



# *Medicines By Design*



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.

## **Disclaimer**

Trade names have been used throughout this booklet to illustrate concepts about medicines that are familiar to readers. The mention of specific products is not an endorsement of their use or effectiveness.



# *Medicines By Design*

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

NIH Publication No. 06-474  
Reprinted July 2006  
<http://www.nigms.nih.gov>

Written by Alison Davis, Ph.D., under contracts  
263-MD-205019 and 263-MD-212730.

Produced by the Office of Communications and Public Liaison  
National Institute of General Medical Sciences  
National Institutes of Health  
U.S. Department of Health and Human Services



# Contents

<b>FOREWORD: A VISIT TO THE DOCTOR</b>	<b>2</b>
<b>CHAPTER 1: ABCs OF PHARMACOLOGY</b>	<b>4</b>
A Drug's Life	5
Perfect Timing	9
Fitting In	10
Bench to Bedside: Clinical Pharmacology	13
<i>Pump It Up</i>	14
<b>CHAPTER 2: BODY, HEAL THYSELF</b>	<b>16</b>
The Body Machine	16
River of Life	18
No Pain, Your Gain	20
Our Immune Army	23
<i>A Closer Look</i>	26
<b>CHAPTER 3: DRUGS FROM NATURE, THEN AND NOW</b>	<b>28</b>
Nature's Medicine Cabinet	28
Ocean Medicines	30
Tweaking Nature	33
Is It Chemistry or Genetics?	34
<i>Testing... I, II, III</i>	36
<b>CHAPTER 4: MOLECULES TO MEDICINES</b>	<b>38</b>
Medicine Hunting	38
21st-Century Science	40
Rush Delivery	41
Transportation Dilemmas	43
Act Like a Membrane	44
<i>The G Switch</i>	46
<b>MEDICINES FOR THE FUTURE</b>	<b>48</b>
<b>GLOSSARY</b>	<b>50</b>



## *Foreword: A Visit to the Doctor*

May 17, 2050—You wake up feeling terrible, and you know it’s time to see a doctor.

In the office, the physician looks you over, listens to your symptoms, and prescribes a drug. But first, the doctor takes a look at your DNA.

That’s right, your DNA. Researchers predict that the medicines of the future may not only look and work differently than those you take today, but tomorrow’s medicines will be tailored to your genes. In 10 to 20 years, many scientists expect that genetics—the study of how genes influence actions, appearance, and health—will pervade medical treatment. Today, doctors usually give you an “average” dose of a medicine based on your body size and age. In contrast, future medicines may match the chemical needs of your body, as influenced by your genes. Knowing your unique genetic make-up could help your doctor prescribe the right medicine in the right amount, to boost its effectiveness and minimize possible side effects.

Along with these so-called pharmacogenetic approaches, many other research directions will help guide the prescribing of medicines. The science of pharmacology—understanding the basics of how our bodies react to medicines and how medicines affect our bodies—is already a vital part of 21st-century research. **Chapter 1, “ABCs of Pharmacology,”** tracks a medicine’s journey through the body and describes different avenues of pharmacology research today.

Stay tuned for changes in the way you take medicines and in how medicines are discovered and produced. In **Chapter 2, “Body, Heal Thyself,”** learn how new knowledge about the body’s own molecular machinery is pointing to new drugs. As scientists understand precisely how cells interact in the body, they can tailor medicines to patch gaps in cell communication pathways or halt signaling circuits that are stuck “on,” as in cancer.

Scientists are developing methods to have animals and plants manufacture custom-made medicines and vaccines. Experimental chickens are laying medicine-containing eggs. Researchers are engineering tobacco plants to produce new cancer treatments. Topics in **Chapter 3, “Drugs From Nature, Then and Now,”** will bring you up to speed on how scientists are looking to nature for a treasure trove of information and resources to manufacture drugs.

Advances in understanding the roots of disease are leading to new ways to package tomorrow’s medicines. Along with biology and chemistry, the engineering and computer sciences are leading us to novel ways of getting drugs where they need to go in the body. Cutting-edge research in drug

delivery, discussed in **Chapter 4, “Molecules to Medicines,”** is advancing progress by helping get drugs to diseased sites and away from healthy cells.

*Medicines By Design* aims to explain how scientists unravel the many different ways medicines work in the body and how this information guides the hunt for drugs of the future. Pharmacology is a broad discipline encompassing every aspect of the study of drugs, including their discovery and development and the testing of their action in the body. Much of the most promising pharmacological research going on at universities across the country is sponsored by the National Institute of General Medical Sciences (NIGMS), a component of the National Institutes of Health (NIH), U.S. Department of Health and Human Services. Working at the crossroads of chemistry, genetics, cell biology, physiology, and engineering, pharmacologists are fighting disease in the laboratory and at the bedside.

## ABCs of Pharmacology

**K**now why some people’s stomachs burn after they swallow an aspirin tablet? Or why a swig of grapefruit juice with breakfast can raise blood levels of some medicines in certain people?

Understanding some of the basics of the science of pharmacology will help answer these questions, and many more, about your body and the medicines you take.

So, then, what’s pharmacology?

Despite the field’s long, rich history and importance to human health, few people know much about this biomedical science. One pharmacologist joked that when she was asked what she did for a living, her reply prompted an unexpected question: “Isn’t ‘farm ecology’ the study of how livestock impact the environment?”

Of course, this booklet isn’t about livestock or agriculture. Rather, it’s about a field of science that studies how the body reacts to medicines and how

medicines affect the body. Pharmacology is often confused with pharmacy, a separate discipline in the health sciences that deals with preparing and dispensing medicines.

For thousands of years, people have looked in nature to find chemicals to treat their symptoms. Ancient healers had little understanding of how various elixirs worked their magic, but we know much more today. Some pharmacologists study how our bodies work, while others study the chemical properties of medicines. Others investigate the physical and behavioral effects medicines have on the body. Pharmacology researchers study drugs used to treat diseases, as well as drugs of abuse. Since medicines work in so many different ways in so many different organs of the body, pharmacology research touches just about every area of biomedicine.

### A Juicy Story



Did you know that, in some people, a single glass of grapefruit juice can alter levels of drugs used to treat allergies, heart disease, and infections? Fifteen years ago, pharmacologists discovered this “grapefruit juice effect” by luck, after giving volunteers grapefruit juice to mask the taste of a medicine. Nearly a decade later, researchers figured out that grapefruit juice affects medicines by lowering levels of a drug-metabolizing enzyme, called CYP3A4, in the intestines.



More recently, Paul B. Watkins of the University of North Carolina at Chapel Hill discovered that other juices like Seville (sour) orange juice—but not regular orange

juice—have the same effect on the body’s handling of medicines. Each of 10 people who volunteered for Watkins’ juice-medicine study took a standard dose of Plendil® (a drug used to treat high blood pressure) diluted in grapefruit juice, sour orange juice, or plain orange juice. The researchers measured blood levels of Plendil at various times afterward. The team observed that both grapefruit juice and sour orange juice increased blood levels of Plendil, as if the people had received a higher dose. Regular orange juice had no effect. Watkins and his coworkers have found that a chemical common to grapefruit and sour oranges, dihydroxybergamottin, is likely the molecular culprit. Another similar molecule in these fruits,

Many scientists are drawn to pharmacology because of its direct application to the practice of medicine. Pharmacologists study the actions of drugs in the intestinal tract, the brain, the muscles, and the liver—just a few of the most common areas where drugs travel during their stay in the body. Of course, all of our organs are constructed from cells, and inside all of our cells are genes. Many pharmacologists study how medicines interact with cell parts and genes, which in turn influences how cells behave. Because pharmacology touches on such diverse areas, pharmacologists must be broadly trained in biology, chemistry, and more applied areas of medicine, such as anatomy and physiology.

### A Drug's Life

How does aspirin zap a headache? What happens after you rub some cortisone cream on a patch of poison ivy-induced rash on your arm? How do decongestant medicines such as Sudafed® dry up your nasal passages when you have a cold? As medicines find their way to their “job sites” in the body, hundreds of things happen along the way. One action triggers another, and medicines work to either mask a symptom, like a stuffy nose, or fix a problem, like a bacterial infection.

### A Model for Success

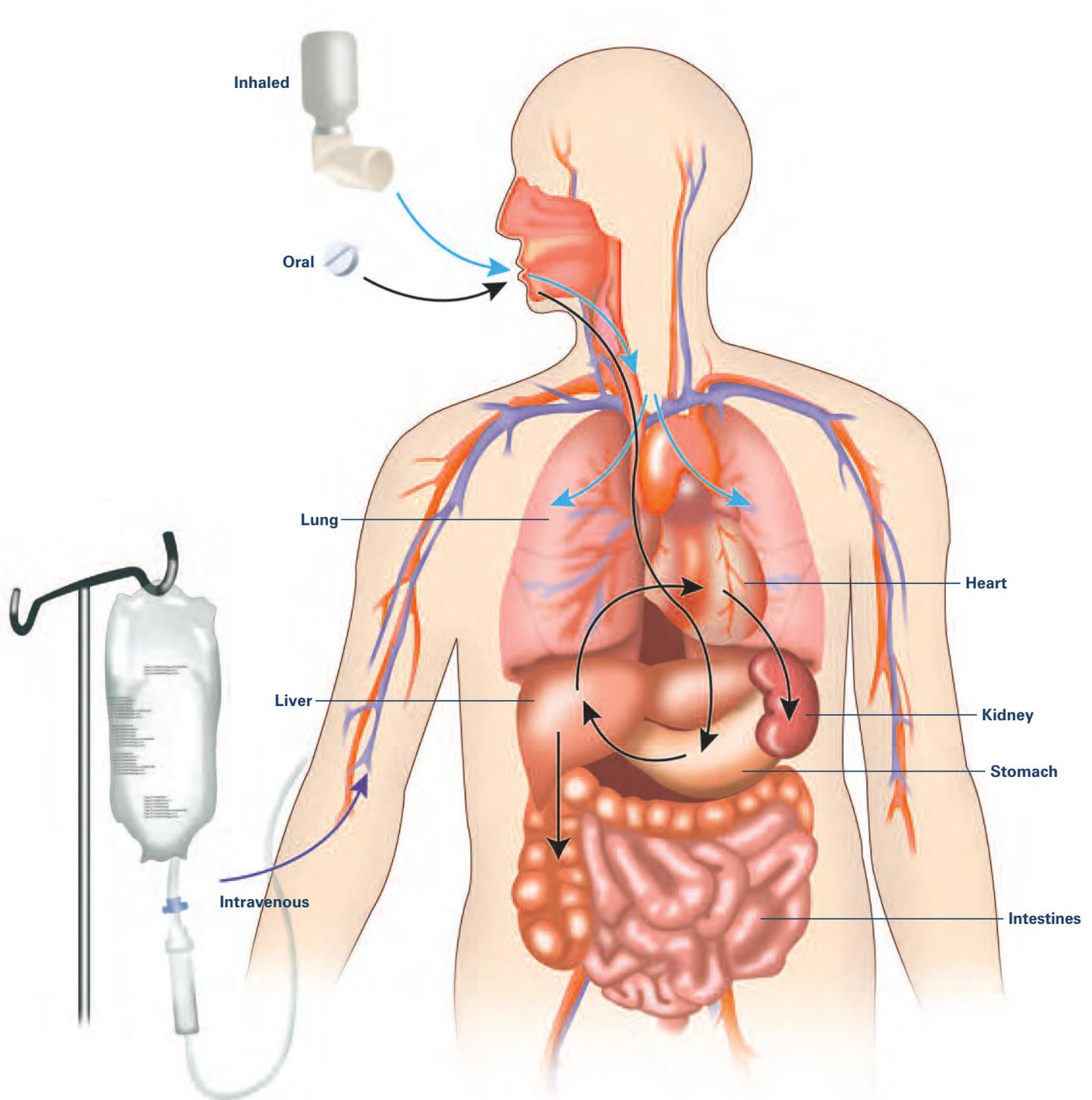
Turning a molecule into a good medicine is neither easy nor cheap. The Center for the Study of Drug Development at Tufts University in Boston estimates that it takes over \$800 million and a dozen years to sift a few promising drugs from about 5,000 failures. Of this small handful of candidate drugs, only one will survive the rigors of clinical testing and end up on pharmacy shelves.

That's a huge investment for what may seem a very small gain and, in part, it explains the high cost of many prescription drugs. Sometimes, problems do not show up until after a drug reaches the market and many people begin taking the drug routinely. These problems range from irritating side effects, such as a dry mouth or drowsiness, to life-threatening problems like serious bleeding or blood clots. The outlook might be brighter if pharmaceutical scientists could do a better job of predicting how potential drugs will act in the body (a science called pharmacodynamics), as well as what side effects the drugs might cause.

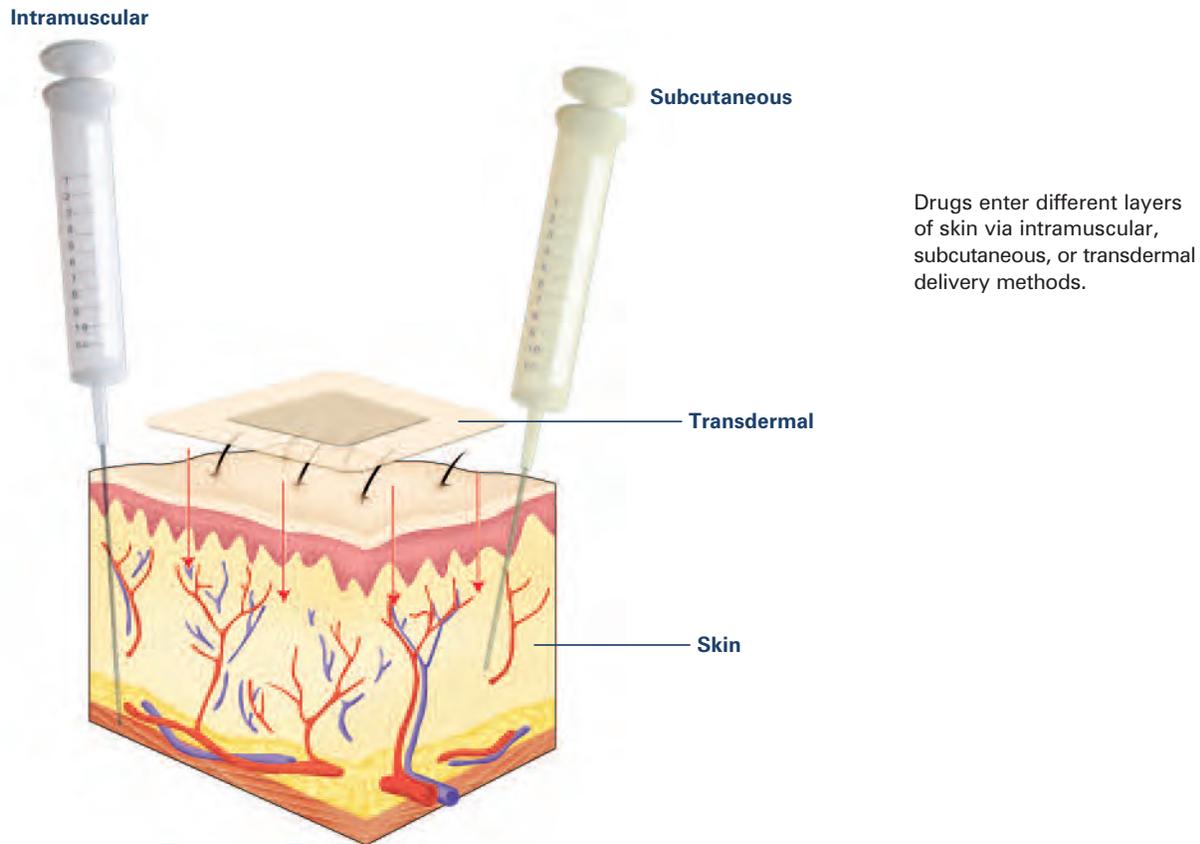
One approach that can help is computer modeling of a drug's properties. Computer modeling can help scientists at pharmaceutical and biotechnology companies filter out, and abandon early on, any candidate drugs that are likely to behave badly in the body. This can save significant amounts of time and money.

Computer software can examine the atom-by-atom structure of a molecule and determine how durable the chemical is likely to be inside a body's various chemical neighborhoods. Will the molecule break down easily? How well will the small intestines take it in? Does it dissolve easily in the watery environment of the fluids that course through the human body? Will the drug be able to penetrate the blood-brain barrier? Computer tools not only drive up the success rate for finding candidate drugs, they can also lead to the development of better medicines with fewer safety concerns.





A drug's life in the body. Medicines taken by mouth (oral) pass through the liver before they are absorbed into the bloodstream. Other forms of drug administration bypass the liver, entering the blood directly.



Drugs enter different layers of skin via intramuscular, subcutaneous, or transdermal delivery methods.

Scientists have names for the four basic stages of a medicine's life in the body: absorption, distribution, metabolism, and excretion. The entire process is sometimes abbreviated ADME. The first stage is *absorption*. Medicines can enter the body in many different ways, and they are absorbed when they travel from the site of administration into the body's circulation. A few of the most common ways to administer drugs are oral (swallowing an aspirin tablet), intramuscular (getting a flu shot in an arm muscle), subcutaneous (injecting insulin just under the skin), intravenous (receiving chemotherapy through a vein), or transdermal (wearing a skin patch). A drug faces its biggest hurdles during absorption. Medicines taken by mouth are shuttled via a special blood vessel leading from the digestive tract to the liver, where

a large amount may be destroyed by metabolic enzymes in the so-called "first-pass effect." Other routes of drug administration bypass the liver, entering the bloodstream directly or via the skin or lungs.

Once a drug gets absorbed, the next stage is *distribution*. Most often, the bloodstream carries medicines throughout the body. During this step, side effects can occur when a drug has an effect in an organ other than the target organ. For a pain reliever, the target organ might be a sore muscle in the leg; irritation of the stomach could be a side effect. Many factors influence distribution, such as the presence of protein and fat molecules in the blood that can put drug molecules out of commission by grabbing onto them.

Drugs destined for the central nervous system (the brain and spinal cord) face an enormous hurdle: a nearly impenetrable barricade called the blood-brain barrier. This blockade is built from a tightly woven mesh of capillaries cemented together to protect the brain from potentially dangerous substances such as poisons or viruses. Yet pharmacologists have devised various ways to sneak some drugs past this barrier.

After a medicine has been distributed throughout the body and has done its job, the drug is

broken down, or *metabolized*. The breaking down of a drug molecule usually involves two steps that take place mostly in the body's chemical processing plant, the liver. The liver is a site of continuous and frenzied, yet carefully controlled, activity. Everything that enters the bloodstream—whether swallowed, injected, inhaled, absorbed through the skin, or produced by the body itself—is carried to this largest internal organ. There, substances are chemically pummeled, twisted, cut apart, stuck together, and transformed.

## Medicines and Your Genes



How you respond to a drug may be quite different from how your neighbor does. Why is that? Despite the fact that you might be about the same age and size, you probably eat different foods, get different amounts of exercise, and have different medical histories. But your genes, which are different from those of anyone else in the world, are really what make you unique. In part, your genes give you many obvious things, such as your looks, your mannerisms, and other characteristics that make you who you are. Your genes can also affect how you respond to the medicines you take. Your genetic code instructs your body how to make hundreds of thousands of different molecules called proteins. Some proteins determine hair color, and some of them are enzymes that process, or metabolize, food or medicines. Slightly different, but normal, variations in the human genetic code can yield proteins that work better or worse when they are metabolizing many different types of drugs and other substances. Scientists use the term pharmacogenetics to describe research on the link between genes and drug response.

One important group of proteins whose genetic code varies widely among people are “sulfation”

enzymes, which perform chemical reactions in your body to make molecules more water-soluble, so they can be quickly excreted in the urine. Sulfation enzymes metabolize many drugs, but they also work on natural body molecules, such as estrogen. Differences in the genetic code for sulfation enzymes can significantly alter blood levels of the many different kinds of substances metabolized by these enzymes. The same genetic differences may also put some people at risk for developing certain types of cancers whose growth is fueled by hormones like estrogen.

Pharmacogeneticist Rebecca Blanchard of Fox Chase Cancer Center in Philadelphia has discovered that people of different ethnic backgrounds have slightly different “spellings” of the genes that make sulfation enzymes. Lab tests revealed that sulfation enzymes manufactured from genes with different spellings metabolize drugs and estrogens at different rates. Blanchard and her coworkers are planning to work with scientists developing new drugs to include pharmacogenetic testing in the early phases of screening new medicines.

The biotransformations that take place in the liver are performed by the body's busiest proteins, its enzymes. Every one of your cells has a variety of enzymes, drawn from a repertoire of hundreds of thousands. Each enzyme specializes in a particular job. Some break molecules apart, while others link small molecules into long chains. With drugs, the first step is usually to make the substance easier to get rid of in urine.

Many of the products of enzymatic breakdown, which are called metabolites, are less chemically active than the original molecule. For this reason, scientists refer to the liver as a “detoxifying” organ. Occasionally, however, drug metabolites can have chemical activities of their own—sometimes as powerful as those of the original drug. When prescribing certain drugs, doctors must take into account these added effects. Once liver enzymes are finished working on a medicine, the now-inactive drug undergoes the final stage of its time in the body, *excretion*, as it exits via the urine or feces.

### Perfect Timing

Pharmacokinetics is an aspect of pharmacology that deals with the absorption, distribution, and excretion of drugs. Because they are following drug actions in the body, researchers who specialize in pharmacokinetics must also pay attention to an additional dimension: time.

Pharmacokinetics research uses the tools of mathematics. Although sophisticated imaging

methods can help track medicines as they travel through the body, scientists usually cannot actually see where a drug is going. To compensate, they often use mathematical models and precise measures of body fluids, such as blood and urine, to determine where a drug goes and how much of the drug or a breakdown product remains after the body processes it. Other sentinels, such as blood levels of liver enzymes, can help predict how much of a drug is going to be absorbed.

Studying pharmacokinetics also uses chemistry, since the interactions between drug and body molecules are really just a series of chemical reactions. Understanding the chemical encounters between drugs and biological environments, such as the bloodstream and the oily surfaces of cells, is necessary to predict how much of a drug will be taken in by the body. This concept, broadly termed bioavailability, is a critical feature that chemists and pharmaceutical scientists keep in mind when designing and packaging medicines. No matter how well a drug works in a laboratory simulation, the drug is not useful if it can't make it to its site of action.

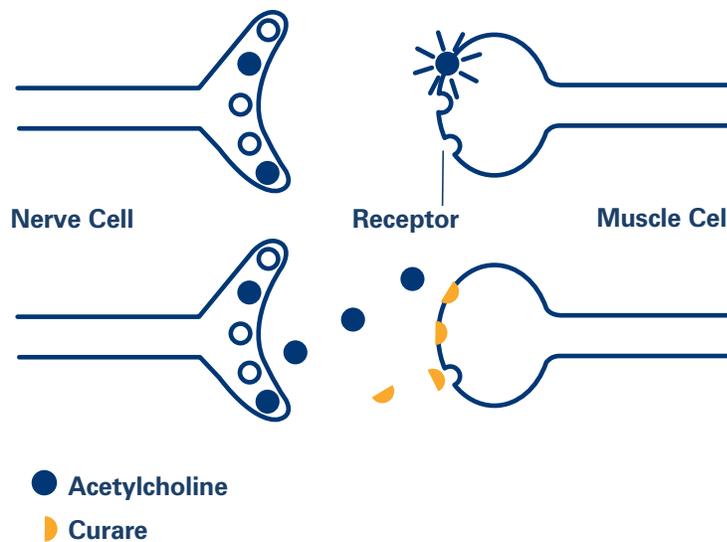


### Fitting In

While it may seem obvious now, scientists did not always know that drugs have specific molecular targets in the body. In the mid-1880s, the French physiologist Claude Bernard made a crucial discovery that steered researchers toward understanding this principle. By figuring out how a chemical called curare works, Bernard pointed to the nervous system as a new focus for pharmacology. Curare—a plant extract that paralyzes muscles—had been used for centuries by Native Americans in South America to poison the tips

of arrows. Bernard discovered that curare causes paralysis by blocking chemical signals between nerve and muscle cells. His findings demonstrated that chemicals can carry messages between nerve cells and other types of cells.

Since Bernard’s experiments with curare, researchers have discovered many nervous system messengers, now called neurotransmitters. These chemical messengers are called agonists, a generic term pharmacologists use to indicate that a molecule triggers some sort of response when encountering a cell (such as muscle contraction or hormone release).



◀ Nerve cells use a chemical messenger called acetylcholine (balls) to tell muscle cells to contract. Curare (half circles) paralyzes muscles by blocking acetylcholine from attaching to its muscle cell receptors.

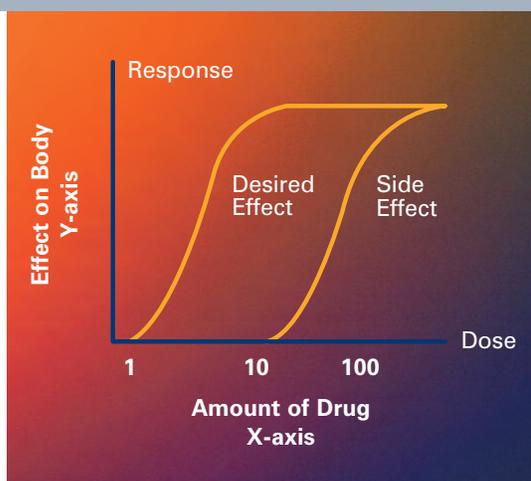
## The Right Dose

One of the most important principles of pharmacology, and of much of research in general, is a concept called “dose-response.” Just as the term implies, this notion refers to the relationship between some effect—let’s say, lowering of blood pressure—and the amount of a drug. Scientists care a lot about dose-response data because these mathematical relationships signify that a medicine is working according to a specific interaction between different molecules in the body.

Sometimes, it takes years to figure out exactly which molecules are working together, but when testing a potential medicine, researchers must first show that three things are true in an experiment. First, if the drug isn’t there, you don’t get any effect. In our example, that means no change in blood pressure. Second, adding more of the drug (up to a certain point) causes an incremental change in effect (lower blood pressure with more drug). Third, taking the drug away (or masking its action with a molecule that blocks the drug)

One of the first neurotransmitters identified was acetylcholine, which causes muscle contraction. Curare works by tricking a cell into thinking *it* is acetylcholine. By fitting—not quite as well, but nevertheless fitting—into receiving molecules called receptors on a muscle cell, curare prevents acetylcholine from attaching and delivering its message. No acetylcholine means no contraction, and muscles become paralyzed.

Most medicines exert their effects by making physical contact with receptors on the surface of a cell. Think of an agonist-receptor interaction like a key fitting into a lock. Inserting a key into a door lock permits the doorknob to be turned and allows the door to be opened. Agonists open cellular locks (receptors), and this is the first step



Dose-response curves determine how much of a drug (X-axis) causes a particular effect, or a side effect, in the body (Y-axis).

means there is no effect. Scientists most often plot data from dose-response experiments on a graph. A typical “dose-response curve” demonstrates the effects of what happens (the vertical Y-axis) when more and more drug is added to the experiment (the horizontal X-axis).

in a communication between the outside of the cell and the inside, which contains all the mini-machines that make the cell run. Scientists have identified thousands of receptors. Because receptors have a critical role in controlling the activity of cells, they are common targets for researchers designing new medicines.

Curare is one example of a molecule called an antagonist. Drugs that act as antagonists compete with natural agonists for receptors but act only as decoys, freezing up the receptor and preventing agonists’ use of it. Researchers often want to block cell responses, such as a rise in blood pressure or an increase in heart rate. For that reason, many drugs are antagonists, designed to blunt overactive cellular responses.

The key to agonists fitting snugly into their receptors is *shape*. Researchers who study how drugs and other chemicals exert their effects in particular organs—the heart, the lungs, the kidneys, and so on—are very interested in the shapes of molecules. Some drugs have very broad effects because they fit into receptors on many different kinds of cells. Some side effects, such as dry mouth or a drop in blood pressure, can result from a drug encountering receptors in places other than the target site. One of a pharmacologist’s

major goals is to reduce these side effects by developing drugs that attach only to receptors on the target cells.

That is much easier said than done. While agonists may fit nearly perfectly into a receptor’s shape, other molecules may also brush up to receptors and sometimes set them off. These types of unintended, nonspecific interactions can cause side effects. They can also affect how much drug is available in the body.

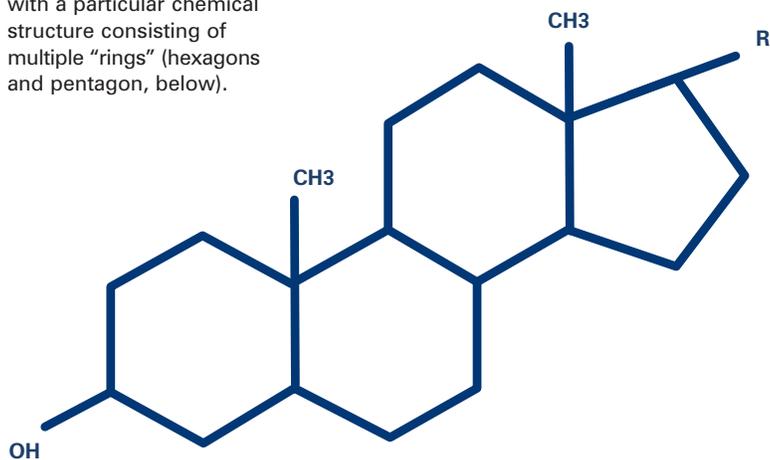
## Steroids for Surgery

In today’s culture, the word “steroid” conjures up notions of drugs taken by athletes to boost strength and physical performance. But steroid is actually just a chemical name for any substance that has a characteristic chemical structure consisting of multiple rings of connected atoms. Some examples

of steroids include vitamin D, cholesterol, estrogen, and cortisone—molecules that are critical for keeping the body running smoothly. Various steroids have important roles in the body’s reproductive system and the structure and function of membranes. Researchers have also discovered that steroids can be active in the brain, where they affect the nervous system. Some steroids may thus find use as anesthetics, medicines that sedate people before surgery by temporarily slowing down brain function.

Douglas Covey of Washington University in St. Louis, Missouri, has uncovered new roles for several of these neurosteroids, which alter electrical activity in the brain. Covey’s research shows that neurosteroids can either activate or tone down receptors that communicate the message of a neurotransmitter called gamma-aminobutyrate, or GABA. The main job of this neurotransmitter is to dampen electrical activity throughout the brain. Covey and other scientists have found that steroids that activate the receptors for GABA decrease brain activity even more, making these steroids good candidates for anesthetic medicines. Covey is also investigating the potential of neuroprotective steroids in preventing the nerve-wasting effects of certain neurodegenerative disorders.

- ▼ A steroid is a molecule with a particular chemical structure consisting of multiple “rings” (hexagons and pentagon, below).



## Bench to Bedside: Clinical Pharmacology

Prescribing drugs is a tricky science, requiring physicians to carefully consider many factors. Your doctor can measure or otherwise determine many of these factors, such as weight and diet. But another key factor is drug interactions. You already know that every time you go to the doctor, he or she will ask whether you are taking any other drugs and whether you have any drug allergies or unusual reactions to any medicines.

Interactions between different drugs in the body, and between drugs and foods or dietary supplements, can have a significant influence, sometimes “fooling” your body into thinking you have taken more or less of a drug than you actually have taken.

By measuring the amounts of a drug in blood or urine, clinical pharmacologists can calculate

how a person is processing a drug. Usually, this important analysis involves mathematical equations, which take into account many different variables. Some of the variables include the physical and chemical properties of the drug, the total amount of blood in a person’s body, the individual’s age and body mass, the health of the person’s liver and kidneys, and what other medicines the person is taking. Clinical pharmacologists also measure drug metabolites to gauge how much drug is in a person’s body. Sometimes, doctors give patients a “loading dose” (a large amount) first, followed by smaller doses at later times. This approach works by getting enough drug into the body before it is metabolized (broken down) into inactive parts, giving the drug the best chance to do its job.

## Nature’s Drugs

Feverfew for migraines, garlic for heart disease, St. John’s wort for depression. These are just a few of the many “natural” substances ingested by millions of Americans to treat a variety of health conditions. The use of so-called alternative medicines is widespread, but you may be surprised to learn that researchers do not know in most cases how herbs work—or if they work at all—inside the human body.

Herbs are not regulated by the Food and Drug Administration, and scientists have not performed careful studies to evaluate their safety and effectiveness. Unlike many prescription (or even over-the-counter) medicines, herbs contain many—sometimes thousands—of ingredients. While some

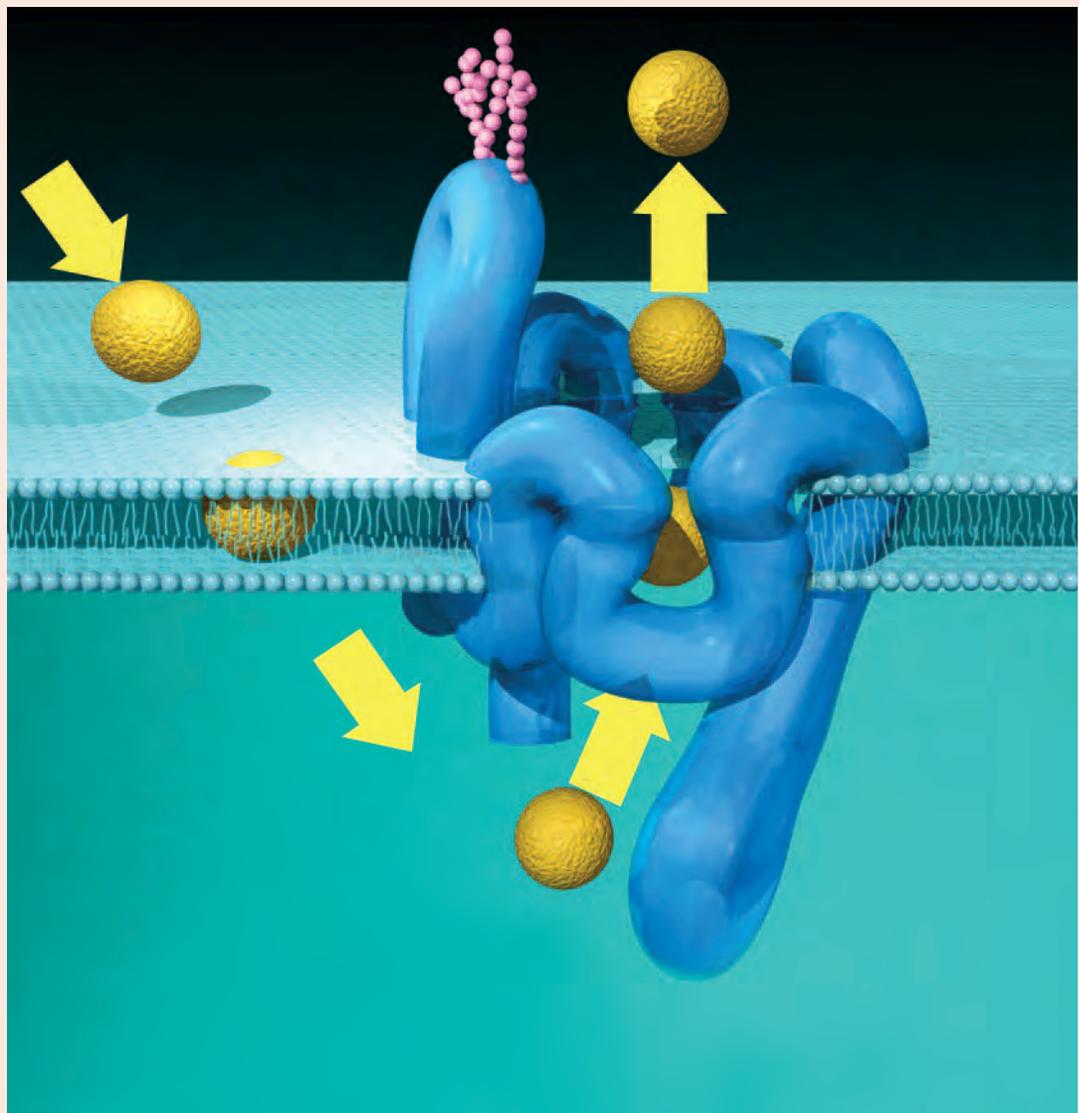
small studies have confirmed the usefulness of certain herbs, like feverfew, other herbal products have proved ineffective or harmful. For example, recent studies suggest that St. John’s wort is of no benefit in treating major depression. What’s more, because herbs are complicated concoctions containing many active components, they can interfere with the body’s metabolism of other drugs, such as certain HIV treatments and birth control pills.



## *Pump It Up*

Bacteria have an uncanny ability to defend themselves against antibiotics. In trying to figure out why this is so, scientists have noted that antibiotic medicines that kill bacteria in a variety of different ways can be thwarted by the bacteria they are designed to destroy. One reason, says Kim Lewis of Northeastern University in Boston, Massachusetts, may be

the bacteria themselves. Microorganisms have ejection systems called multidrug-resistance (MDR) pumps—large proteins that weave through cell-surface membranes. Researchers believe that microbes have MDR pumps mainly for self-defense. The pumps are used to monitor incoming chemicals and to spit out the ones that might endanger the bacteria.



Lewis suggests that plants, which produce many natural bacteria-killing molecules, have gotten “smart” over time, developing ways to outwit bacteria. He suspects that evolution has driven plants to produce natural chemicals that block bacterial MDR pumps, bypassing this bacterial protection system. Lewis tested his idea by first genetically knocking out the gene for the MDR pump from the common bacterium *Staphylococcus aureus* (*S. aureus*). He and his coworkers then exposed the altered bacteria to a very weak antibiotic called berberine that had been chemically extracted from barberry plants. Berberine is usually woefully ineffective against *S. aureus*, but it proved lethal for bacteria missing the MDR pump. What’s more, Lewis found that berberine also killed unaltered bacteria given another barberry chemical that inhibited the MDR pumps. Lewis suggests that by co-administering inhibitors of MDR pumps along with antibiotics, physicians may be able to outsmart disease-causing microorganisms.

MDR pumps aren’t just for microbes. Virtually all living things have MDR pumps, including people. In the human body, MDR pumps serve all sorts of purposes, and they can sometimes frustrate efforts to get drugs where they need to go. Chemotherapy medicines, for

example, are often “kicked out” of cancer cells by MDR pumps residing in the cells’ membranes. MDR pumps in membranes all over the body—in the brain, digestive tract, liver, and kidneys—perform important jobs in moving natural body molecules like hormones into and out of cells.

Pharmacologist Mary Vore of the University of Kentucky in Lexington has discovered that certain types of MDR pumps do not work properly during pregnancy, and she suspects that estrogen and other pregnancy hormones may be partially responsible. Vore has recently focused efforts on determining if the MDR pump is malformed in pregnant women who have intrahepatic cholestasis of pregnancy (ICP). A relatively rare condition, ICP often strikes during the third trimester and can cause significant discomfort such as severe itching and nausea, while also endangering the growing fetus. Vore’s research on MDR pump function may also lead to improvements in drug therapy for pregnant women.

Many body molecules and drugs (yellow balls) encounter multidrug-resistance pumps (blue) after passing through a cell membrane.



## Got It?

Explain the difference between an agonist and an antagonist.

How does grapefruit juice affect blood levels of certain medicines?

What does a pharmacologist plot on the vertical and horizontal axes of a dose-response curve?

Name one of the potential risks associated with taking herbal products.

What are the four stages of a drug’s life in the body?

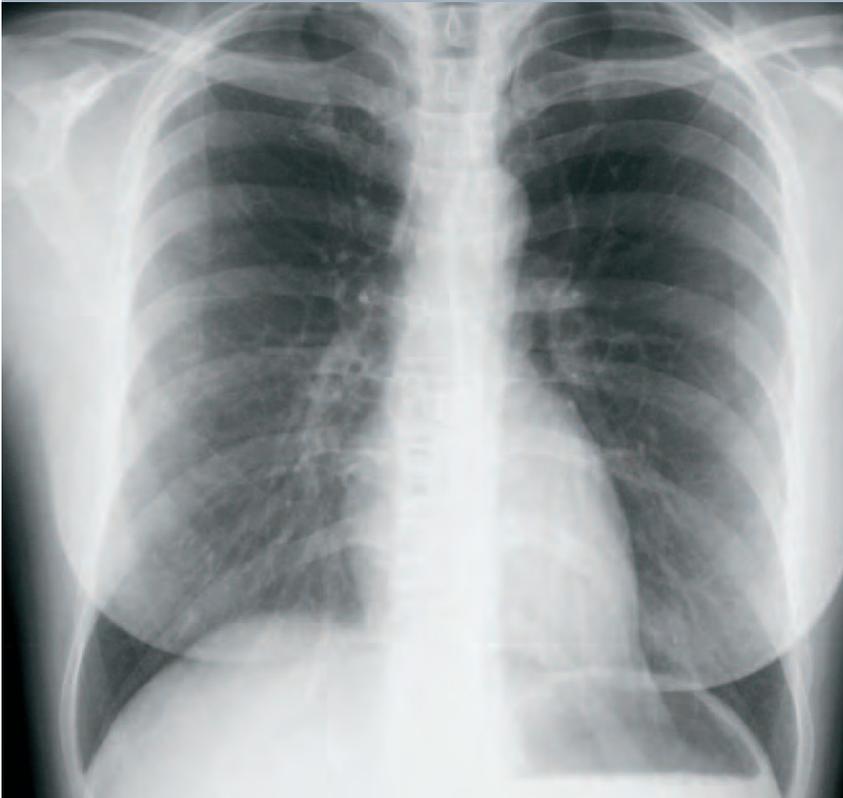
## Body, Heal Thyself

**S**cientists became interested in the workings of the human body during the “scientific revolution” of the 15th and 16th centuries. These early studies led to descriptions of the circulatory, digestive, respiratory, nervous, and excretory systems. In time, scientists came to think of the body as a kind of machine that uses a series of chemical reactions to convert food into energy.

### The Body Machine

Scientists still think about the body as a well-oiled machine, or set of machines, powered by a control system called metabolism. The conversion of food into energy integrates chemical reactions taking place simultaneously throughout the body to assure that each organ has enough nutrients and is performing its job properly. An important principle central to metabolism is that the body’s basic unit is the cell. Like a miniature body, each cell is surrounded by a skin, called a membrane. In turn, each cell contains tiny organs, called organelles, that perform specific metabolic tasks.

### Discovery By Accident



The work of a scientist is often likened to locking together the pieces of a jigsaw puzzle. Slowly and methodically, one by one, the pieces fit together to make a pretty picture. Research is a puzzle, but the jigsaw analogy is flawed. The truth is, scientists don’t have a puzzle box to know what the finished picture is supposed to look like. If you know the result of an experiment ahead of time, it’s not really an experiment.

Being a scientist is hard work, but most researchers love the freedom to explore their curiosities. They test ideas methodically, finding answers to new problems, and every day brings a new challenge. But researchers must keep their eyes and ears open for surprises. On occasion, luck wins out and breakthroughs happen “by accident.” The discovery of vaccines, X rays, and penicillin each came about when a scientist was willing to say, “Hmmm, I wonder why...” and followed up on an unexpected finding.

The cell is directed by a “command center,” the nucleus, where the genes you inherited from your parents reside. Your genes—your body’s own personalized instruction manual—are kept safe in packages called chromosomes. Each of your cells has an identical set of 46 chromosomes, 23 inherited from your mother and 23 from your father.

One important type of metabolism that occurs constantly in our bodies is the reading and interpreting of genes to make proteins. These proteins underlie the millions of chemical reactions that run our bodies. Proteins perform structural roles, keeping cells shaped properly. Proteins also work as enzymes that speed along chemical reactions—without an enzyme’s assistance, many reactions would take years to happen.

### Want a CYP?

Your body is a model of economy. Metabolism—your body’s way of making energy and body parts from food and water—takes place in every cell in every organ. Complex, interlocking pathways of cellular signals make up metabolism, linking together all the systems that make your body run. For this reason, researchers have a tough time understanding the process, because they are often faced with studying parts one by one or a few at a time. Nevertheless, scientists have learned a lot by focusing on individual metabolic pathways, such as the one that manufactures important regulatory molecules called prostaglandins (see page 21).

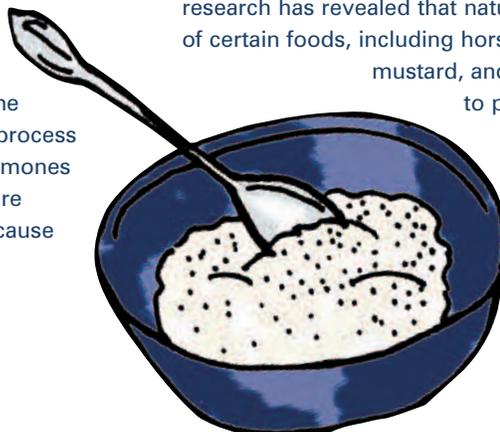


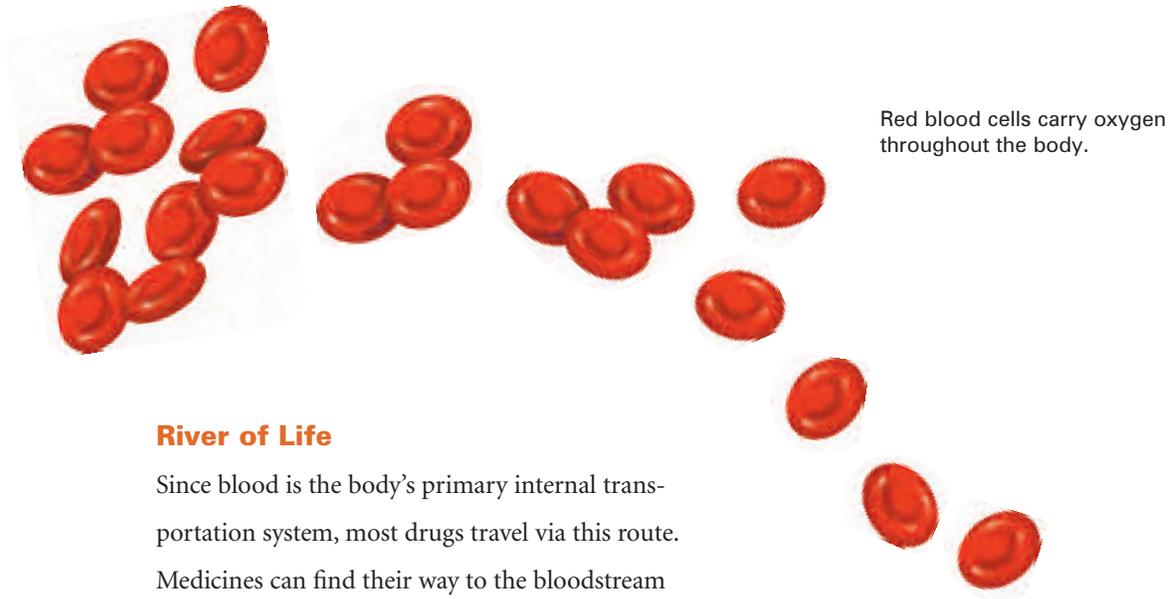
Important enzymes called cytochrome P450s (CYP, pronounced “sip,” 450s) process essential molecules such as some hormones and vitamins. The CYP 450 enzymes are a major focus for pharmacologists because

they metabolize—either break down or activate—hundreds of prescribed medicines and natural substances. Scientists who specialize in pharmacogenetics (see page 8) have discovered that the human genetic code contains many different spellings for CYP 450 genes, resulting in CYP 450 proteins with widely variable levels of activity. Some CYP 450 enzymes also metabolize carcinogens, making these chemicals “active” and more prone to causing cancer.

Toxicologist Linda Quattrochi of the University of Colorado at Denver and Health Sciences Center is studying the roles played by certain CYP 450 enzymes in the metabolism of carcinogens. Her research has revealed that natural components of certain foods, including horseradish, oranges,

mustard, and green tea, appear to protect the body by blocking CYP 450 enzymatic activation of carcinogens.





Red blood cells carry oxygen throughout the body.

### River of Life

Since blood is the body's primary internal transportation system, most drugs travel via this route. Medicines can find their way to the bloodstream in several ways, including the rich supply of blood vessels in the skin. You may remember, as a young child, the horror of seeing blood escaping your body through a skinned knee. You now know that the simplistic notion of skin literally "holding everything inside" isn't quite right. You survived the scrape just fine because blood contains

magical molecules that can make a clot form within minutes after your tumble. Blood is a rich concoction containing oxygen-carrying red blood cells and infection-fighting white blood cells. Blood cells are suspended in a watery liquid called plasma that contains clotting proteins, electrolytes, and many other important molecules.

## *Burns: More Than Skin Deep*

More than simply a protective covering, skin is a highly dynamic network of cells, nerves, and blood vessels. Skin plays an important role in preserving fluid balance and in regulating body temperature and sensation. Immune cells in skin help the body prevent and fight disease. When you get burned, all of these protections are in jeopardy. Burn-induced skin loss can give bacteria and other microorganisms easy access to the nutrient-rich fluids that course through the body, while at the same time allowing these fluids to leak out rapidly. Enough fluid loss can thrust a burn or trauma patient into shock, so doctors must replenish skin lost to severe burns as quickly as possible.

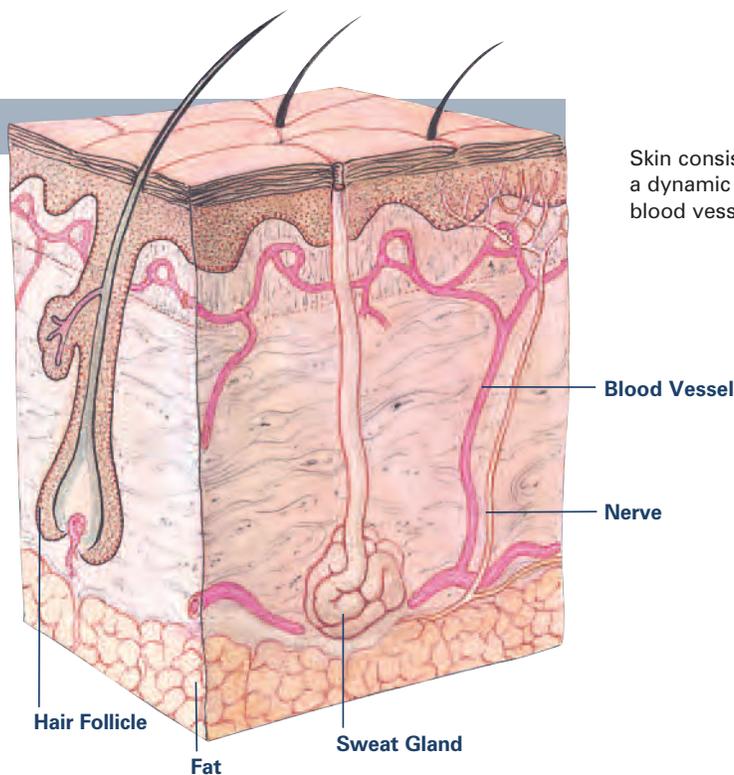
In the case of burns covering a significant portion of the body, surgeons must do two things

fast: strip off the burned skin, then cover the unprotected underlying tissue. These important steps in the immediate care of a burn patient took scientists decades to figure out, as they performed carefully conducted experiments on how the body responds to burn injury. In the early 1980s, researchers doing this work developed the first version of an artificial skin covering called Integra® Dermal Regeneration Template™, which doctors use to drape over the area where the burned skin has been removed. Today, Integra Dermal Regeneration Template is used to treat burn patients throughout the world.

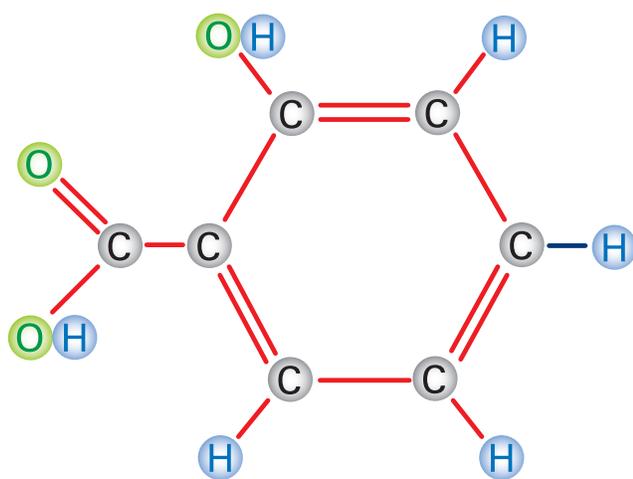
Blood also ferries proteins and hormones such as insulin and estrogen, nutrient molecules of various kinds, and carbon dioxide and other waste products destined to exit the body.

While the bloodstream would seem like a quick way to get a needed medicine to a diseased organ, one of the biggest problems is getting the medicine to the *correct* organ. In many cases, drugs end up where they are not needed and cause side effects, as we've already noted. What's more, drugs may encounter many different obstacles while journeying through the bloodstream. Some medicines get "lost" when they stick tightly to certain proteins in the blood, effectively putting the drugs out of business.

Scientists called physiologists originally came up with the idea that all internal processes work together to keep the body in a balanced state. The bloodstream links all our organs together, enabling them to work in a coordinated way. Two organ systems are particularly interesting to pharmacologists: the nervous system (which transmits electrical signals over wide distances) and the endocrine system (which communicates messages via traveling hormones). These two systems are key targets for medicines.

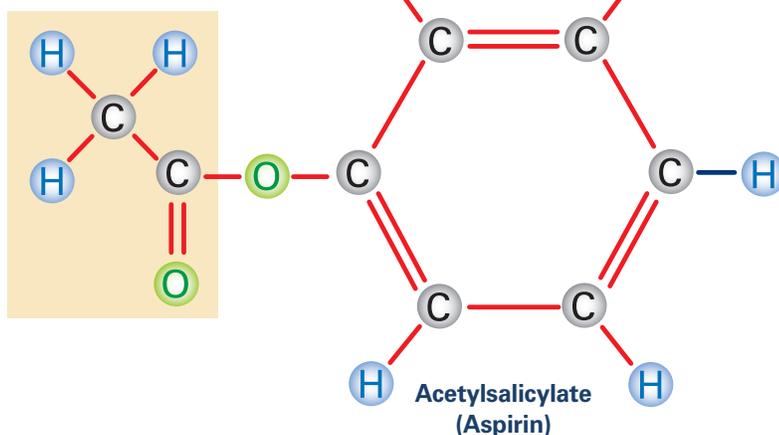


Skin consists of three layers, making up a dynamic network of cells, nerves, and blood vessels.



Salicylate

- ▶ Acetylsalicylate is the aspirin of today. Adding a chemical tag called an acetyl group (shaded yellow box, right) to a molecule derived from willow bark (salicylate, above) makes the molecule less acidic (and easier on the lining of the digestive tract), but still effective at relieving pain.

Acetylsalicylate  
(Aspirin)

## No Pain, Your Gain

Like curare's effects on acetylcholine, the interactions between another drug—*aspirin*—and metabolism shed light on how the body works. This little white pill has been one of the most widely used drugs in history, and many say that it launched the entire pharmaceutical industry.

As a prescribed drug, aspirin is 100 years old. However, in its most primitive form, aspirin is much older. The bark of the willow tree contains a substance called salicin, a known antidote to headache and fever since the time of the Greek physician Hippocrates, around 400 B.C. The body converts salicin to an acidic substance called salicylate. Despite its usefulness dating back to ancient times, early records indicate that salicylate wreaked havoc on the stomachs of people who ingested this natural chemical. In the late 1800s, a scientific

breakthrough turned willow-derived salicylate into a medicine friendlier to the body. Bayer® scientist Felix Hoffman discovered that adding a chemical tag called an acetyl group (see figure, page 20) to salicylate made the molecule less acidic and a little gentler on the stomach, but the chemical change did not seem to lessen the drug's ability to relieve his father's rheumatism. This molecule, acetylsalicylate, is the aspirin of today.

Aspirin works by blocking the production of messenger molecules called prostaglandins. Because of the many important roles they play in metabolism, prostaglandins are important targets for drugs and are very interesting to pharmacologists. Prostaglandins can help muscles relax and open up blood vessels, they give you a fever when you're infected with bacteria, and they also marshal the immune system by stimulating the process called inflammation. Sunburn, bee stings, tendinitis, and arthritis are just a few examples of painful inflammation caused by the body's release of certain types of prostaglandins in response to an injury.



Inflammation leads to pain in arthritis.

Aspirin belongs to a diverse group of medicines called NSAIDs, a nickname for the tongue-twisting title **n**onsteroidal **a**nti-**i**nflammatory **d**rugs. Other drugs that belong to this large class of medicines include Advil<sup>®</sup>, Aleve<sup>®</sup>, and many other popular pain relievers available without a doctor's prescription. All these drugs share aspirin's ability to knock back the production of prostaglandins by blocking an enzyme called cyclooxygenase. Known as COX, this enzyme is a critical driver of the body's metabolism and immune function.

COX makes prostaglandins and other similar molecules collectively known as eicosanoids from a molecule called arachidonic acid. Named for the Greek word *eikos*, meaning “twenty,” each eicosanoid contains 20 atoms of carbon.

You've also heard of the popular pain reliever acetaminophen (Tylenol<sup>®</sup>), which is famous for reducing fever and relieving headaches. However, scientists do not consider Tylenol an NSAID, because it does little to halt inflammation (*remember that part of NSAID stands for “anti-inflammatory”*). If your joints are aching from a long hike you weren't exactly in shape for, aspirin or Aleve may be better than Tylenol because inflammation is the thing making your joints hurt.

To understand how enzymes like COX work, some pharmacologists use special biophysical techniques and X rays to determine the three-dimensional shapes of the enzymes. These kinds of experiments teach scientists about molecular function by providing clear pictures of how all the folds and bends of an enzyme—usually a protein or group of interacting proteins—help it do its job. In drug development, one successful approach has been to use this information to design decoys to jam up the working parts of enzymes like COX. Structural studies unveiling the shapes of COX enzymes led to a new class of drugs used to treat arthritis. Researchers designed these drugs to selectively home in on one particular type of COX enzyme called COX-2.

By designing drugs that target only one form of an enzyme like COX, pharmacologists may be able to create medicines that are great at stopping inflammation but have fewer side effects. For example, stomach upset is a common side effect caused by NSAIDs that block COX enzymes. This side effect results from the fact that NSAIDs bind to different types of COX enzymes—each of which has a slightly different shape. One of these enzymes is called COX-1. While both COX-1 and COX-2 enzymes make prostaglandins, COX-2 beefs up the production of prostaglandins in sore,

inflamed tissue, such as arthritic joints. In contrast, COX-1 makes prostaglandins that protect the digestive tract, and blocking the production of these protective prostaglandins can lead to stomach upset, and even bleeding and ulcers.

Very recently, scientists have added a new chapter to the COX story by identifying COX-3, which may be Tylenol's long-sought molecular target. Further research will help pharmacologists understand more precisely how Tylenol and NSAIDs act in the body.

### Our Immune Army

Scientists know a lot about the body's organ systems, but much more remains to be discovered. To design "smart" drugs that will seek out diseased cells and not healthy ones, researchers need to understand the body inside and out. One system in particular still puzzles scientists: the immune system.

Even though researchers have accumulated vast amounts of knowledge about how our bodies fight disease using white blood cells and thousands of natural chemical weapons, a basic dilemma persists—how does the body know what to fight? The immune system constantly watches for foreign

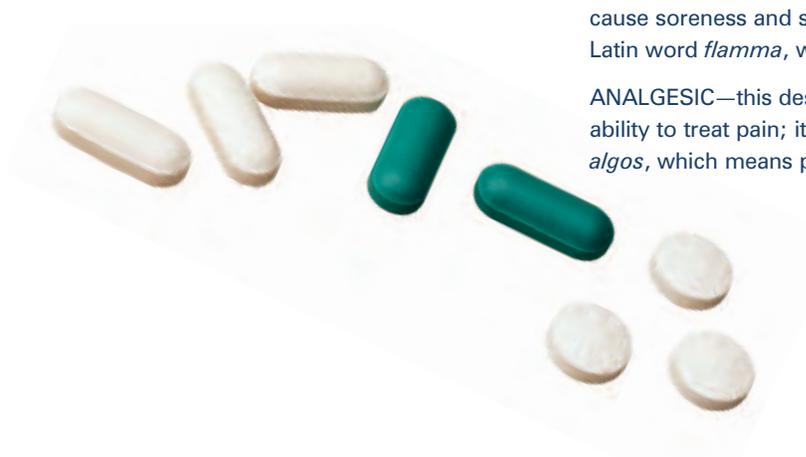
## The "Anti" Establishment

Common over-the-counter medicines used to treat pain, fever, and inflammation have many uses. Here are some of the terms used to describe the particular effects of these drugs:

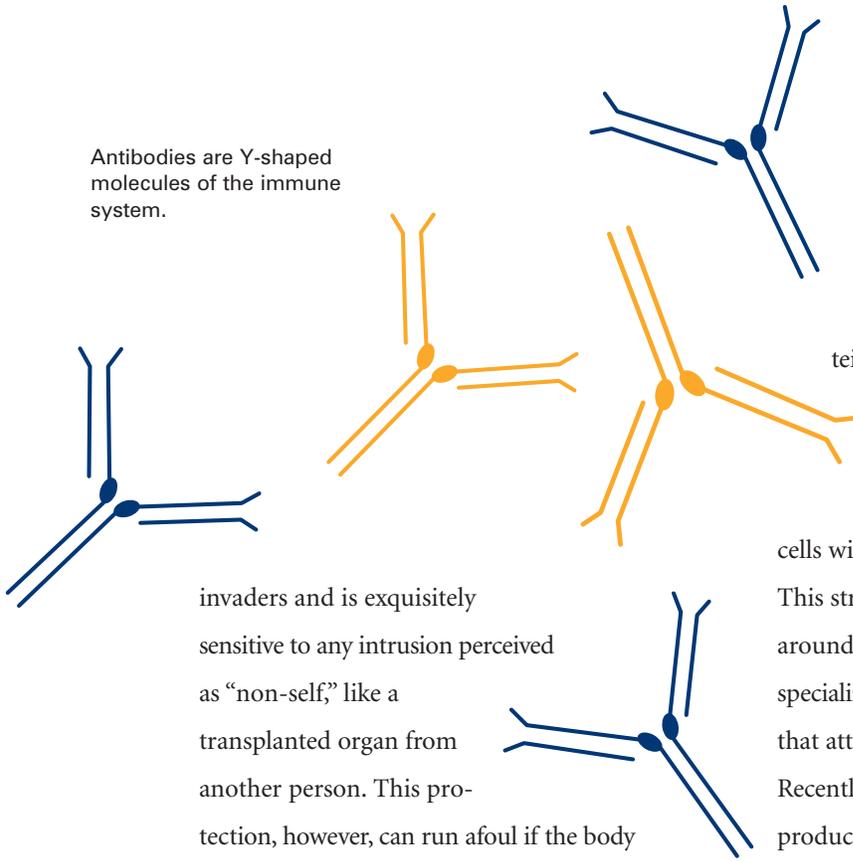
**ANTI-PYRETIC**—this term means fever-reducing; it comes from the Greek word *pyresis*, which means fire.

**ANTI-INFLAMMATORY**—this word describes a drug's ability to reduce inflammation, which can cause soreness and swelling; it comes from the Latin word *flamma*, which means flame.

**ANALGESIC**—this description refers to a medicine's ability to treat pain; it comes from the Greek word *algos*, which means pain.



Antibodies are Y-shaped molecules of the immune system.



Antibodies are spectacularly specific proteins that seek out and mark for destruction anything they do not recognize as belonging to the body. Scientists have learned how to join antibody-making

cells with cells that grow and divide continuously. This strategy creates cellular “factories” that work around the clock to produce large quantities of specialized molecules, called monoclonal antibodies, that attach to and destroy single kinds of targets. Recently, researchers have also figured out how to produce monoclonal antibodies in the egg whites of chickens. This may reduce production costs of these increasingly important drugs.

invaders and is exquisitely sensitive to any intrusion perceived as “non-self,” like a transplanted organ from another person. This protection, however, can run afoul if the body slips up and views its own tissue as foreign. Autoimmune disease, in which the immune system mistakenly attacks and destroys body tissue that it believes to be foreign, can be the terrible consequence.

The powerful immune army presents significant roadblocks for pharmacologists trying to create new drugs. But some scientists have looked at the immune system through a different lens. Why not teach the body to launch an attack on its own diseased cells? Many researchers are pursuing immunotherapy as a way to treat a wide range of health problems, especially cancer. With advances in biotechnology, researchers are now able to tailor-produce in the lab modified forms of antibodies—our immune system’s front-line agents.

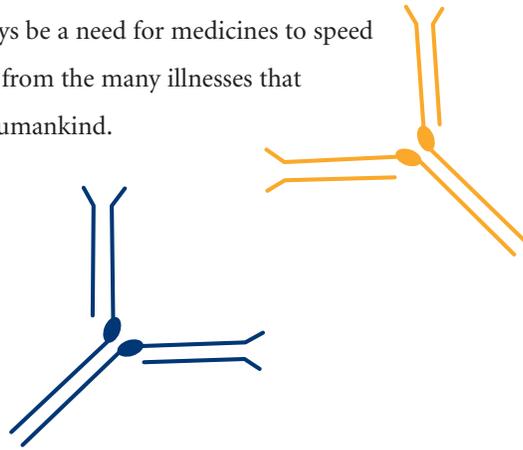
Doctors are already using therapeutic monoclonal antibodies to attack tumors. A drug called Rituxan<sup>®</sup> was the first therapeutic antibody approved by the Food and Drug Administration to treat cancer. This monoclonal antibody targets a unique tumor “fingerprint” on the surface of immune cells, called B cells, in a blood cancer called non-Hodgkin’s lymphoma. Another therapeutic antibody for cancer, Herceptin<sup>®</sup>, latches onto breast cancer cell receptors that signal growth to either mask the receptors from view or lure immune cells to kill the cancer cells. Herceptin’s actions prevent breast cancer from spreading to other organs.

Researchers are also investigating a new kind of “vaccine” as therapy for diseases such as cancer. The vaccines are not designed to prevent cancer,

but rather to treat the disease when it has already taken hold in the body. Unlike the targeted-attack approach of antibody therapy, vaccines aim to recruit the entire immune system to fight off a tumor. Scientists are conducting clinical trials of vaccines against cancer to evaluate the effectiveness of this treatment approach.

The body machine has a tremendously complex collection of chemical signals that are relayed back and forth through the blood and into and out of cells. While scientists are hopeful that future

research will point the way toward getting a sick body to heal itself, it is likely that there will always be a need for medicines to speed recovery from the many illnesses that plague humankind.



## *A Shock to the System*

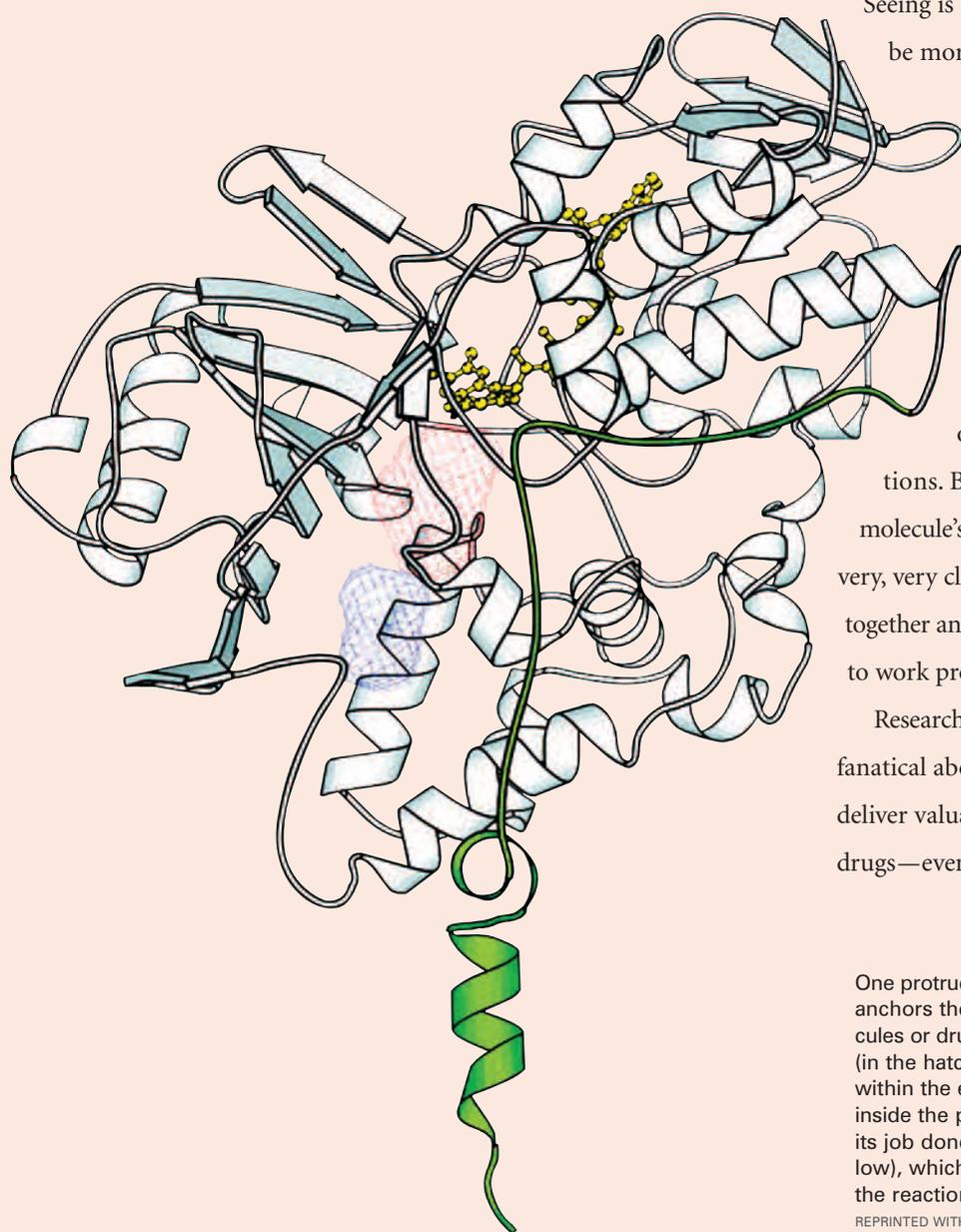


A body-wide syndrome caused by an infection called sepsis is a leading cause of death in hospital intensive care units, striking 750,000 people every year and killing more than 215,000. Sepsis is a serious public health problem, causing more deaths annually than heart disease. The most severe form of sepsis occurs when bacteria leak into the bloodstream, spilling their poisons and leading to a dangerous condition called septic shock. Blood pressure plunges dangerously low, the heart has

difficulty pumping enough blood, and body temperature climbs or falls rapidly. In many cases, multiple organs fail and the patient dies.

Despite the obvious public health importance of finding effective ways to treat sepsis, researchers have been frustratingly unsuccessful. Kevin Tracey of the North Shore-Long Island Jewish Research Institute in Manhasset, New York, has identified an unusual suspect in the deadly crime of sepsis: the nervous system. Tracey and his coworkers have discovered an unexpected link between cytokines, the chemical weapons released by the immune system during sepsis, and a major nerve that controls critical body functions such as heart rate and digestion. In animal studies, Tracey found that electrically stimulating this nerve, called the vagus nerve, significantly lowered blood levels of TNF, a cytokine that is produced when the body senses the presence of bacteria in the blood. Further research has led Tracey to conclude that production of the neurotransmitter acetylcholine underlies the inflammation-blocking response. Tracey is investigating whether stimulating the vagus nerve can be used as a component of therapy for sepsis and as a treatment for other immune disorders.

## A Closer Look



Seeing is believing. The cliché could not be more apt for biologists trying to understand how a complicated enzyme works. For decades, researchers have isolated and purified individual enzymes from cells, performing experiments with these proteins to find out how they do their job of speeding up chemical reactions. But to thoroughly understand a molecule's function, scientists have to take a very, very close look at how all the atoms fit together and enable the molecular "machine" to work properly.

Researchers called structural biologists are fanatical about such detail, because it can deliver valuable information for designing drugs—even for proteins that scientists have

One protruding end (green) of the MAO B enzyme anchors the protein inside the cell. Body molecules or drugs first come into contact with MAO B (in the hatched blue region) and are worked on within the enzyme's "active site," a cavity nestled inside the protein (the hatched red region). To get its job done, MAO B uses a helper molecule (yellow), which fits right next to the active site where the reaction takes place.

REPRINTED WITH PERMISSION FROM J. BIOL. CHEM. (2002) 277:23973-6.  
[HTTP://WWW.JBC.ORG](http://www.jbc.org)

studied in the lab for a long time. For example, biologists have known for 40 years that an enzyme called monoamine oxidase B (MAO B) works in the brain to help recycle communication molecules called neurotransmitters. MAO B and its cousin MAO A work by removing molecular pieces from neurotransmitters, part of the process of inactivating them. Scientists have developed drugs to block the actions of MAO enzymes, and by doing so, help preserve the levels of neurotransmitters in people with such disorders as Parkinson's disease and depression.

However, MAO inhibitors have many undesirable side effects. Tremors, increased heart rate, and problems with sexual function are some of the mild side effects of MAO inhibitors, but more serious problems include seizures, large dips in blood pressure, and difficulty breathing. People taking MAO inhibitors cannot eat foods containing the substance tyramine, which is found in wine, cheese, dried fruits, and many other foods. Most of the side effects occur because drugs that attach to MAO enzymes do not have a perfect fit for either MAO A or MAO B.

Dale Edmondson of Emory University in Atlanta, Georgia, has recently uncovered new knowledge that may help researchers design better, more specific drugs to interfere with these critical brain enzymes. Edmondson and his coworkers Andrea Mattevi and Claudia Binda of the University of Pavia in Italy got a crystal-clear glimpse of MAO B by determining its three-dimensional structure. The researchers also saw how one MAO inhibitor, Eldepryl<sup>®</sup>, attaches to the MAO B enzyme, and the scientists predict that their results will help in the design of more specific drugs with fewer side effects.



## Got It?

Define metabolism.

How does aspirin work?

Name three functions of blood.

Give two examples of immunotherapy.

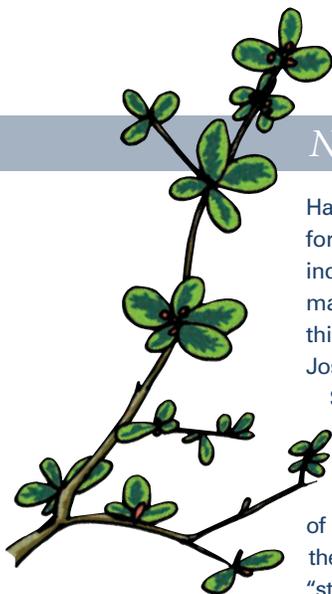
What is a technique scientists use to study a protein's three dimensional structure?

## Drugs From Nature, Then and Now

Long before the first towns were built, before written language was invented, and even before plants were cultivated for food, the basic human desires to relieve pain and prolong life fueled the search for medicines. No one knows for sure what the earliest humans did to treat their ailments, but they probably sought cures in the plants, animals, and minerals around them.

### Nature's Medicine Cabinet

Times have changed, but more than half of the world's population still relies entirely on plants for medicines, and plants supply the active ingredients of most traditional medical products. Plants have also served as the starting point for countless drugs on the market today. Researchers generally agree that natural products from plants and other organisms have been the most consistently successful source for ideas for new drugs, since nature is a master chemist. Drug discovery scientists often refer to these ideas as “leads,” and chemicals that have desirable properties in lab tests are called lead compounds.

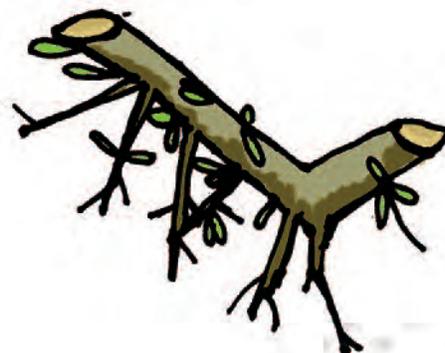


### Natural Cholesterol-Buster

Having high cholesterol is a significant risk factor for heart disease, a leading cause of death in the industrialized world. Pharmacology research has made major strides in helping people deal with this problem. Scientists Michael Brown and Joseph Goldstein, both of the University of Texas Southwestern Medical Center at Dallas, won the 1985 Nobel Prize in physiology or medicine for their fundamental work determining how the body metabolizes cholesterol. This research, part of which first identified cholesterol receptors, led to the development of the popular cholesterol-lowering “statin” drugs such as Mevacor® and Lipitor®.

New research from pharmacologist David Mangelsdorf, also at the University of Texas Southwestern Medical Center at Dallas, is pointing to another potential treatment for high cholesterol. The “new” substance has the tongue-twisting name guggulsterone, and it isn't really new at all. Guggulsterone comes from the sap of the guggul tree, a species native to India, and has been used in India's Ayurvedic medicine since at least 600 B.C. to treat a wide variety of ailments, including obesity and cholesterol disorders. Mangelsdorf

and his coworker David Moore of Baylor College of Medicine in Houston, Texas, found that guggulsterone blocks a protein called the FXR receptor that plays a role in cholesterol metabolism, converting cholesterol in the blood to bile acids. According to Mangelsdorf, since elevated levels of bile acids can actually boost cholesterol, blocking FXR helps to bring cholesterol counts down.



Sap from the guggul tree, a species native to India, contains a substance that may help fight heart disease.

Relatively speaking, very few species of living things on Earth have actually been seen and named by scientists. Many of these unidentified organisms aren't necessarily lurking in uninhabited places. A few years ago, for instance, scientists identified a brand-new species of millipede in a rotting leaf pile in New York City's Central Park, an area visited by thousands of people every day.

Scientists estimate that Earth is home to at least 250,000 different species of plants, and that up to 30 million species of insects crawl or fly somewhere around the globe. Equal numbers of species of fungi, algae, and bacteria probably also exist. Despite these vast numbers, chemists have tested

only a few of these organisms to see whether they harbor some sort of medically useful substance.

Pharmaceutical chemists seek ideas for new drugs not only in plants, but in any part of nature where they may find valuable clues. This includes searching for organisms from what has been called the last unexplored frontier: the seawater that blankets nearly three-quarters of Earth.

## Cancer Therapy Sees the Light

A novel drug delivery system called photodynamic therapy combines an ancient plant remedy, modern blood transfusion techniques, and light. Photodynamic therapy has been approved by the Food and Drug Administration to treat several cancers and certain types of age-related macular degeneration, a devastating eye disease that is the leading cause of blindness in North America and Europe. Photodynamic therapy is also being tested as a treatment for some skin and immune disorders.

The key ingredient in this therapy is psoralen, a plant-derived chemical that has a peculiar property: It is inactive until exposed to light. Psoralen is the active ingredient in a Nile-dwelling weed called ammi. This remedy was used by ancient Egyptians, who noticed that people became prone to sunburn after eating the weed. Modern researchers explained this phenomenon by discovering that psoralen, after being digested, goes to the skin's surface, where it is activated by the



Some forms of cancer can be treated with photodynamic therapy, in which a cancer-killing molecule is activated by certain wavelengths of light.

JOSEPH FRIEDBERG

sun's ultraviolet rays. Activated psoralen attaches tenaciously to the DNA of rapidly dividing cancer cells and kills them. Photopheresis, a method that exposes a psoralen-like drug to certain wavelengths of light, is approved for the treatment of some forms of lymphoma, a cancer of white blood cells.

## Ocean Medicines

Marine animals fight daily for both food and survival, and this underwater warfare is waged with chemicals. As with plants, researchers have recognized the potential use of this chemical weaponry to kill bacteria or raging cancer cells. Scientists isolated the first marine-derived cancer drug, now known as Cytosar-U<sup>®</sup>, decades ago. They found this chemical, a staple for treating leukemia and lymphoma, in a Caribbean sea sponge. In recent years, scientists have discovered dozens of similar ocean-derived chemicals that appear to be powerful cancer cell killers. Researchers are testing these natural products for their therapeutic properties.

For example, scientists have unearthed several promising drugs from sea creatures called tunicates.

More commonly known as sea squirts, tunicates are a group of marine organisms that spend most of their lives attached to docks, rocks, or the undersides of boats. To an untrained eye they look like nothing more than small, colorful blobs, but tunicates are evolutionarily more closely related to vertebrates like ourselves than to most other invertebrate animals.

One tunicate living in the crystal waters of West Indies coral reefs and mangrove swamps turned out to be the source of an experimental cancer drug called ecteinascidin. Ken Rinehart, a chemist who was then at the University of Illinois at Urbana-Champaign discovered this natural substance. PharmaMar, a pharmaceutical company based in Spain, now holds the licenses for ecteinascidin, which it calls Yondelis<sup>™</sup>, and is

## Miracle Cures



CHRISTINE L. CASE

Led by the German scientist Paul Ehrlich, a new era in pharmacology began in the late 19th century. Although Ehrlich's original idea seems perfectly obvious now, it was considered very strange at the time. He proposed that every disease should be treated with a chemical specific for that disease, and that the pharmacologist's task was to find these treatments by systematically testing potential drugs.

The approach worked: Ehrlich's greatest triumph was his discovery of salvarsan, the first effective treatment for the sexually transmitted disease syphilis. Ehrlich discovered salvarsan after screening 605 different arsenic-containing compounds. Later, researchers around the world had great success in developing new drugs by following Ehrlich's methods. For example, testing of sulfur-containing dyes led to the 20th century's first "miracle drugs"—the sulfa drugs, used to treat bacterial infections. During the 1940s, sulfa drugs were rapidly replaced by a new, more powerful, and safer antibacterial drug, penicillin—originally extracted from the soil-dwelling fungus *Penicillium*.

- ▲ A penicillin-secreting *Penicillium* mold colony inhibits the growth of bacteria (zig-zag smear growing on culture dish).



Yondelis is an experimental cancer drug isolated from the marine organism *Ecteinascidia turbinata*.

conducting clinical trials on this drug. Lab tests indicate that Yondelis can kill cancer cells, and the first set of clinical studies has shown that the drug is safe for use in humans. Further phases of clinical testing—to evaluate whether Yondelis effectively treats soft-tissue sarcomas (tumors of the muscles, tendons, and supportive tissues)—and other types of cancer—are under way.

Animals that live in coral reefs almost always rely on chemistry to ward off hungry predators. Because getting away quickly isn't an option in this environment, lethal chemical brews are the weaponry of choice for these slow-moving or even sedentary animals. A powerful potion comes from one of these animals, a stunningly gorgeous

species of snail found in the reefs surrounding Australia, Indonesia, and the Philippines. The animals, called cone snails, have a unique venom containing dozens of nerve toxins. Some of these venoms instantly shock prey, like the sting of an electric eel or the poisons of scorpions and sea anemones. Others cause paralysis, like the venoms of cobras and puffer fish.

Pharmacologist Baldomero Olivera of the University of Utah in Salt Lake City, a native of the Philippines whose boyhood fascination with cone snails matured into a career studying them, has discovered one cone snail poison that has become a potent new pain medicine. Olivera's experiments have shown that the snail toxin is



A poison produced by the cone snail *C. geographus* has become a powerful new pain medicine.

1,000 times more powerful than morphine in treating certain kinds of chronic pain. The snail-derived drug, named Prialt™ by the company (Elan Corporation, plc in Dublin, Ireland) that developed and markets it, jams up nerve transmission in the spinal cord and blocks certain pain signals from reaching the brain. Scientists predict that many more cone snail toxins will be drug leads, since 500 different species of this animal populate Earth.

## Prospecting Biology?



The cancer drug Taxol originally came from the bark and needles of yew trees.

Are researchers taking advantage of nature when it comes to hunting for new medicines? Public concern has been raised about scientists scouring the world's tropical rainforests and coral reefs to look for potential natural chemicals that may end up being useful drugs. While it is true that rainforests in particular are home to an extraordinarily rich array of species of animals and plants, many life-saving medicines derived from

natural products have been discovered in temperate climates not much different from our kitchens and backyards.

Many wonder drugs have arisen from non-endangered species, such as the bark of the willow tree, which was the original source of aspirin.

The antibiotic penicillin, from an ordinary mold, is another example. Although scientists first found the chemical that became the widely prescribed cancer drug Taxol® in the bark of an endangered species of tree called the Pacific yew, researchers have since found a way to manufacture Taxol in the lab, starting with an extract from pine needles of the much more abundant European yew. In many cases, chemists have also figured out ways to make large quantities of rainforest- and reef-derived chemicals in the lab (see main text).

## Tweaking Nature

Searching nature's treasure trove for potential medicines is often only the first step. Having tapped natural resources to hunt for new medicines, pharmaceutical scientists then work to figure out ways to cultivate natural products or to make them from scratch in the lab. Chemists play an essential role in turning marine and other natural products, which are often found in minute quantities, into useful medicines.

In the case of Yondelis, chemist Elias J. Corey of Harvard University in Boston, Massachusetts,

deciphered nature's instructions on how to make this powerful medicinal molecule. That's important, because researchers must harvest more than a ton of Caribbean sea squirts to produce just 1 gram of the drug. By synthesizing drugs in a lab, scientists can produce thousands more units of a drug, plenty to use in patients if it proves effective against disease.

Scientists are also beginning to use a relatively new procedure called combinatorial genetics to custom-make products that don't even exist in nature. Researchers have discovered ways to

## Toxicogenetics: Poisons and Your Genes

Just as your genes help determine how you respond to certain medicines, your genetic code can also affect your susceptibility to illness. Why is it that two people with a similar lifestyle and a nearly identical environment can have such different propensities to getting sick? Lots of factors contribute, including diet, but scientists believe that an important component of disease risk is the genetic variability of people's reactions to chemicals in the environment.

On hearing the word "chemical," many people think of smokestacks and pollution. Indeed, our world is littered with toxic chemicals, some natural and some synthetic. For example, nearly all of us would succumb quickly to the poisonous bite of a cobra, but it is harder to predict which of us will develop cancer from exposure to carcinogens like cigarette smoke.

Toxicologists are researchers who study the effects of poisonous substances on living organisms. One toxicologist, Serrine Lau of the University of Texas at Austin, is trying to unravel the genetic mystery of why people are more or less susceptible to kidney damage after coming



into contact with some types of poisons. Lau and her coworkers study the effects of a substance called hydroquinone (HQ), an industrial pollutant and a contaminant in cigarette smoke and diesel engine exhaust. Lau is searching for genes that play a role in triggering cancer in response to HQ exposure. Her research and the work of other so-called toxicogeneticists should help scientists find genetic "signatures" that can predict risk of developing cancer in people exposed to harmful carcinogens.

remove the genetic instructions for entire metabolic pathways from certain microorganisms, alter the instructions, and then put them back. This method can generate new and different “natural” products.

### Is It Chemistry or Genetics?

Regardless of the way researchers find new medicines, drug discovery often takes many unexpected twists and turns. Scientists must train their eyes to look for new opportunities lurking in the outcomes of their experiments. Sometimes, side trips in the lab can open up entirely new avenues of discovery.

Take the case of cyclosporine, a drug discovered three decades ago that suppresses the immune system and thereby prevents the body from rejecting transplanted organs. Still a best-selling medicine, cyclosporine was a research breakthrough. The drug made it possible for surgeons to save the lives of many critically ill patients by transplanting organs. But it's not hard to imagine that the very properties that make cyclosporine so powerful in putting a lid on the immune system can cause serious side effects, by damping immune function too much.

Years after the discovery of cyclosporine, researchers looking for less toxic versions of this drug found a natural molecule called FK506 that seemed to produce the same immune-suppressing

effects at lower doses. The researchers found, to their great surprise, that cyclosporine and FK506 were chemically very different. To try to explain this puzzling result, Harvard University organic chemist Stuart Schreiber (then at Yale University in New Haven, Connecticut) decided to take on the challenge of figuring out how to make FK506 in his lab, beginning with simple chemical building blocks.

Schreiber succeeded, and he and scientists at Merck & Co., Inc. (Whitehouse Station, New Jersey) used the synthetic FK506 as a tool to unravel the molecular structure of the receptor for FK506 found on immune cells. According to Schreiber, information about the receptor's structure from these experiments opened his eyes to consider an entirely new line of research.

Schreiber reasoned that by custom-making small molecules in the lab, scientists could probe the function of the FK506 receptor to systematically study how the immune system works. Since then, he and his group have continued to use synthetic small molecules to explore biology. Although Schreiber's strategy is not truly genetics, he calls the approach chemical genetics, because the method resembles the way researchers go about their studies to understand the functions of genes.

In one traditional genetic approach, scientists alter the “spelling” (nucleotide components) of a gene and put the altered gene into a model organism—for example, a mouse, a plant, or a yeast cell—to see what effect the gene change has on the biology of that organism. Chemical genetics harnesses the power of chemistry to custom-produce any molecule and introduce it into cells, then look for biological changes that result. Starting with chemicals instead of genes gives drug development a step up. If the substance being tested produces a desired effect, such as stalling the growth of cancer cells, then the molecule can be chemically manipulated in short order since the chemist already knows how to make it.

### Blending Science

These days, it’s hard for scientists to know what to call themselves. As research worlds collide in wondrous and productive ways, the lines get blurry when it comes to describing your expertise. Craig Crews of Yale University, for example, mixes a combination of molecular pharmacology, chemistry, and genetics. In fact, because of his multiple scientific curiosities, Crews is a faculty member in three different Yale departments: molecular, cellular, and developmental biology; chemistry; and pharmacology. You might wonder how he has time to get anything done.

He’s getting plenty done—Crews is among a new breed of researchers delving into a growing scientific area called chemical genetics (see main text). Taking this approach, scientists use chemistry to attack biological problems that traditionally have been solved through genetic experiments such as the genetic engineering of bacteria, yeast, and mice. Crews’ goal is to explore how natural products work in living systems and to identify new targets for designing drugs. He has discovered how an



▲ The herb feverfew (bachelor’s button) contains a substance called parthenolide that appears to block inflammation.

inflammation-fighting ingredient in the medicinal herb feverfew may work inside cells. He found that the ingredient, called parthenolide, appears to disable a key process that gets inflammation going. In the case of feverfew, a handful of controlled scientific studies in people have hinted that the herb, also known by its plant name “bachelor’s button,” is effective in combating migraine headaches, but further studies are needed to confirm these preliminary findings.

## Testing...I, II, III

To translate pharmacology research into patient care, potential drugs ultimately have to be tested in people. This multistage process is known as clinical trials, and it has led researchers to validate life-saving treatments for many diseases, such as childhood leukemia and Hodgkin's disease. Clinical trials, though costly and very time-consuming, are the only way researchers can know for sure whether experimental treatments work in humans.

Scientists conduct clinical trials in three phases (I, II, and III), each providing the answer to a different fundamental question about a potential new drug: Is it safe? Does it work? Is it better than the standard treatment? Typically, researchers do years of basic work in the lab and in animal models before they can even consider testing an experimental treatment in people. Importantly, scientists who wish to test drugs in people must follow strict



rules that are designed to protect those who volunteer to participate in clinical trials. Special groups called Institutional Review Boards, or IRBs, evaluate all proposed research involving humans to determine the potential risks and anticipated benefits. The goal of an IRB is to make sure that the risks are minimized and that they are reasonable compared to the knowledge expected to be gained by performing the study. Clinical studies cannot go forward without IRB approval. In addition, people in clinical studies must agree to the terms of a trial by participating in a process called informed consent and signing a form, required by law, that says they understand the risks and benefits involved in the study.

Phase I studies test a drug's safety in a few dozen to a hundred people and are designed to figure out what happens to a drug in the body—how it is absorbed, metabolized, and excreted. Phase I studies usually take several months. Phase II trials test whether or not a drug produces a desired effect. These studies take longer—from several months to a few years—and can involve up to several hundred patients. A phase III study further examines

the effectiveness of a drug as well as whether the drug is better than current treatments. Phase III studies involve hundreds to thousands of patients, and these advanced trials typically last several years. Many phase II and phase III studies are randomized, meaning that one group of patients gets the experimental drug being tested while a second, control group gets either a standard treatment or placebo (that is, no treatment, often masked as a “dummy” pill or injection). Also, usually phase II and phase III studies are “blinded”—the patients and the researchers do not know who is getting the experimental drug. Finally, once a new drug has completed phase III testing, a pharmaceutical company can request approval from the Food and Drug Administration to market the drug.



## Got It?

Scientists are currently testing cone snail toxins for the treatment of which health problem?

How are people protected when they volunteer to participate in a clinical trial?

Why do plants and marine organisms have chemicals that could be used as medicines?

What is a drug “lead?”

Name the first marine derived cancer medicine.

## Molecules to Medicines

**A**s you've read so far, the most important goals of modern pharmacology are also the most obvious. Pharmacologists want to design, and be able to produce in sufficient quantity, drugs that will act in a specific way without too many side effects. They also want to deliver the correct amount of a drug to the proper place in the body. But turning molecules into medicines is more easily said than done. Scientists struggle to fulfill the twin challenges of drug design and drug delivery.

### Medicine Hunting

While sometimes the discovery of potential medicines falls to researchers' good luck, most often pharmacologists, chemists, and other scientists looking for new drugs plod along methodically for years, taking suggestions from nature or clues from knowledge about how the body works.

Finding chemicals' cellular targets can educate scientists about how drugs work. Aspirin's molecular target, the enzyme cyclooxygenase, or COX (see page 22), was discovered this way in the early 1970s in Nobel Prize-winning work by pharmacologist John Vane, then at the Royal College of Surgeons in London, England. Another example is colchicine, a relatively old drug that is still widely used to treat gout, an excruciatingly painful type of arthritis in which needle-like crystals of uric acid clog joints, leading to swelling, heat, pain, and

### A Drug By Another Name



WHO/DRISTAMMERS

▲ Drugs used to treat bone ailments may be useful for treating infectious diseases like malaria.

As pet owners know, you *can* teach some old dogs new tricks. In a similar vein, scientists have in some cases found new uses for "old" drugs. Remarkably, the potential new uses often have little in common with a drug's product label (its "old" use). For example, chemist Eric Oldfield of the University of Illinois at Urbana-Champaign discovered that one class of drugs called bisphosphonates, which are currently approved to treat osteoporosis and other bone disorders, may also be useful for treating malaria, Chagas' disease, leishmaniasis, and AIDS-related infections like toxoplasmosis.

Previous research by Oldfield and his coworkers had hinted that the active ingredient in the bisphosphonate medicines Fosamax<sup>®</sup>, Actonel<sup>®</sup>,

and Aredia<sup>®</sup> blocks a critical step in the metabolism of parasites, the microorganisms that cause these diseases. To test whether this was true, Oldfield gave the medicines to five different types of parasites, each grown along with human cells in a plastic lab dish. The scientists found that small amounts of the osteoporosis drugs killed the parasites while sparing human cells. The researchers are now testing the drugs in animal models of the parasitic diseases and so far have obtained cures—in mice—of certain types of leishmaniasis. If these studies prove that bisphosphonate drugs work in larger animal models, the next step will be to find out if the medicines can thwart these parasitic diseases in humans.

stiffness. Lab experiments with colchicine led scientists to this drug's molecular target, a cell-scaffolding protein called tubulin. Colchicine works by attaching itself to tubulin, causing certain parts of a cell's architecture to crumble, and this action can interfere with a cell's ability to move around. Researchers suspect that in the case of gout, colchicine works by halting the migration of immune cells called granulocytes that are responsible for the inflammation characteristic of gout.

Current estimates indicate that scientists have identified roughly 500 to 600 molecular targets where medicines may have effects in the body. Medicine hunters can strategically “discover” drugs by designing molecules to “hit” these targets. That has already happened in some cases. Researchers knew just what they were looking for when they designed the successful AIDS drugs called HIV protease inhibitors. Previous knowledge of the three-dimensional structure of certain HIV proteins (the target) guided researchers to develop drugs shaped to block their action. Protease inhibitors have extended the lives of many people with AIDS.

However, sometimes even the most targeted approaches can end up in big surprises. The New York City pharmaceutical firm Pfizer had a blood pressure-lowering drug in mind, when instead its scientists discovered Viagra<sup>®</sup>, a best-selling drug approved to treat erectile dysfunction. Initially, researchers had planned to create a heart drug, using knowledge they had about molecules that



NATIONAL AGRICULTURE LIBRARY, ARS, USDA

Colchicine, a treatment for gout, was originally derived from the stem and seeds of the meadow saffron (autumn crocus).

make blood clot and molecular signals that instruct blood vessels to relax. What the scientists did not know was how their candidate drug would fare in clinical trials.

Sildenafil (Viagra's chemical name) did not work very well as a heart medicine, but many men who participated in the clinical testing phase of the drug noted one side effect in particular: erections. Viagra works by boosting levels of a natural molecule called cyclic GMP that plays a key role in cell signaling in many body tissues. This molecule does a good job of opening blood vessels in the penis, leading to an erection.

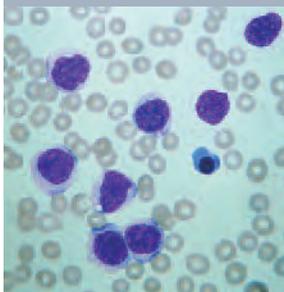
## 21st-Century Science

While strategies such as chemical genetics can quicken the pace of drug discovery, other approaches may help expand the number of molecular targets from several hundred to several thousand. Many of these new avenues of research hinge on biology.

Relatively new brands of research that are stepping onto center stage in 21st-century science include genomics (the study of all of an organism's genetic material), proteomics (the study of all of an organism's proteins), and bioinformatics (using computers to sift through large amounts of biological data). The “omics” revolution in

biomedicine stems from biology's gradual transition from a gathering, descriptive enterprise to a science that will someday be able to model and predict biology. If you think 25,000 genes is a lot (the number of genes in the human genome), realize that each gene can give rise to different variations of the same protein, each with a different molecular job. Scientists estimate that humans have hundreds of thousands of protein variants. Clearly, there's lots of work to be done, which will undoubtedly keep researchers busy for years to come.

### *A Chink in Cancer's Armor*



Doctors use the drug Gleevec to treat a form of leukemia, a disease in which abnormally high numbers of immune cells (larger, purple circles in photo) populate the blood.

Recently, researchers made an exciting step forward in the treatment of cancer. Years of basic research investigating circuits of cellular communication led scientists to tailor-make a new kind of cancer medicine. In May 2001, the drug Gleevec™ was approved to treat a rare cancer of the blood called chronic myelogenous leukemia (CML). The Food and Drug Administration described Gleevec's approval as “...a testament to the groundbreaking scientific research taking place in labs throughout America.”

Researchers designed this drug to halt a cell-communication pathway that is always “on” in CML. Their success was founded on years of experiments in the basic biology of how cancer cells grow. The discovery of Gleevec is an example of the success

of so-called molecular targeting: understanding how diseases arise at the level of cells, then figuring out ways to treat them. Scores of drugs, some to treat cancer but also many other health conditions, are in the research pipeline as a result of scientists' eavesdropping on how cells communicate.

## Rush Delivery

Finding new medicines and cost-effective ways to manufacture them is only half the battle. An enormous challenge for pharmacologists is figuring out how to get drugs to the right place, a task known as drug delivery.

Ideally, a drug should enter the body, go directly to the diseased site while bypassing healthy tissue, do its job, and then disappear. Unfortunately, this rarely happens with the typical methods of delivering drugs: swallowing and injection. When swallowed, many medicines made of protein are never absorbed into the bloodstream because they are quickly chewed up by enzymes as they pass through the digestive system. If the drug does get to the blood from the intestines, it falls prey to liver enzymes. For doctors prescribing such drugs, this first-pass effect (see page 7) means that several doses of an oral drug are needed before enough makes it to the blood. Drug injections also cause problems, because they are expensive, difficult for patients to self-administer, and are unwieldy if the drug must be taken daily. Both methods of administration also result in fluctuating levels of the drug in the blood, which is inefficient and can be dangerous.

What to do? Pharmacologists can work around the first-pass effect by delivering medicines via the

skin, nose, and lungs. Each of these methods bypasses the intestinal tract and can increase the amount of drug getting to the desired site of action in the body. Slow, steady drug delivery directly to the bloodstream—without stopping at the liver first—is the primary benefit of skin patches, which makes this form of drug delivery particularly useful when a chemical must be administered over a long period.

Hormones such as testosterone, progesterone, and estrogen are available as skin patches. These forms of medicines enter the blood via a meshwork of small arteries, veins, and capillaries in the skin. Researchers also have developed skin patches for a wide variety of other drugs. Some of these include Duragesic<sup>®</sup> (a prescription-only pain medicine), Transderm Scop<sup>®</sup> (a motion-sickness drug), and Transderm Nitro<sup>®</sup> (a blood vessel-widening drug used to treat chest pain associated with heart disease). Despite their advantages, however, skin patches have a significant drawback. Only very small drug molecules can get into the body through the skin.

Inhaling drugs through the nose or mouth is another way to rapidly deliver drugs and bypass the liver. Inhalers have been a mainstay of asthma therapy for years, and doctors prescribe nasal steroid drugs for allergy and sinus problems.

Researchers are investigating insulin powders that can be inhaled by people with diabetes who rely on insulin to control their blood sugar daily. This still-experimental technology stems from novel uses of chemistry and engineering to manufacture insulin particles of just the right size. Too large, and the insulin particles could lodge in the lungs;

too small, and the particles will be exhaled. If clinical trials with inhaled insulin prove that it is safe and effective, then this therapy could make life much easier for people with diabetes.

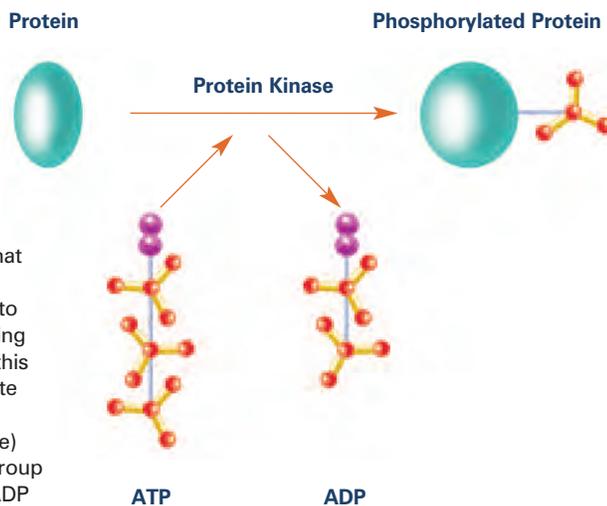
## Reading a Cell MAP

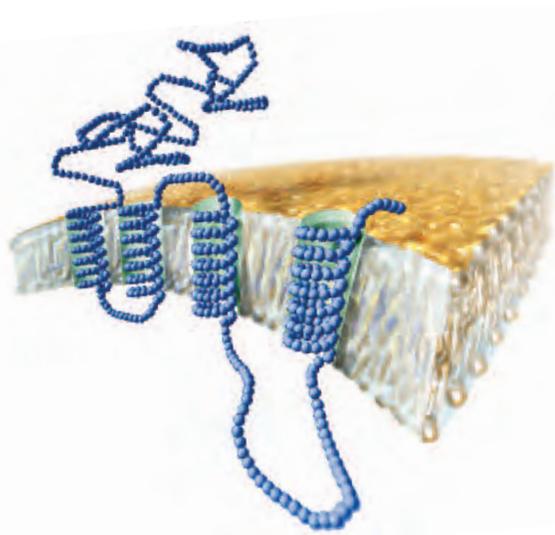
Scientists try hard to listen to the noisy, garbled “discussions” that take place inside and between cells. Less than a decade ago, scientists identified one very important cellular communication stream called MAP (**m**itogen-**a**ctivated **p**rotein) kinase signaling. Today, molecular pharmacologists such as Melanie H. Cobb of the University of Texas Southwestern Medical Center at Dallas are studying how MAP kinase signaling pathways malfunction in unhealthy cells.

Some of the interactions between proteins in these pathways involve adding and taking away tiny molecular labels called phosphate groups. Kinases are the enzymes that add phosphate groups to proteins, and this process is called phosphorylation. Marking proteins in this way assigns the proteins a code, instructing the cell to do something, such as divide or grow. The body employs many, many signaling pathways involving hundreds of different kinase enzymes. Some of the important functions performed by MAP kinase pathways include instructing immature cells how to “grow up” to be specialized cell types like muscle cells, helping cells in the pancreas respond to the hormone insulin, and even telling cells how to die.

Since MAP kinase pathways are key to so many important cell processes, researchers consider them good targets for drugs. Clinical trials are under way to test various molecules that, in animal studies, can effectively lock up MAP kinase signaling when it’s not wanted, for example, in cancer and in diseases involving an overactive immune system, such as arthritis. Researchers predict that if drugs to block MAP kinase signaling prove effective in people, they will likely be used in combination with other medicines that treat a variety of health conditions, since many diseases are probably caused by simultaneous errors in multiple signaling pathways.

Kinases are enzymes that add phosphate groups (red-yellow structures) to proteins (green), assigning the proteins a code. In this reaction, an intermediate molecule called ATP (adenosine triphosphate) donates a phosphate group from itself, becoming ADP (adenosine diphosphate).





Proteins that snake through membranes help transport molecules into cells.

[HTTP://WWW.PHARMACOLOGY.UCLA.EDU](http://www.pharmacology.ucla.edu)

### Transportation Dilemmas

Scientists are solving the dilemma of drug delivery with a variety of other clever techniques. Many of the techniques are geared toward sneaking through the cellular gate-keeping systems' membranes. The challenge is a chemistry problem—most drugs are water-soluble, but membranes are oily. Water and oil don't mix, and thus many drugs can't enter the cell. To make matters worse, size matters too. Membranes are usually constructed to permit the entry of only small nutrients and hormones, often through private cellular alleyways called transporters.

Many pharmacologists are working hard to devise ways to work not against, but *with* nature,

by learning how to hijack molecular transporters to shuttle drugs into cells. Gordon Amidon, a pharmaceutical chemist at the University of Michigan-Ann Arbor, has been studying one particular transporter in mucosal membranes lining the digestive tract. The transporter, called hPEPT1, normally serves the body by ferrying small, electrically charged particles and small protein pieces called peptides into and out of the intestines.

Amidon and other researchers discovered that certain medicines, such as the antibiotic penicillin and certain types of drugs used to treat high blood pressure and heart failure, also travel into the intestines via hPEPT1. Recent experiments revealed that the herpes drug Valtrex<sup>®</sup> and the AIDS drug Retrovir<sup>®</sup> also hitch a ride into intestinal cells using the hPEPT1 transporter. Amidon wants to extend this list by synthesizing hundreds of different molecules and testing them for their ability to use hPEPT1 and other similar transporters. Recent advances in molecular biology, genomics, and bioinformatics have sped the search for molecules that Amidon and other researchers can test.

Scientists are also trying to slip molecules through membranes by cloaking them in disguise. Steven Regen of Lehigh University in Bethlehem, Pennsylvania, has manufactured miniature chemical umbrellas that close around and shield a molecule when it encounters a fatty membrane and then spread open in the watery environment inside a cell. So far, Regen has only used test molecules, not actual drugs, but he has succeeded in getting molecules that resemble small segments of DNA across membranes. The ability to do this in humans could be a crucial step in successfully delivering therapeutic molecules to cells via gene therapy.

### Act Like a Membrane

Researchers know that high concentrations of chemotherapy drugs will kill every single cancer cell growing in a lab dish, but getting enough of these powerful drugs to a tumor in the body without killing too many healthy cells along the way has been exceedingly difficult. These powerful drugs can do more harm than good by severely sickening a patient during treatment.

Some researchers are using membrane-like particles called liposomes to package and deliver drugs to tumors. Liposomes are oily, microscopic capsules that can be filled with biological cargo, such as a drug. They are very, very small—only

## Anesthesia Dissected



Scientists who study anesthetic medicines have a daunting task—for the most part, they are “shooting in the dark” when it comes to identifying the molecular targets of these drugs. Researchers do know that anesthetics share one common ingredient: Nearly all of them somehow target membranes, the oily wrappings surrounding cells. However, despite the fact that anesthesia is a routine part of surgery, exactly how anesthetic medicines work in the body has remained a mystery for more than 150 years. It’s an important problem, since anesthetics have multiple effects on key body functions, including critical processes such as breathing.

Scientists define anesthesia as a state in which no movement occurs in response to what should be painful. The problem is, even though a patient loses a pain response, the anesthesiologist can’t tell what is happening inside the person’s organs and cells. Further complicating the issue, scientists know that many different types of drugs—with

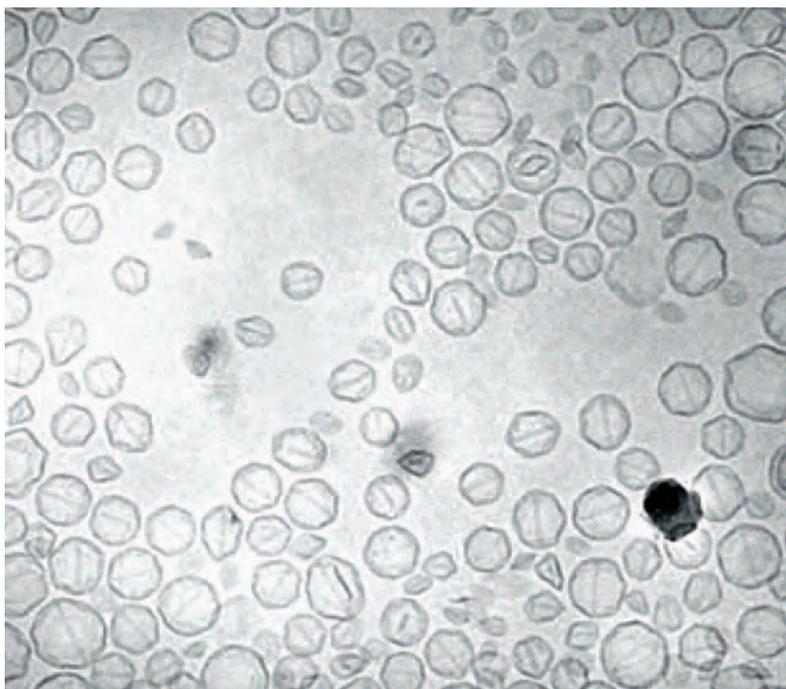
little physical resemblance to each other—can all produce anesthesia. This makes it difficult to track down causes and effects.

Anesthesiologist Robert Veselis of the Memorial Sloan-Kettering Institute for Cancer Research in New York City clarified how certain types of these mysterious medicines work. Veselis and his coworkers measured electrical activity in the brains of healthy volunteers receiving anesthetics while they listened to different sounds. To determine how sedated the people were, the researchers measured reaction time to the sounds the people heard. To measure memory effects, they quizzed the volunteers at the end of the study about word lists they had heard before and during anesthesia. Veselis’ experiments show that the anesthetics they studied affect separate brain areas to produce the two different effects of sedation and memory loss. The findings may help doctors give anesthetic medicines more effectively and safely and prevent reactions with other drugs a patient may be taking.

one one-thousandth the width of a single human hair. Researchers have known about liposomes for many years, but getting them to the right place in the body hasn't been easy. Once in the bloodstream, these foreign particles are immediately shipped to the liver and spleen, where they are destroyed.

Materials engineer David Needham of Duke University in Durham, North Carolina, is investigating the physics and chemistry of liposomes to better understand how the liposomes and their cancer-fighting cargo can travel through the body. Needham worked for 10 years to create a special kind of liposome that melts at just a few degrees above body temperature. The end result is a tiny molecular "soccer ball" made from two different oils that wrap around a drug. At room temperature, the liposomes are solid and they stay solid at body temperature, so they can be injected into the bloodstream. The liposomes are designed to spill their drug cargo into a tumor when heat is applied to the cancerous tissue. Heat is known to perturb tumors, making the blood vessels surrounding cancer cells extra-leaky. As the liposomes approach the warmed tumor tissue, the "stitches" of the miniature soccer balls begin to dissolve, rapidly leaking the liposome's contents.

Needham and Duke oncologist Mark Dewhirst teamed up to do animal studies with the heat-activated liposomes. Experiments in mice and

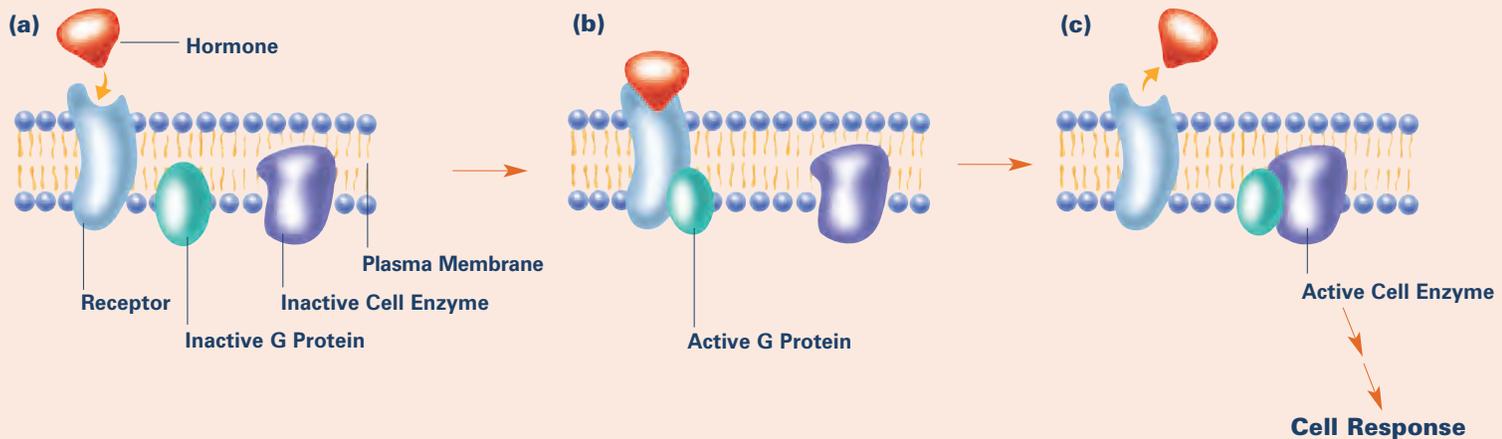


LAWRENCE MAVER, LUDGER ICKENSTEN, KATRINA EDWARDS

David Needham designed liposomes resembling tiny molecular "soccer balls" made from two different oils that wrap around a drug.

dogs revealed that, when heated, the drug-laden capsules flooded tumors with a chemotherapy drug and killed the cancer cells inside. Researchers hope to soon begin the first stage of human studies testing the heat-triggered liposome treatment in patients with prostate and breast cancer. The results of these and later clinical trials will determine whether liposome therapy can be a useful weapon for treating breast and prostate cancer and other hard-to-treat solid tumors.

## The G Switch



G proteins act like relay batons to pass messages from circulating hormones into cells.

- (a) A hormone (red) encounters a receptor (blue) in the membrane of a cell.
- (b) A G protein (green) becomes activated and makes contact with the receptor to which the hormone is attached.
- (c) The G protein passes the hormone's message to the cell by switching on a cell enzyme (purple) that triggers a response.

Imagine yourself sitting on a cell, looking outward to the bloodstream rushing by. Suddenly, a huge glob of something hurls toward you, slowing down just as it settles into a perfect dock on the surface of your cell perch. You don't realize it, but your own body sent this substance—a hormone called epinephrine—to protect you, telling you to get out of the way of a car that just about side-swiped yours while drifting out of its lane. Your body reacts, whipping up the familiar, spine-tingling, "fight-or-flight" response that gears you to respond quickly to potentially threatening situations such as this one.

How does it all happen so fast?

Getting into a cell is a challenge, a strictly guarded process kept in control by a protective gate called the plasma membrane. Figuring out how molecular triggers like epinephrine communicate important messages to the inner parts of cells earned two scientists the Nobel Prize in physiology or medicine in 1994. Getting a cellular message across the

membrane is called signal transduction, and it occurs in three steps. First, a message (such as epinephrine) encounters the outside of a cell and makes contact with a molecule on the surface called a receptor. Next, a connecting transducer, or switch molecule, passes the message inward, sort of like a relay baton. Finally, in the third step, the signal gets amplified, prompting the cell to do something: move, produce new proteins, even send out more signals.

One of the Nobel Prize winners, pharmacologist Alfred G. Gilman of the University of Texas Southwestern Medical Center at Dallas, uncovered the identity of the switch molecule, called a G protein. Gilman named the switch, which is actually a huge family of switch molecules, not after himself but after the type of cellular fuel it uses: an energy currency called GTP. As with any switch, G proteins must be turned on only when needed, then shut off. Some illnesses, including fatal diseases like cholera, occur when a G protein is errantly left on. In the case of cholera, the poisonous weaponry of the cholera bacterium “freezes” in place one particular type of G protein that controls water balance. The effect is constant fluid leakage, causing life-threatening diarrhea.

In the few decades since Gilman and the other Nobel Prize winner, the late National Institutes of Health scientist Martin Rodbell, made their fundamental discovery about G protein switches, pharmacologists all over

the world have focused on these signaling molecules. Research on G proteins and on all aspects of cell signaling has prospered, and as a result scientists now have an avalanche of data. In the fall of 2000, Gilman embarked on a groundbreaking effort to begin to untangle and reconstruct some of this information to guide the way toward creating a “virtual cell.” Gilman leads the Alliance for Cellular Signaling, a large, interactive research network. The group has a big dream: to understand everything there is to know about signaling inside cells. According to Gilman, Alliance researchers focus lots of attention on G proteins and also on other signaling systems in selected cell types. Ultimately, the scientists hope to test drugs and learn about disease through computer modeling experiments with the virtual cell system.



## Got It?

What is a liposome?

Name three drug delivery methods.

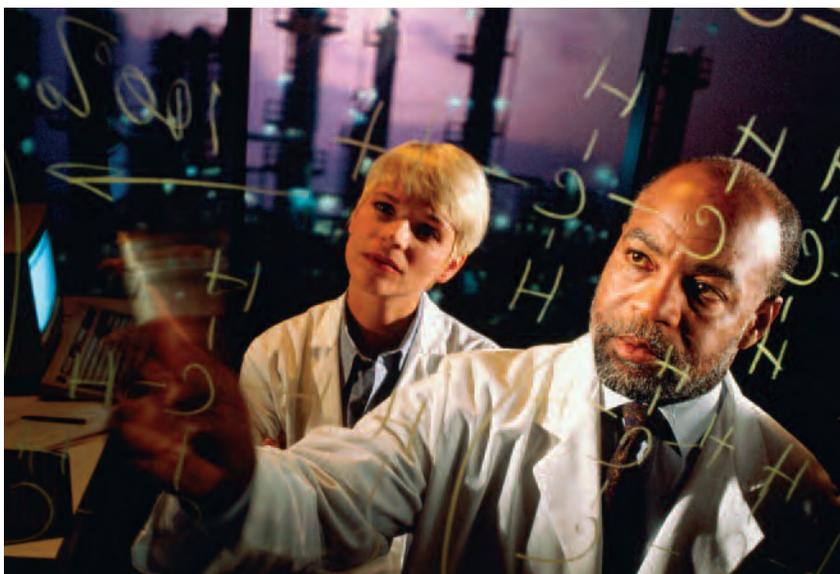
Describe how G proteins work.

What do kinases do?

Discuss the “omics” revolution in biomedical research.

## *Medicines for the Future*

**T**he advances in drug development and delivery described in this booklet reflect scientists' growing knowledge about human biology. This knowledge has allowed them to develop medicines targeted to specific molecules or cells. In the future, doctors may be able to treat or prevent diseases with drugs that actually repair cells or protect them from attack. No one knows which of the techniques now being developed will yield valuable future medicines, but it is clear that thanks to pharmacology research, tomorrow's doctors will have an unprecedented array of weapons to fight disease.



## Careers in Pharmacology

Wanna be a pharmacologist? If you choose pharmacology as a career, here are some of the places you might find yourself working:

**College or University.** Most basic biomedical research across the country is done by scientists at colleges and universities. Academic pharmacologists perform research to determine how medicines interact with living systems. They also teach pharmacology to graduate, medical, pharmacy, veterinary, dental, or undergraduate students.

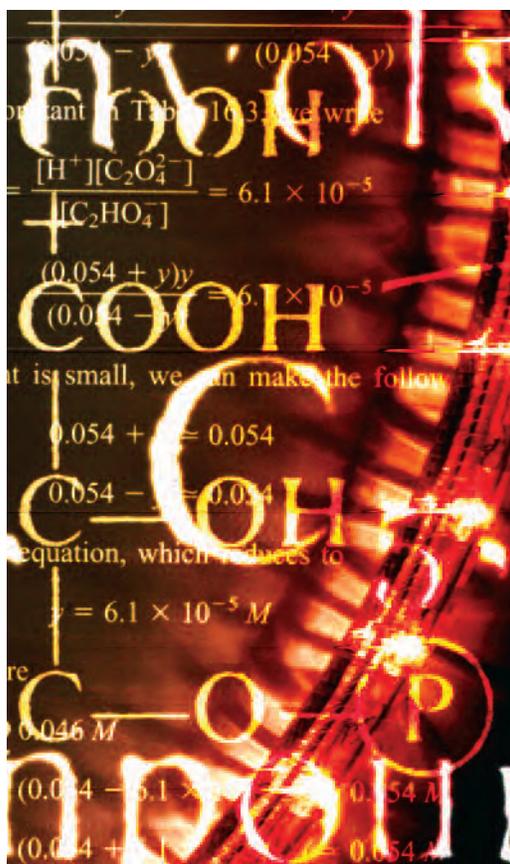
**Pharmaceutical Company.** Pharmacologists who work in industry participate in drug development as part of a team of scientists. A key aspect of pharmaceutical industry research is making sure new medicines are effective and safe for use in people.

**Hospital or Medical Center.** Most clinical pharmacologists are physicians who have specialized training in the use of drugs and combinations of

drugs to treat various health conditions. These scientists often work with patients and spend a lot of time trying to understand issues relating to drug dosage, including side effects and drug interactions.

**Government Agency.** Pharmacologists and toxicologists play key roles in formulating drug laws and chemical regulations. Federal agencies such as the National Institutes of Health and the Food and Drug Administration hire many pharmacologists for their expertise in how drugs work. These scientists help develop policies about the safe use of medicines.

You can learn more about careers in pharmacology by contacting professional organizations such as the American Society for Pharmacology and Experimental Therapeutics (<http://www.aspet.org/>) or the American Society for Clinical Pharmacology and Therapeutics (<http://www.ascpt.org/>).



## Glossary

**ADME** | Abbreviation for the four steps in a medicine's journey through the body: absorption, distribution, metabolism, and excretion.

**Agonist** | A molecule that triggers a cellular response by interacting with a receptor.

**Analgesic** | A medicine's ability to relieve pain, or a drug that alleviates pain; the term comes from the Greek word *algos*, which means pain.

**Antagonist** | A molecule that prevents the action of other molecules, often by competing for a cellular receptor; opposite of agonist.

**Antibiotic** | A substance that can kill or inhibit the growth of certain microorganisms.

**Antibody** | A protein of the immune system, produced in response to an antigen (a foreign, often disease-causing, substance).

**Anti-inflammatory** | A drug's ability to reduce inflammation, which can cause soreness and swelling.

**Antipyretic** | Fever-reducing; the term comes from the Greek word *pyresis*, which means fire.

**Arachidonic acid** | A molecule that synthesizes regulatory molecules such as prostaglandins; it is found in fatty animal tissue and foods such as egg yolk and liver.

**Bacterium** | One-celled organism without a nucleus that reproduces by cell division; can infect humans, plants, or animals.

**Bioavailability** | The ability of a drug or other chemical to be taken up by the body and made available in the tissue where it is needed.

**Bioinformatics** | A field of research that relies on computers to store and analyze large amounts of biological data.

**Biotechnology** | The industrial use of living organisms or biological methods derived through basic research.

**Biotransformation** | The conversion of a substance from one form to another by the actions of organisms or enzymes.

**Blood-brain barrier** | A blockade consisting of cells and small blood vessels that limits the movement of substances from the bloodstream into the brain.

**Carcinogen** | Any substance that, when exposed to living tissue, may cause cancer.

**Cell** | The basic subunit of any living organism; the simplest unit that can exist as an independent living system.

**Central nervous system** | The brain and spinal cord.

**Chemical bond** | Physical force holding atoms together to form a molecule.

**Chemical genetics** | A research approach resembling genetics in which scientists custom-produce synthetic, protein-binding small molecules to explore biology.

**Cholesterol** | A lipid unique to animal cells that is used in the construction of cell membranes and as a building block for some hormones.

**Chromosome** | A structure in the cell nucleus that contains hereditary material (genes); humans have 23 pairs of chromosomes in each body cell, one of each pair from the mother and the other from the father.

**Clinical trial** | A scientific study to determine the effects of potential medicines in people; usually conducted in three phases (I, II, III), to determine whether the drug is safe, effective, and better than current therapies, respectively.

**Combinatorial genetics** | A research process in which scientists remove the genetic instructions for entire metabolic pathways from certain microorganisms, alter the instructions, and then put them back.

**Cyclooxygenase** | An enzyme, also known as COX, that makes prostaglandins from a molecule called arachidonic acid; the molecular target of nonsteroidal anti-inflammatory drugs.

**Cytochrome P450** | A family of enzymes found in animals, plants, and bacteria that have an important role in drug metabolism.

**DNA (deoxyribonucleic acid)** | A double-stranded, helical molecule that encodes genetic information.

**Dose** | The amount of medicine to be taken at one time.

**Dose-response curve** | A graph drawn to show the relationship between the dose of a drug or other chemical and the effect it produces.

**Enzyme** | A molecule (usually a protein) that speeds up, or catalyzes, a chemical reaction without being permanently altered or consumed.

**Essential fatty acid** | A long, fat-containing molecule involved in human body processes that is synthesized by plants but not by the human body and is therefore a dietary requirement.

**First-pass effect** | The breakdown of orally administered drugs in the liver and intestines.

**G protein** | One of a group of switch proteins involved in a signaling system that passes incoming messages across cell membranes and within cells.

**Gene** | A unit of heredity; a segment of a DNA molecule containing the code for making a protein or, sometimes, an RNA molecule.

**Genetics** | The scientific study of genes and heredity, of how particular qualities or traits are transmitted from parents to offspring.

**Genomics** | The study of all of an organism's genetic material.

**Hormone** | A messenger molecule that helps coordinate the actions of various tissues; made in one part of the body and transported, via the bloodstream, to tissues and organs elsewhere in the body.

**Immunotherapy** | A medical treatment to stimulate a patient's immune system to attack and destroy disease-causing cells.

**Inflammation** | The body's characteristic reaction to infection or injury, resulting in redness, swelling, heat, and pain.

**Informed consent** | The agreement of a person (or his or her legally authorized representative) to serve as a research subject, with full knowledge of all anticipated risks and benefits of the experiment.

**Kinase** | An enzyme that adds phosphate groups to proteins.

**Lipid** | A fatty, waxy, or oily molecule that will not dissolve in water; it contains hydrogen, carbon, and oxygen.

**Liposome** | Oily, microscopic capsules designed to package and deliver biological cargo, such as drugs, to cells in the body.

**Membrane** | A thin covering surrounding a cell and separating it from the environment; consists of a double layer of molecules called phospholipids and has proteins embedded in it.

**Metabolism** | All enzyme-catalyzed reactions in a living organism that builds and breaks down organic molecules, producing or consuming energy in the process.

**Metabolite** | A chemical intermediate in metabolic reactions; a product of metabolism.

**Model organism** | A bacterium, animal, or plant used by scientists to study basic research questions; common model organisms include yeast, flies, worms, frogs, and fish.

**Monoclonal antibody** | An antibody that recognizes only one type of antigen; sometimes used as immunotherapy to treat diseases such as cancer.

**NSAID (nonsteroidal anti-inflammatory drug)** | Any of a class of drugs that reduces pain, fever, or inflammation by interfering with the synthesis of prostaglandins.

**Neurotransmitter** | A chemical messenger that allows neurons (nerve cells) to communicate with each other and with other cells.

**Nucleus** | The membrane-bound structure within a cell that contains most of the cell's genetic material.

**Organelle** | A specialized, membrane-bound structure that has a defined cellular function; for example, the nucleus.

**Peptide** | A small protein fragment.

**Pharmacodynamics** | The study of how drugs act at target sites of action in the body.

**Pharmacogenetics** | The study of how people's genes affect their response to medicines.

**Pharmacokinetics** | The study of how the body absorbs, distributes, breaks down, and eliminates drugs.

**Pharmacologist** | A scientist focusing on pharmacology.

**Pharmacology** | The study of how drugs interact with living systems.

**Pharmacy** | An area in the health sciences that deals with the preparation, dispensing, and appropriate use of medicines.

**Physiology** | The study of how living organisms function.

**Prostaglandins** | Any of a class of hormone-like, fat-soluble, regulatory molecules made from fatty acids such as arachidonic acid; prostaglandins participate in diverse body functions, and their production is blocked by NSAIDs.

**Protein** | A large molecule composed of one or more chains of amino acids (the building blocks of proteins) in a specific order and a folded shape determined by the sequence of nucleotides in the gene encoding the protein; essential for all life processes.

**Proteomics** | The systematic, large-scale study of all proteins in an organism.

**Receptor** | A specialized molecule that receives information from the environment and conveys it to other parts of the cell; the information is transmitted by a specific chemical that must fit the receptor, like a key in a lock.

**Recombinant DNA technology** | Modern techniques in molecular biology to manipulate an organism's genes by introducing, eliminating, or changing genes.

**RNA (ribonucleic acid)** | A molecule that serves as an intermediate step in the synthesis of proteins from instructions coded in DNA; some RNA molecules also perform regulatory functions in cells and viruses.

**Sepsis** | A clinical condition in which infectious agents (bacteria, fungi) or products of infection (bacterial toxins) enter the blood and profoundly affect body systems.

**Side effect** | The effect of a drug, other than the desired effect, sometimes in an organ other than the target organ.

**Signal transduction** | The process by which a hormone or growth factor outside the cell transmits a message into the cell.

**Site of action** | The place in the body where a drug exerts its effects.

**Steroid** | A type of molecule that has a multiple ring structure, with the rings sharing molecules of carbon.

**Structural biology** | A field of study dedicated to determining the three-dimensional structures of biological molecules to better understand the function of these molecules.

**Therapeutic drug** | A drug used to treat a disease or condition; contrast with drug of abuse.

**Toxicology** | The study of how poisonous substances interact with living organisms.

**Virus** | An infectious agent composed of a protein coat around a DNA or RNA core; to reproduce, viruses depend on living cells.

**X-ray crystallography** | A technique used to determine the detailed, three-dimensional structure of molecules based on the scattering of X rays through a crystal of the molecule.

## Discrimination Prohibited

Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, the programs of the National Institute of General Medical Sciences must be operated in compliance with these laws and Executive Orders.

## Accessibility

This publication can be made available in formats that are more accessible to people with disabilities. To request this material in a different format, contact the NIGMS Office of Communications and Public Liaison at 301-496-7301, TDD 301-402-6327; send e-mail to [info@nigms.nih.gov](mailto:info@nigms.nih.gov); or write to the office at the following address: 45 Center Drive MSC 6200, Bethesda, MD 20892-6200. If you have questions about this publication, you can use the same contact information to reach the writer, Alison Davis, Ph.D.

## Additional Copies and Web Links

To order additional copies of *Medicines By Design* or other free publications available from NIGMS, go to <http://publications.nigms.nih.gov/order/classroom.htm> or use the contact information above.

*Medicines By Design* is available online at <http://publications.nigms.nih.gov/medbydesign>.

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

NIH Publication No. 06 474  
Reprinted July 2006  
<http://www.nigms.nih.gov>