to the daughter cells. Microtubules also serve as tracks for transporting vesicles and give structure to flagella and cilia.

Mitochondrion (MITE-oh-KON-dree-un) (plural: mitochondria) | The cell's power plant; the organelle that converts energy from food into ATP, fueling the cell. Mitochondria contain their own small genomes and appear to have descended from free-living bacteria.

Mitosis (my-TOE-sis) | The type of cell division that eukaryotic cells use to make new body cells. Mitosis results in two daughter cells that are genetically identical to the parent cell.

Model system (*or* Model organism) | A cell type or simple organism—such as a bacterium, yeast, plant, fruit fly, or mouse—used to answer basic questions about biology.

Mutation (myoo-TAY-shun) | A change in a DNA sequence.

Myelin (MY-eh-lin) | A fatty covering that forms a protective sheath around nerve fibers and dramatically speeds the transmission of nerve signals.

Nanometer (NAN-oh-MEE-tur) | One billionth (10^{-9}) of a meter or one thousandth of a micrometer. The nanometer is frequently used to measure organelles and small structures within cells.

Necrosis (neh-CROH-sis) | Unplanned cell death caused by outside circumstances, such as traumatic injury or infection. See *apoptosis*.

Neuron | A cell in the nervous system that is specialized to carry information through electrical impulses and chemical messengers. Also called a nerve cell.

Neurotransmitter | A chemical messenger that passes signals between nerve cells or between a nerve cell and another type of cell.

Nuclear envelope | A barrier that encloses the nucleus and is made up of two membranes perforated by nuclear pores.

Nuclear pores | An opening in the nuclear envelope that allows the passage of small molecules such as salts, small proteins, and RNA molecules.

Nucleus | The organelle in eukaryotic cells that contains genetic material.

Oocyte (oh-oh-SITE) | The developing female reproductive cell; an immature egg.

Organ | A group of tissues that perform a particular job. Animals have more than a dozen organs, including the heart, brain, eye, liver, and lung.

Organelle (OR-gun-EL) | A specialized, membrane-bounded structure that has a specific function in a cell. Examples include the nucleus, mitochondria, Golgi, ER, and lysosomes.

Prokaryotic cell (PRO-kare-ee-AW-tick) | A cell that lacks a nucleus. Bacteria are prokaryotes. See *eukaryotic cell*.

Prometaphase (pro-MET-uh-faze) | The second of six phases of cell division, following prophase and preceding metaphase. In prometaphase, the nuclear membrane breaks apart and the spindle starts to interact with the chromosomes.

Prophase (PRO-faze) | The first of six phases of cell division. In prophase, chromosomes condense and become visible and the spindle forms.

Proteasome (PRO-tee-uh-some) | A cellular machine that digests proteins that have been tagged with ubiquitin for destruction.

Protein | A molecule composed of amino acids lined up in a precise order determined by a gene, then folded into a specific three-dimensional shape. Proteins are responsible for countless biological functions and come in a wide range of shapes and sizes.

Reactive oxygen species | One of several types of small molecules containing oxygen with an unstable number of electrons. Reactive oxygen species can damage many kinds of biological molecules.

Ribosome (RYE-bo-sohm) | A molecular complex in which proteins are made. In eukaryotic cells, ribosomes either are free in the cytoplasm or are attached to the rough endoplasmic reticulum.

RNA, ribonucleic (RYE-bo-new-CLAY-ick) **acid** | A molecule very similar to DNA that plays a key role in making proteins. There are three main types: messenger RNA (mRNA) is an RNA version of a gene and serves as a template for making a protein, ribosomal RNA (rRNA) is a major component of ribosomes, and transfer RNA (tRNA) transports amino acids to the ribosome and helps position them properly during protein production.

RNAi (RNA interference) | The process of using small pieces of double-stranded RNA to reduce the activity of specific genes. The process occurs naturally in many organisms and is now commonly used in basic research. It has the potential to be therapeutically useful.

RNA polymerase (puh-LIH-mer-ase) | An enzyme that makes RNA using DNA as a template in a process called transcription.

Spindle | A football-shaped array of fibers made of microtubules and associated proteins that forms before cells divide. Some of the fibers attach to the chromosomes and help draw them to opposite ends of the cell.

Telomerase (tee-LAW-mer-ase) | An enzyme that adds telomeres to the ends of eukaryotic chromosomes, preventing the chromosome from shrinking during each cell division.

Telomere (TEE-lo-meer) | A repetitive segment of DNA at the ends of eukaryotic chromosomes. Telomeres do not contain genes and, in the absence of telomerase, they shorten with each cell division.

Telophase (TEE-lo-faze) | The fifth of six phases of cell division, following anaphase and preceding cytokinesis. In telophase, nuclear membranes form around each of the two sets of chromosomes, the chromosomes begin to spread out, and the spindle begins to break down.

Tissue | A group of cells that act together to carry out a specific function in the body. Examples include muscle tissue, nervous system tissue (including the brain, spinal cord, and nerves), and connective tissue (including ligaments, tendons, bones, and fat). Organs are made up of tissues.

Transcription | The process of copying information from genes (made of DNA) into messenger RNA.

Translation | The process of making proteins based on genetic information encoded in messenger RNA. Translation occurs in ribosomes.

Ubiquitin (yoo-BIH-kwe-tin) | A small protein that attaches to and marks other proteins for destruction by the proteasome.

Vesicle (VEH-sih-kle) | A small, membrane-bounded sac that transports substances between organelles as well as to and from the cell membrane.

Virus | An infectious agent composed of proteins and genetic material (either DNA or RNA) that requires a host cell, such as a plant, animal, or bacterium, in which to reproduce. A virus is neither a cell nor a living organism because it can not reproduce independently.

Zygote (ZYE-gote) | A cell resulting from the fusion of an egg and a sperm.

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