Inside the Cell

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

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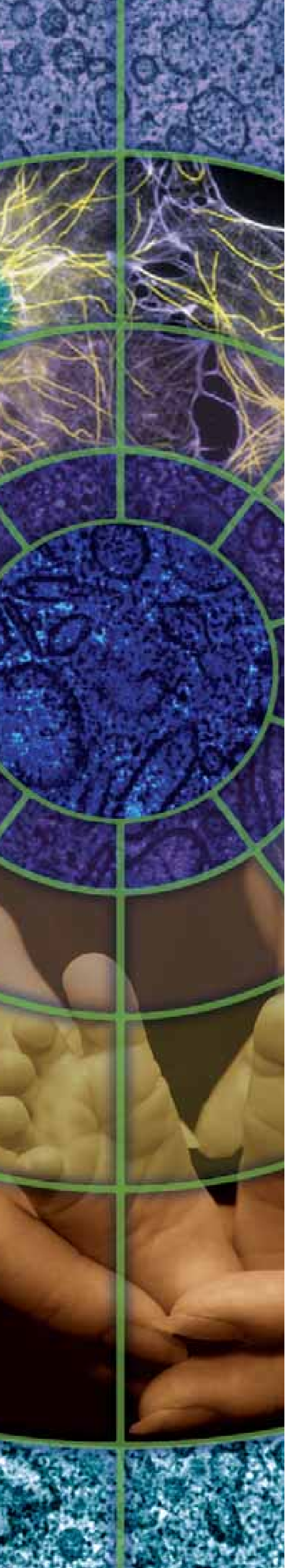
The National Institute of General Medical Sciences (NIGMS) supports basic biomedical research on genes, proteins, and cells. It also funds studies on fundamental processes such as how cells communicate, how our bodies use energy, and how we respond to medicines. The results of this research increase 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.

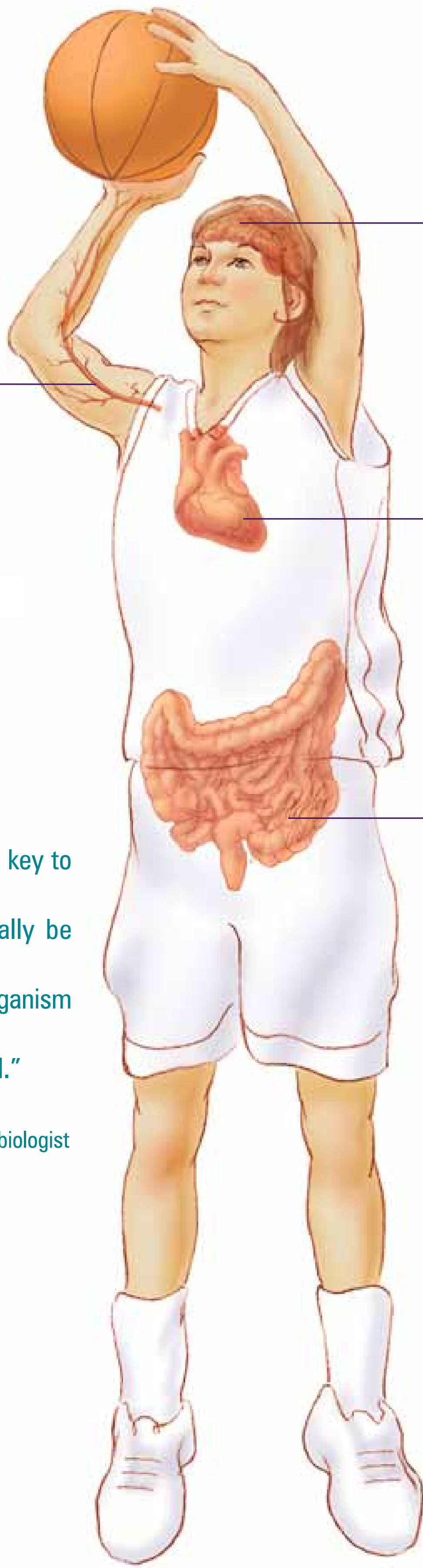
Cells are the smallest form of life—the functional and structural units of all living things. Your body contains trillions of cells, organized into more than 200 major types.

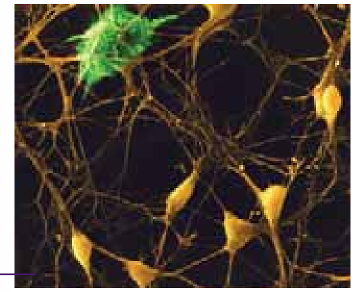
At any given time, each cell is doing thousands of jobs. Some of these tasks are so essential for life that they are carried out by virtually all cells. Others are done only by cells that are highly skilled for the work, whether it is covering up your insides (skin cells), preventing you from sloshing 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.

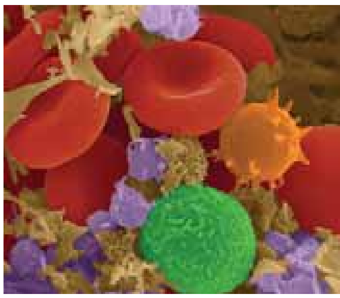
In **Chapter 1, "An Owner's Guide to the Cell,"** we'll explore some of the basic structures that allow cells to accomplish their tasks and some of the ways scientists study cells. In **Chapter 2, "Cells 101: Business Basics,"** we'll focus on the functions shared by virtually all cells: making fuel 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.

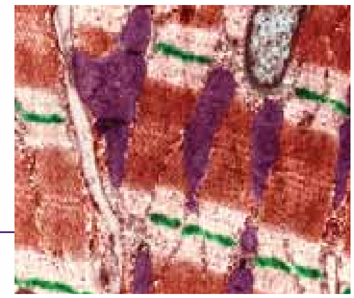
Although scientists daily learn more about cells and their roles in our bodies, the field is still an exciting frontier of uncharted territory and unanswered questions. Maybe someday, you will help answer those questions.



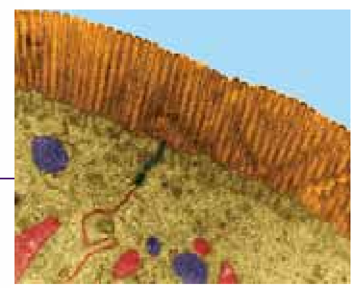




Blood Cells



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.

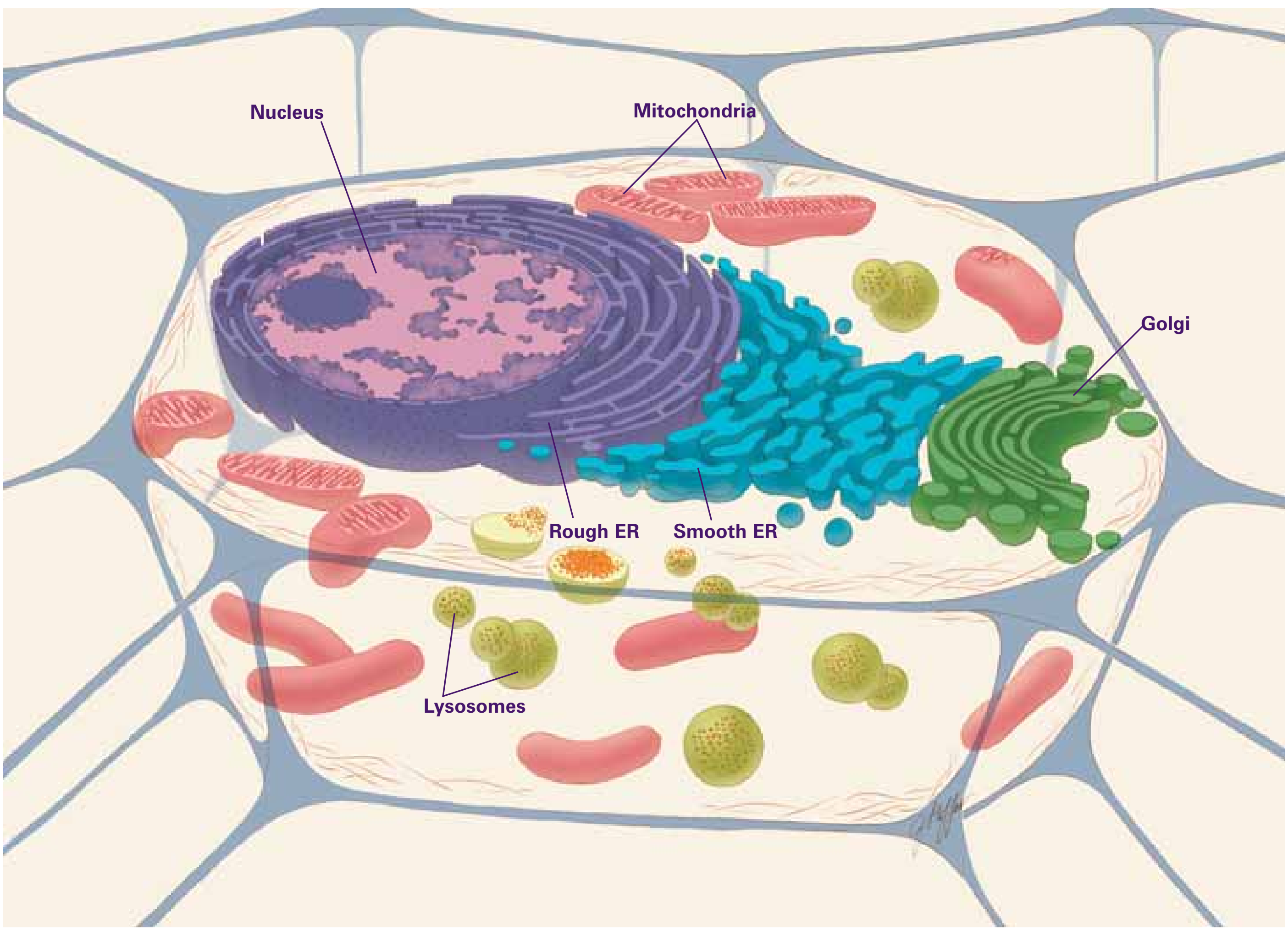
BY ALISA ZAPP MACHALEK

An Owner's Guide to the Cell

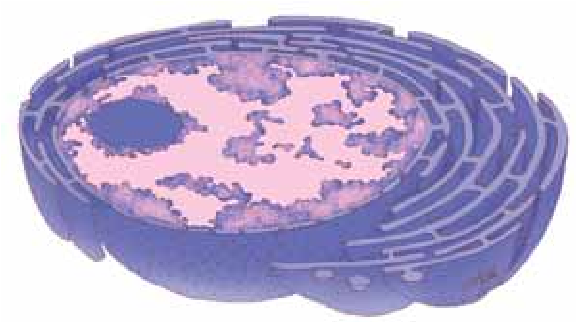
Welcome! I hope the transformation wasn't too alarming. You have shrunk down to about 3 millionths of your normal size. You are now about 0.5 **micrometers** tall (a micrometer is 1/1000 of a millimeter). But don't worry, you'll return to your normal size before you finish this chapter.

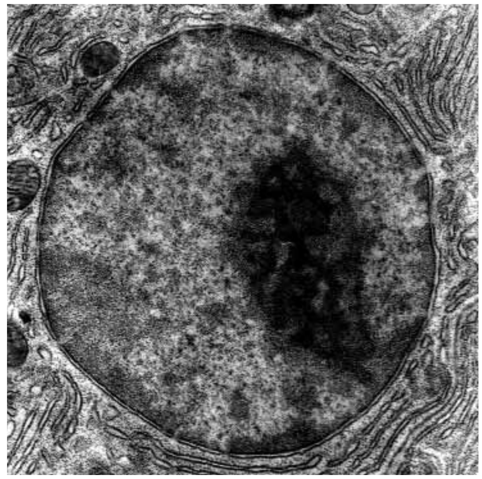
At this scale, a medium-sized human **cell** looks as long, high, and wide as a football field. But from where we are, you can't see nearly that far. Clogging your view is a rich stew of molecules, fibers, and various cell structures called **organelles**. Like the internal **organs** in your body, organelles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

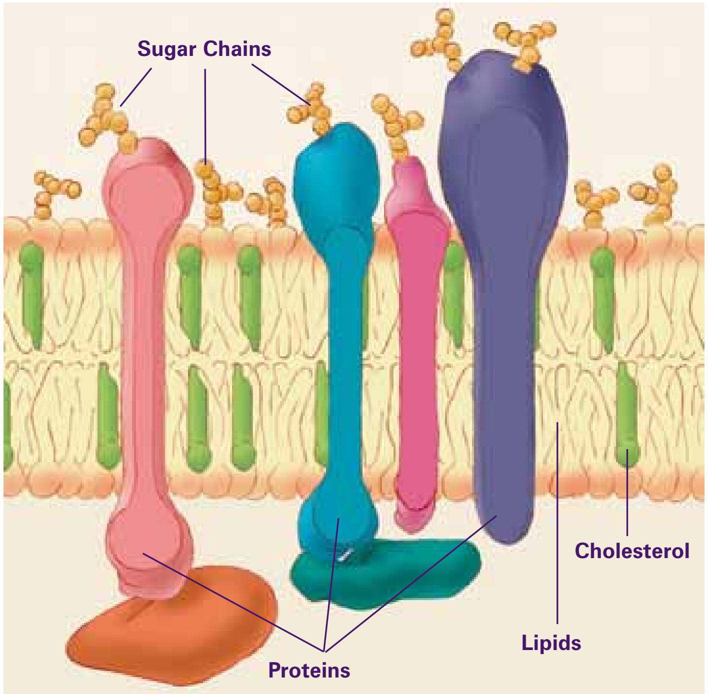
The nucleus is the most prominent organelle and can occupy up to 10 percent of the space inside a cell. It contains the equivalent of the cell's gray matter—its genetic material, or **DNA**. In the form of **genes**, each with a host of helper molecules, DNA determines the cell's identity, masterminds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

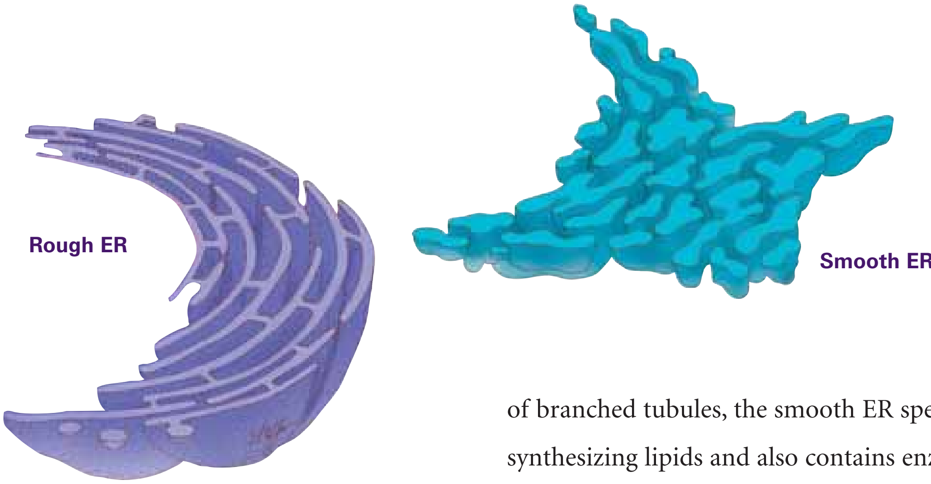
If you peer over the side of the nucleus, you'll notice groups of enormous, interconnected sacs snuggling close by. Each sac is only a few inches across but can extend to lengths of 100 feet or more. This network of sacs, the **endoplasmic reticulum** (ER), often makes up more than 10 percent of a cell's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

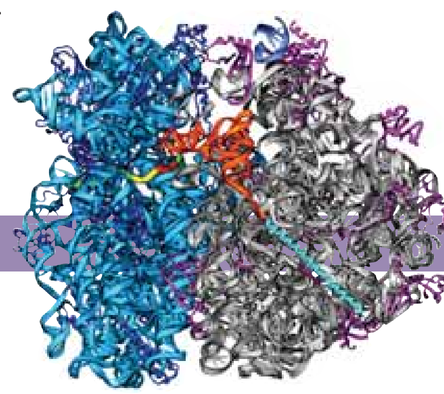
Rough ER

Rx: Ribosome Blockers

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*

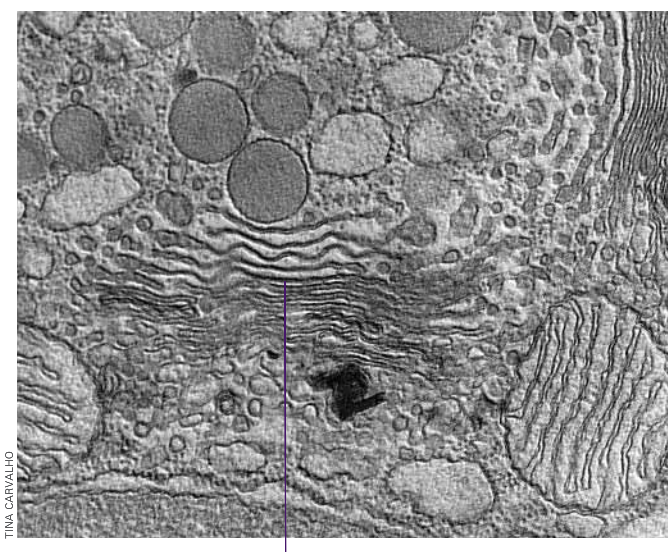


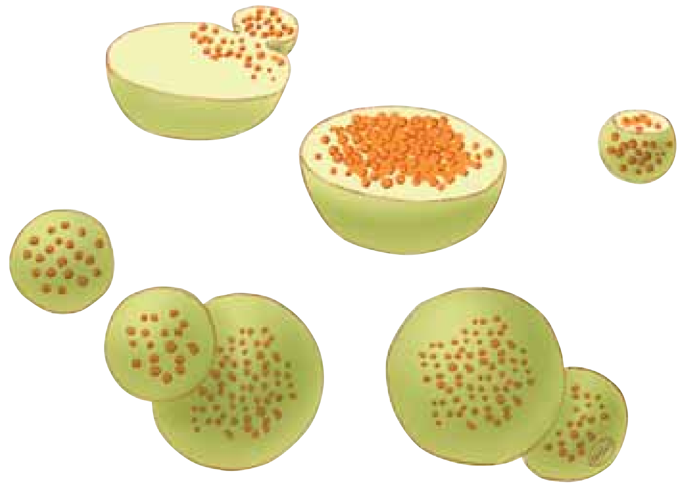
In a dramatic technical feat, scientists obtained the first structural snapshot of an entire ribosome in 1999. This more recent image captures a bacterial ribosome in the act of making a protein (the long, straight spiral in the lightest shade of blue). It also shows that—unlike typical cellular machines, 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

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**.





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.

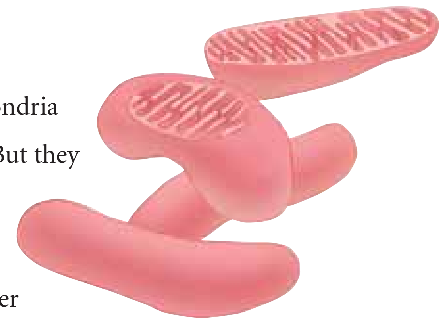
Mitochondria: Cellular Power Plants

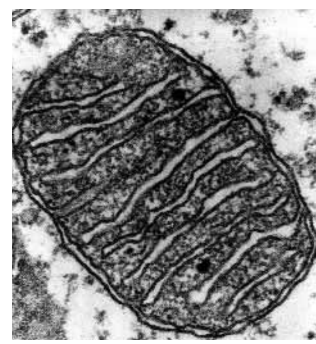
Blink. Breathe. Wiggle your toes. These subtle movements—as well as the many chemical reactions that take place inside organelles—require vast amounts of cellular energy. The main energy source in your body is a small molecule called **ATP**, for adenosine triphosphate.

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.

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.

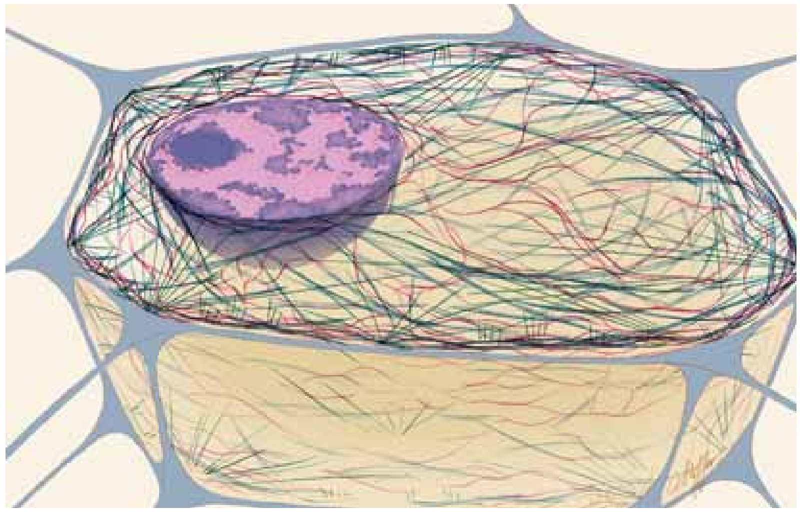




D.S. FRIEND, BRIGHAM AND WOMENS HOSPITAL

	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.

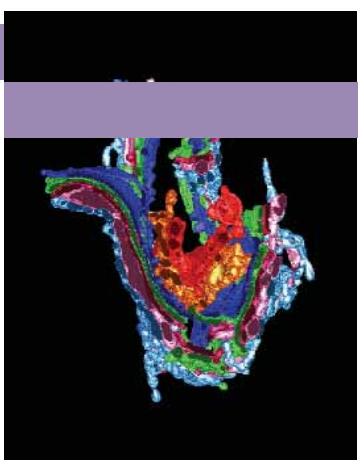
Cytoskeleton: The Cell's Skeleton...and More

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



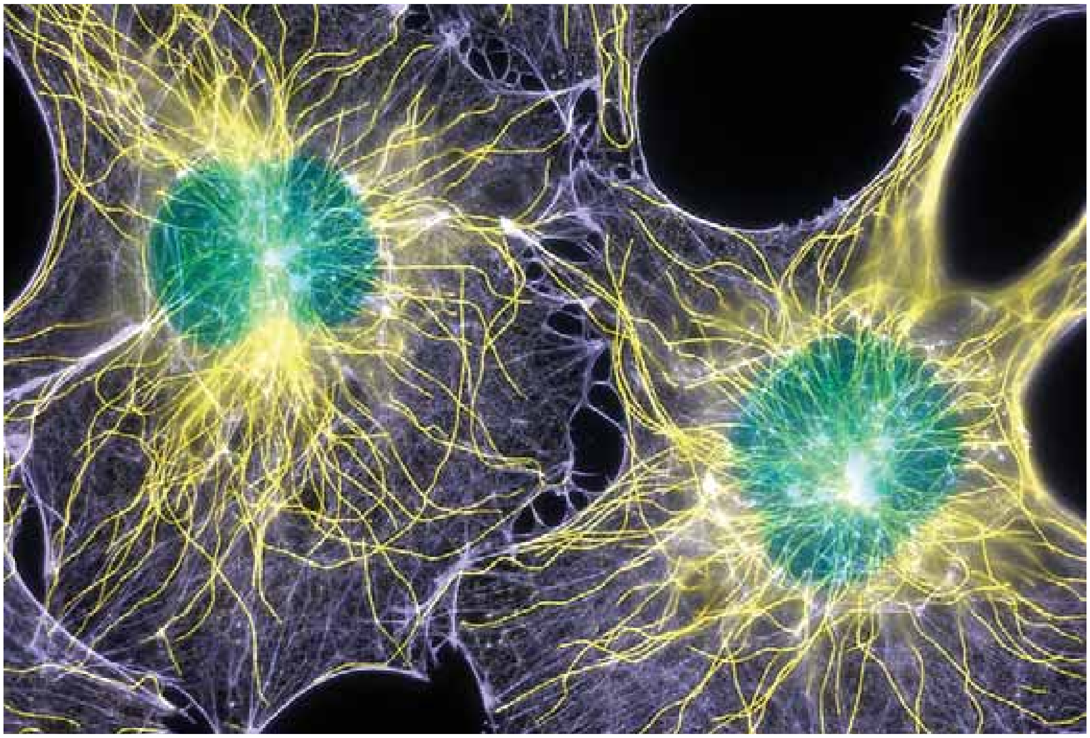
KATHRYN HOWELL

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.

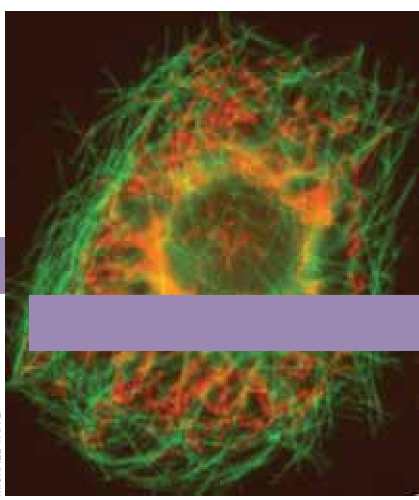
The Tour Ends Here

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

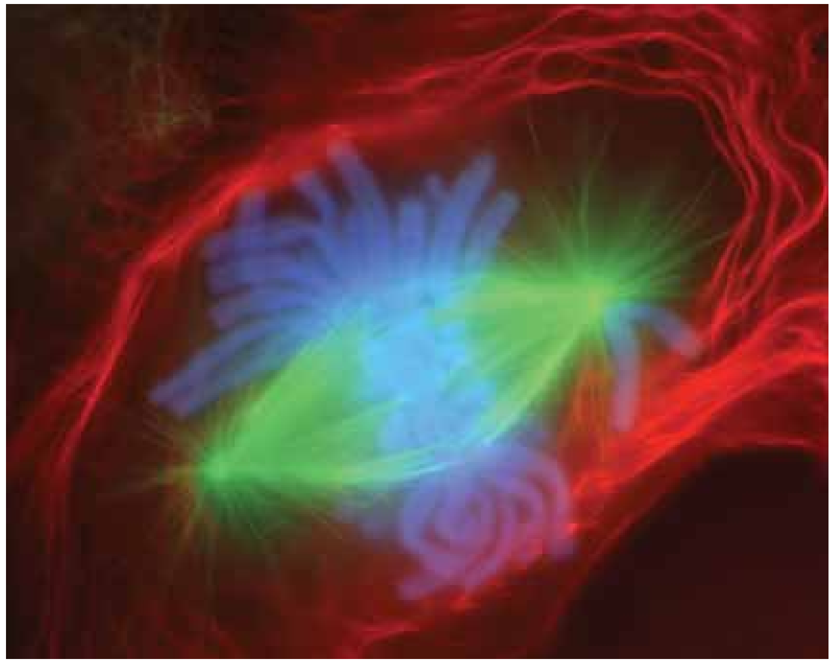
In this fruit fly cell, mitochondria (in red) form a web throughout the cell. Microtubules are labeled in green.

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.*



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.

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

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