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.

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Written by Alison Davis, Ph.D., under contracts
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Contents

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.

CHAPTER 1

ABCs of Pharmacology

Know 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.

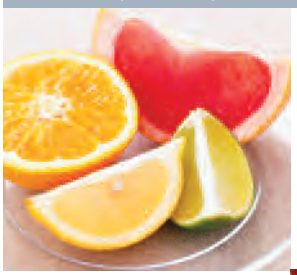
So, then, what's pharmacology?

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.

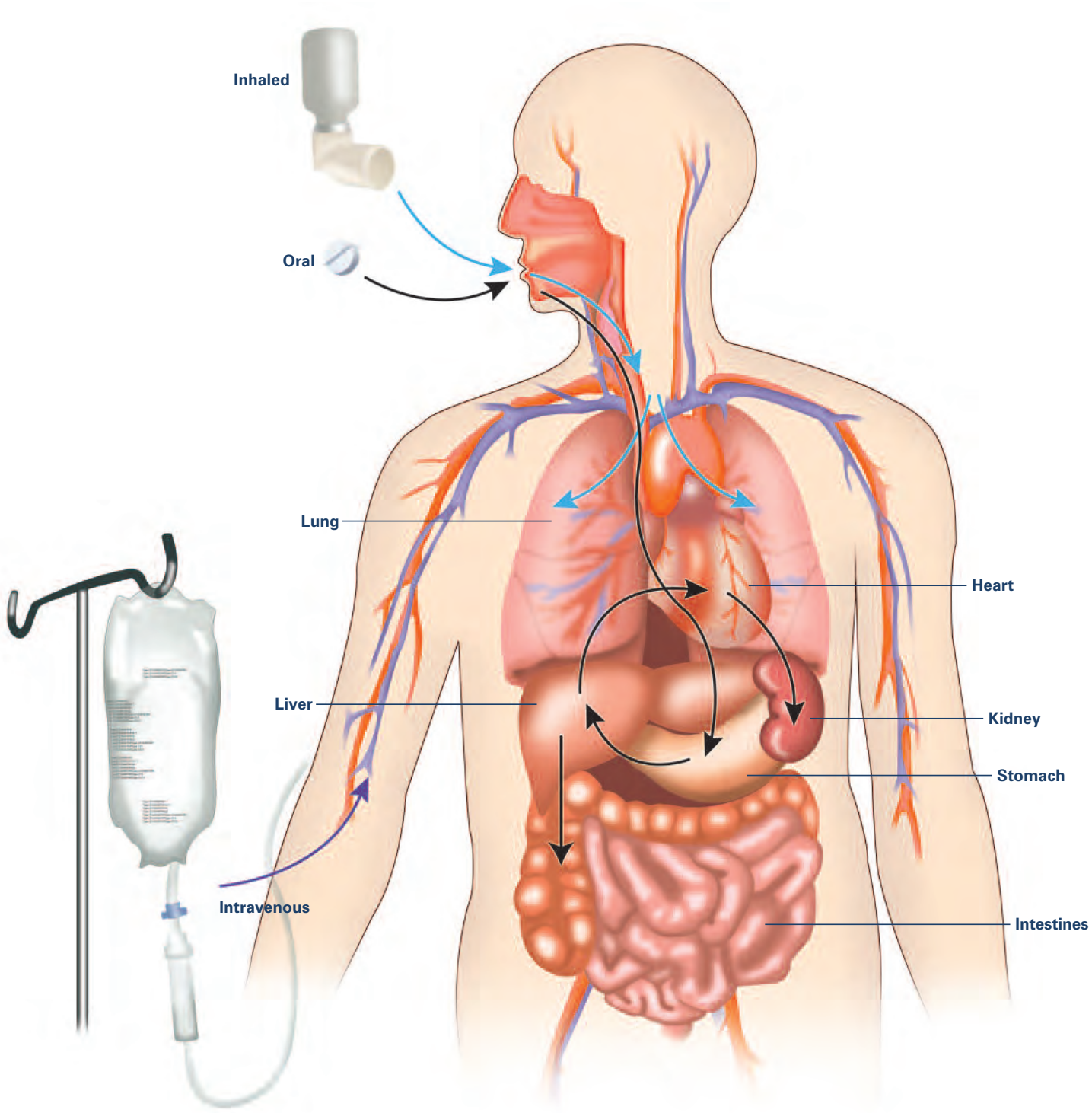
A Model for Success

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.

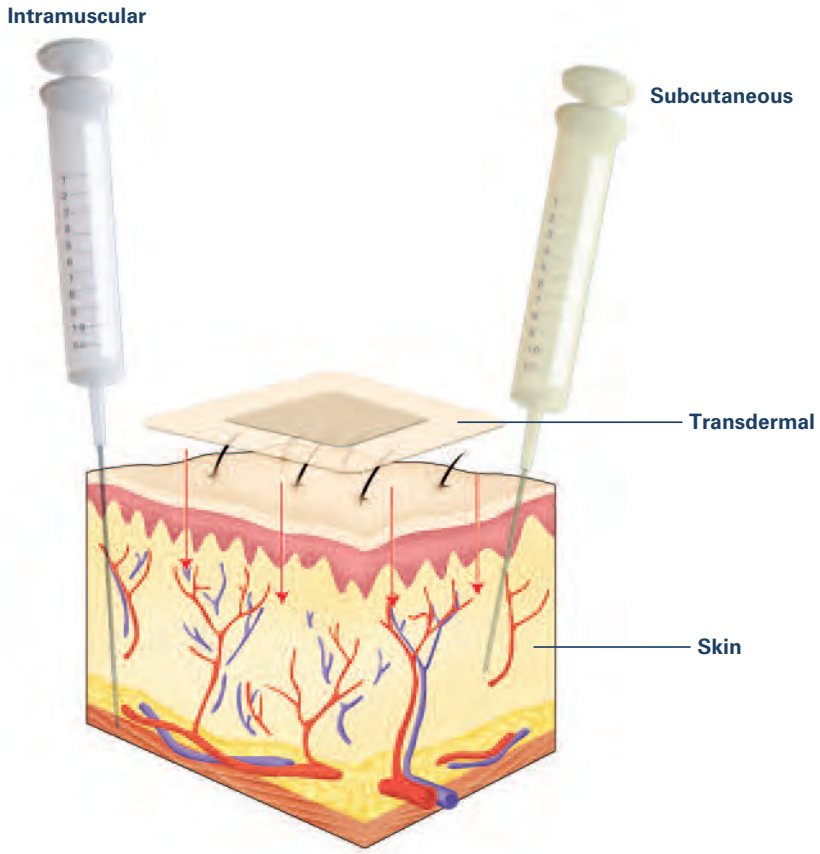
That's a huge investment for what may seem a very small gain and, in part, it explains the high cost of many prescription drugs. Sometimes, problems do not show up until after a drug reaches the market and many people begin taking the drug routinely. These problems range from irritating side effects, 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.

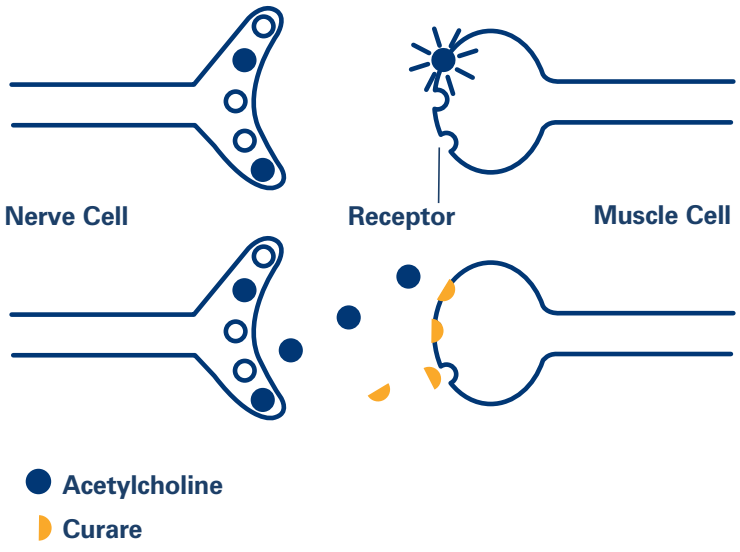
Pharmacokinetics research uses the tools of mathematics. Although sophisticated imaging methods can help track medicines as they travel through the body, scientists usually cannot actually see where a drug is going. To compensate, they often use mathematical models and precise measures of body fluids, 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).

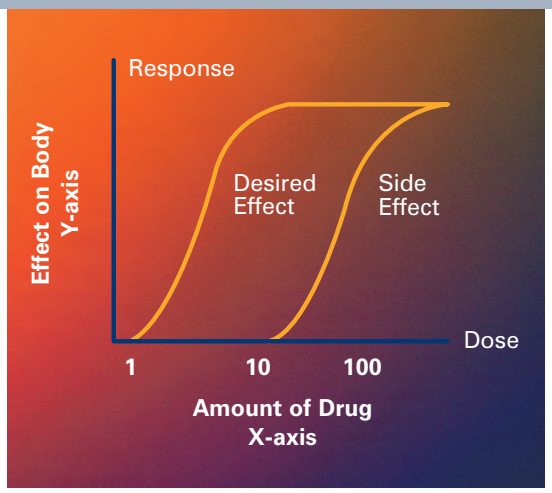


Nerve cells use a chemical messenger called acetylcholine (balls) to tell muscle cells to contract. Curare (half circles) paralyzes muscles by blocking acetylcholine from attaching to its muscle cell receptors.

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) 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).



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

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 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.

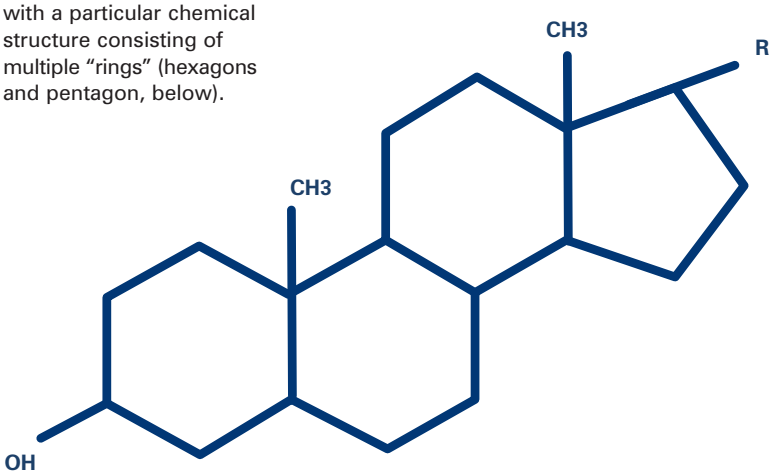
Curare is one example of a molecule called an antagonist. Drugs that act as antagonists compete with natural agonists for receptors but act only as decoys, freezing up the receptor and preventing agonists' use of it. Researchers often want to block cell responses, such as a rise in blood pressure or 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.



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

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.

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.