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ABSTRACT

This booklet, geared toward an advanced high school or early college-level audience, describes how basic chemistry and biochemistry research can spur a better understanding of human health. It reveals how networks of chemical reactions keep our bodies running smoothly. Some of the tools and technologies used to explore these reactions are described, and the research of a number of chemists is highlighted. Questions at the end of each chapter are also included. Chapter 1, "Actions and Reactions," aims to convey the essential and wondrous notion that the chemistry inside a body never stops. Chapter 2, "Harnessing Biology's Magic," explores how biotechnology offers rich potential toward bettering human health. Chapter 3, "Sugars and Fats: Are We What We Eat?" describes how carbohydrates and lipids provide much of the structural scaffolding for cells, organs, and tissues. Chapter 4, "A Chemist's Toolbox," offers a glimpse into the technological wonder propelling the chemistry of today and tomorrow. Chapter 5, "The Healing Power of Chemistry," visits some unusual places that may yield future medicines. (ASK)

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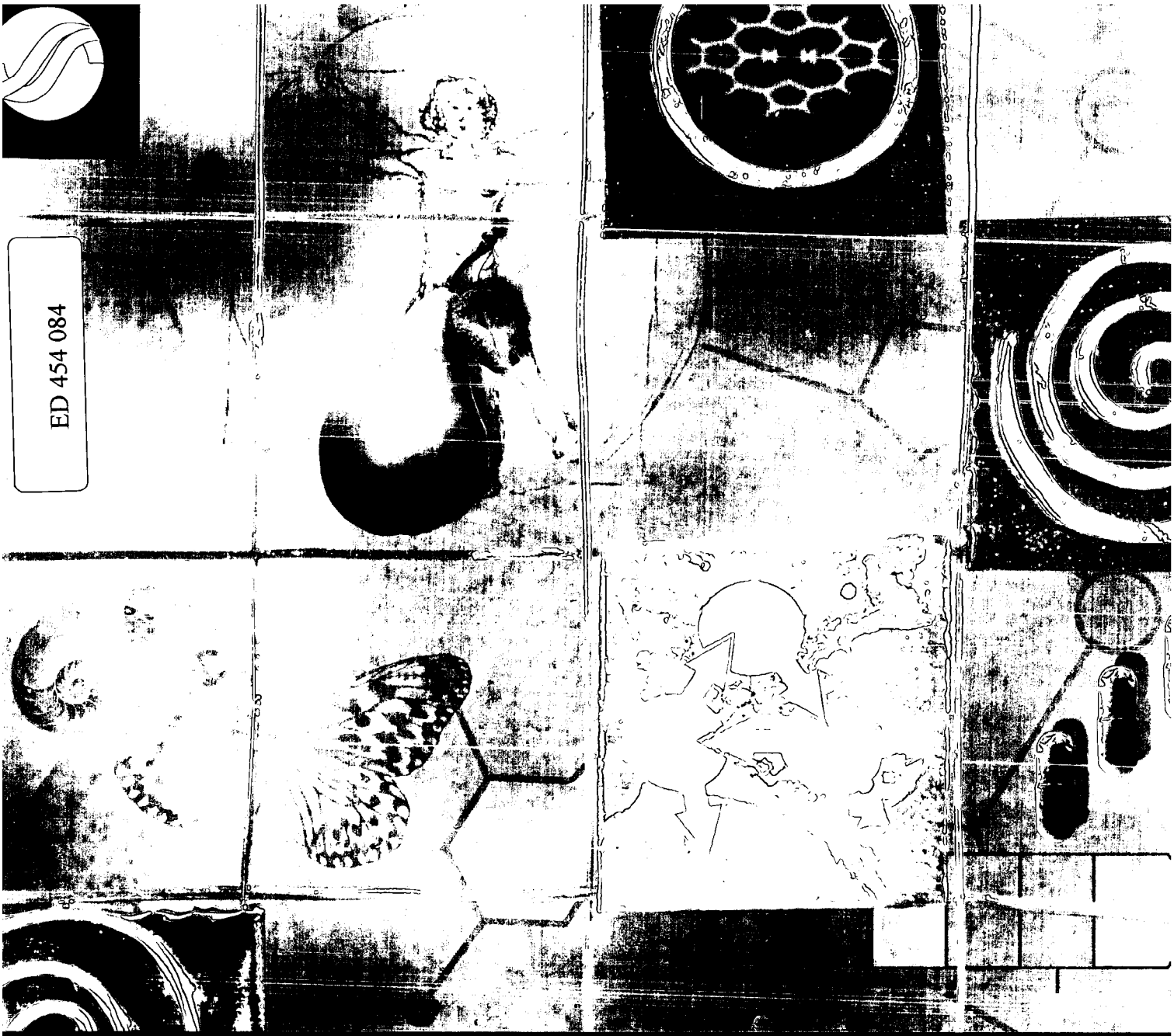

The Chemistry of Health

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Contents

FOREWORD IV

THE PATHWAYS OF LIFE VI

CHAPTER 1: ACTIONS AND REACTIONS 2

It's a Gas! 4

Chemical Biology in Action: Just Say NO 5

Chemical Biology in Action: Folic Acid Saves the Day 6

Building Blocks 8

From Mice to...Bacteria? 10

Chemical Biology in Action: Chemistry to the Rescue 11

Question Box: Computer Labs 12

CHAPTER 2: HARNESSING BIOLOGY'S MAGIC 14

It's Biology, It's Chemistry...It's Engineering! 14

Endless Possibilities 16

Chemistry for a Greener World 17

Tiny Bits of Help 18

Metals Can Be Good for You... 19

...or Metals Can Be Bad for You 20

Metals in Health and Disease 20

Question Box: Future Factories 21

CHAPTER 3: SUGARS AND FATS: ARE WE WHAT WE EAT? 22

Form and Function 23

Fats That Protect Bacteria Can Harm People 25

Sugar-Coated Proteins 26

Chemical Biology in Action: Sticky Situations 27

A Complicated Recipe 28

One-Pot Synthesis 31

Question Box: Putting Things in Order 32

CHAPTER 4: A CHEMIST'S TOOLBOX **34**

A Model Cell 35

This Is Organic Chemistry? 36

A Room Without Much View 38

Pass the Chip, Please 39

The Many Faces of DNA 41

Question Box: Life on the Edge 44

CHAPTER 5: THE HEALING POWER OF CHEMISTRY **46**

Looking to Sea 47

Making Medicines 50

Chemical Biology in Action: Library Research Pays Off 51

Getting It Left or Getting It Right? 52

Losing Medicines 55

Chemical Biology in Action: The Shape of Things to Come 56

Making Good Medicines Better 57

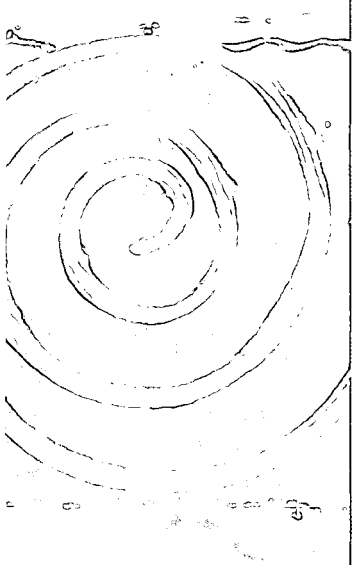
Question Box: Tools for New Medicines 58

CHEMISTRY FOR THE FUTURE **60**

GLOSSARY **61**

Foreword

How could anybody fit all of chemistry into 60 pages? You're skeptical that such a feat could possibly be accomplished, and with good reason. *The Chemistry of Health* cannot pretend to cover such an enormous area of science in so few pages. We wouldn't even want to try. Instead, this science education booklet aims to offer a sampling of how basic chemistry and biochemistry research can spur a better understanding of human health. We also want you to witness the fascination of research alive in today's chemistry labs.



Chemistry is anything but stale or static. Countless numbers of chemical reactions work ceaselessly inside your body, allowing you to think, breathe, and eat. **Chapter 1, "Actions and Reactions,"** aims to convey the essential and wondrous notion that the chemistry inside your body never stops. Cascades of repeating biochemical relays keep your organ systems operating smoothly and efficiently. Your body's metabolic factories break down the food you eat and recycle the components back into basic building blocks from which your tissues and organs are built.

Scientists hunger for information since, like everybody else, they are curious people. But a key reason biological scientists strive to learn how living systems work is so they can redesign the broken metabolic circuits that contribute to many diseases. Chemists, like most biologists, want to learn how best to employ primitive organisms like bacteria and yeast, not only to probe fundamental biological questions but also to produce the valuable commodities we call medicines. **Chapter 2, "Harnessing Biology's Magic,"** explores how biotechnology offers rich potential toward bettering human health.

Perhaps one of the most amazing triumphs of the human body is the fact that all you really need to do to keep your body running is to eat and to sleep. The rest seems to take care of itself. Of course, much sophisticated biochemistry goes on behind the scenes, as your body efficiently churns out energy from the sugars, fats, and proteins you eat every day. **Chapter 3, "Sugars and**

Fats: Are We What We Eat?" describes how carbohydrates and lipids (the scientific names for sugars and fats) provide much of the structural scaffolding for cells, organs, and tissues. This chapter also highlights a new frontier in chemistry research—how the sugars that adorn the surface of cells affect the way cells move about in the body. This knowledge holds great promise in helping researchers devise ways to prevent diseases such as cancer and conditions such as inflammation that rely on cell movement.

As technology advances at a swift pace, researchers' tools evolve to be ever smaller and more efficient. The first computers ever made were so huge they nearly filled a room. Today, most people's personal computers fit snugly into a desk corner. Some of the computers of tomorrow may fit into the palm of your hand, or even perhaps be too small to see! Chemists are masters of materials, and an increasing number are looking to Nature's toolbox to create tiny biological probes and instruments. Scientists can now eavesdrop on the movements of single molecules and create miniature devices such as robots and computers, using traditionally "biological" ingredients like the building blocks of DNA. **Chapter 4, "A Chemist's Toolbox,"** offers a glimpse into the technological wonder propelling the chemistry of today and tomorrow.

And finally, **Chapter 5, "The Healing Power of Chemistry,"** visits some unusual places that may yield future medicines. Medicinal chemists search far and wide for molecules that could be useful drugs to treat diseases. Scientists take careful note of the chemical warfare waged among creatures of the land and sea. For example, molecules produced by microbes for defense against other organisms their own size can point the way toward developing powerful antibiotic drugs to treat infections in people.

Much of the science described in the pages that follow has been funded through U.S. tax dollars invested in biomedical research projects at universities. The National Institute of General Medical Sciences (NIGMS), which funded most of these research projects, is unique among the components of the National Institutes of Health (NIH) in that its main goal is to promote basic biomedical research that at first may not be linked to any particular body part or disease. In time, however, these scientific studies on the most fundamental of life's processes—what goes on inside and between cells—can shed brilliant light on important health issues, including what causes certain diseases and how to treat them safely and effectively.

Alison Davis, Ph.D.
Science Writer, NIGMS
September 2000

The Pathways of Life

Dear "Ask the Doctor":

After a recent annual physical exam, my doctor's office informed me that I have "elevated liver enzymes." Now she says I need to come back for further tests. What does all this mean, and am I in danger?"

Confused
Anytown, USA

Is Confused in danger? Could be; but most likely not. To get to the bottom of questions like this, doctors ask patients a lot of questions.

"How do you feel?"

"Have you eaten anything unusual lately?"

"On any new medications?"

And often, doctors will perform more tests, prompting the patient's body to yield a hint as to what's wrong—some clue as to why a most carefully maintained balance of natural chemicals has gone askew.

Like Confused, many of us have an encounter with biochemistry without even knowing it.

In health and in disease, our bodies are biochemical laboratories abuzz with activity, where molecules are constantly being made, used, broken down, and recycled. What does the lion's share of the work? Indispensable molecules called enzymes.

When routine blood tests reveal abnormally high liver enzyme levels, for instance, there are many potential causes, depending on which enzyme levels are awry and how off-kilter the levels are. The culprit could be as serious as alcoholism or infection with one of the hepatitis viruses, both of which can cripple the liver over time. Or the cause could be as innocuous as taking certain common medicines or having a few extra drinks at a party.

Many of the body's enzymes reside inside cells. If cells are damaged, they break apart and spill their contents into neighboring body fluids, like blood. The presence of higher-than-normal levels of enzymes in the blood can signify trouble in the tissues or organs (such as the liver) that those cells normally populate. But sometimes, abnormal lab results mean nothing at all. Elevated enzyme levels caused by the body's processing of "toxins"—including substances like chemicals in the environment, prescribed medicines, or alcohol—usually return to normal once the foreign substance is gone from the scene.

The liver is not the only place enzymes hang out. Every cell in every organ—from the liver to the heart to the skin—is chock full of enzymes.

Anything but innocent bystanders, enzymes are the reason why cells are bustling centers of activity.

Enzymes underlie our ability to move, to think, to sense our world. Enzymes help us wink an eye, savor an ice cream cone, and catch a sticky drip about to fall off the edge of the cone. Enzymes, and their essential cellular associates—other proteins, nucleotides, sugars, and fats—allow a stubbed toe to heal properly and nurture a fetus growing inside a woman's body.

But when they are not working properly, enzymes can cause disease. Cancer can happen when the enzymes that copy the genetic material DNA make mistakes, giving rise to an errant gene that produces a faulty protein, or no protein at all. If that particular protein is the one that keeps a given set of cells from multiplying out of control, then its absence can bring about dire consequences.

Although a scientist may study a couple of isolated enzymes in the laboratory, inside the body enzymes are never lonely. They link up to form vibrant networks and pathways. The study of biochemical pathways and networks, and how they reverberate and influence each other, is the science of life and the chemistry of health.

In Control

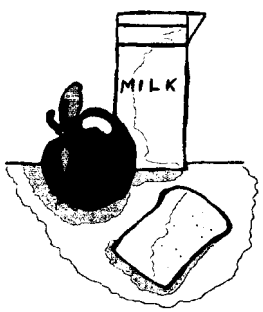
It seems to happen the same way every time: You go to the doctor for a check-up, and a couple of days later, you end up with a cold. Your conclusion: Sitting in the doctor's waiting room made you sick. Believe it or not, this everyday situation resembles scenarios scientists face all the time in their labs. A scientist's perpetual challenge is to evaluate cause and effect, and then make conclusions. Key to this process is researchers' use of "controls." A scientist only knows for sure that A causes B if he or she knows that during the experiment, the presence of A was necessary for effect B to happen. That is—A doesn't also cause C, D, E, and F. Or, that B didn't happen on its own, without any input from A. In the waiting room example, for instance, it could be that going to the doctor truly does make you prone to getting sick, because in the waiting room, you are exposed to more germs than usual. But perhaps there's no relationship at all—just by coincidence you happen to get the sniffles around the time you go for your yearly check-up. Is it always in the spring when pollen counts are rising? Scientists must carefully design experiments so that they can account for the influences of as many variables as they can think of. Usually, researchers do this by comparing the test group with a control, or untreated, group. Only then do their experiments really "work."

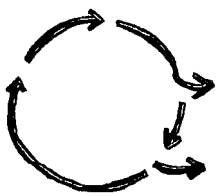
Actions and Reactions

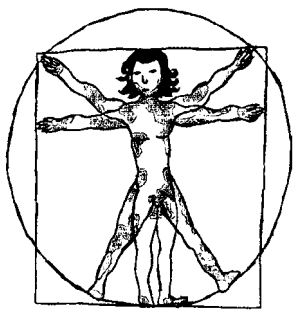
Even though you're probably sitting down while you're reading this, your body is anything but static. Thousands of enzymes in your body toil away every second of every day, breaking apart the components of the foods you eat into energy for essential life processes. Vision, movement, memory—you name it, there are enzymes at work behind the scenes.

Enzymes work by making it possible for chemical reactions inside your body to take place. While that might not seem significant, consider the fact that without the help of enzymes, the conversion of nutrients and minerals into usable biological molecules such as proteins and nucleic acids might take weeks, even years. Enzymes can make this happen in minutes, sometimes seconds.

How do they do it all, and so well? Enzymes act like the accelerator pedal of a car. But they also play the role of matchmaker, bringing together starting materials (called substrates) and converting them into finished materials (called reaction products). One secret to an enzyme's success in this endeavor is its shape. An enzyme is shaped so that it can hug its substrate tightly. This molecular embrace triggers chemical changes, shuffling chemical attractive forces called "bonds" and producing new molecules. Only enzymes that have an exact fit with their substrates do a decent job of speeding up chemical reactions. But things don't end there; reactions are not singular events. They re-occur, over and over again. Enzymes are the key players linking up chain reactions of the chemical events that culminate in our everyday physiology. Much like a cascade of dominoes, the product of one chemical reaction becomes the substrate for another. Enzymes form the core of these ordered pathways, which themselves are the basis for metabolism. In a grand sense, metabolism is the



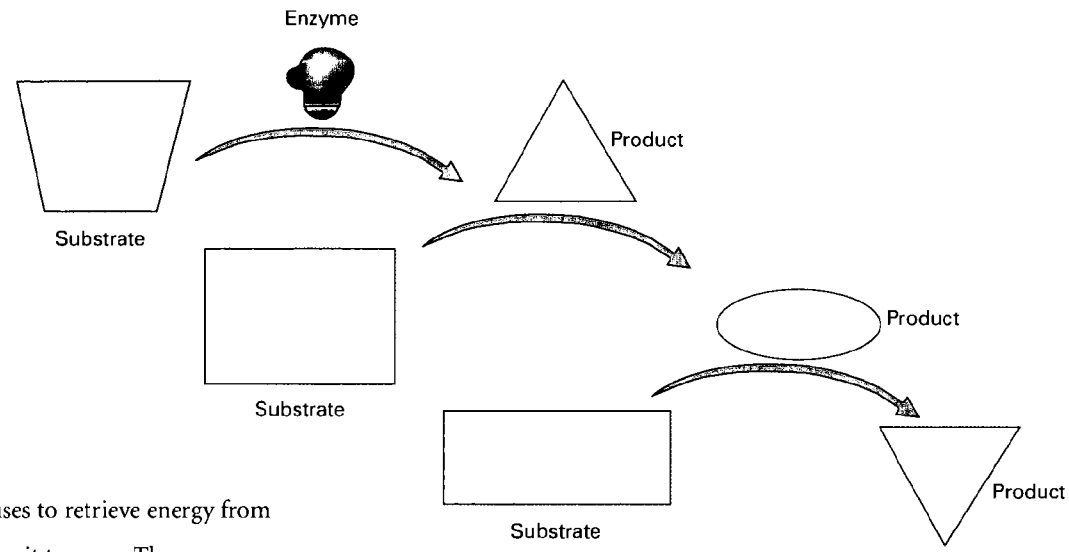




bi•o•chem•is•try (bi′o kem′is tree):
n., the chemistry of living organisms.

What Is Biochemistry?

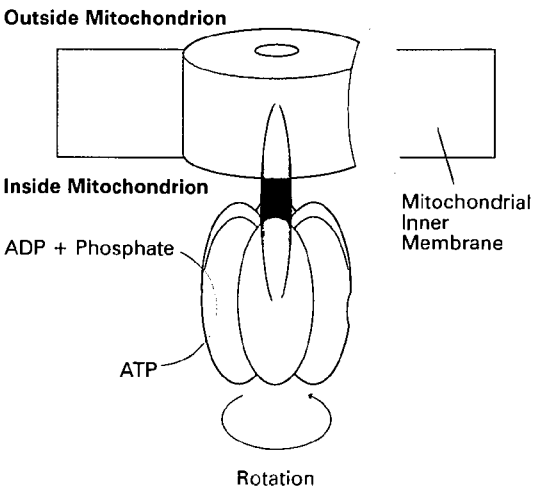
Simply stated, biochemistry is life. Practically stated, biochemistry is our life: what we are and how we live. Our bodies are very busy factories, extracting energy from the foods we eat, building cells and tissues, and knitting everything together into a functioning unit using molecular tools called enzymes. Creatures as distinct as bacteria, giraffes, and people use many of the same biochemical toolsets to survive, eat, move, and interact with their respective environments. Biochemistry underlies our health.



△ Cascades of enzymes make up metabolism.

process any organism uses to retrieve energy from the environment and use it to grow. The proper functioning of small and big body parts hinges upon effective communication within and between pathways. That includes everything from tiny specks of DNA that string together into all of your genes to a complicated, multicelled organ such as the heart. By understanding the language of physiological communication systems, scientists can devise ways to patch the circuits when they become broken, in illness and disease.

The Motion of Life



△ The world's smallest motor, ATP synthase, generates energy for the cell.

Fish swim, birds fly, babies crawl. Enzymes, too, are constantly on the move. The world's smallest motor, in fact, is an enzyme found in the powerhouse of the cell (the mitochondrion) which generates energy in the form of a molecule called adenosine triphosphate, or ATP. Often dubbed the energy currency of life, ATP shuttles to and fro throughout cells, and is "traded" during chemical reactions. These molecular transactions drive reactions forward to make a product. Several decades of work earned three scientists—Paul Boyer of the University of California, Los Angeles, John Walker of the Medical Research Council (in the United Kingdom), and Jens Skou of Aarhus University in Denmark—the Nobel Prize for figuring out how the motor, a molecule called ATP synthase, functions as a set of molecular levers, gears, and ratchets.

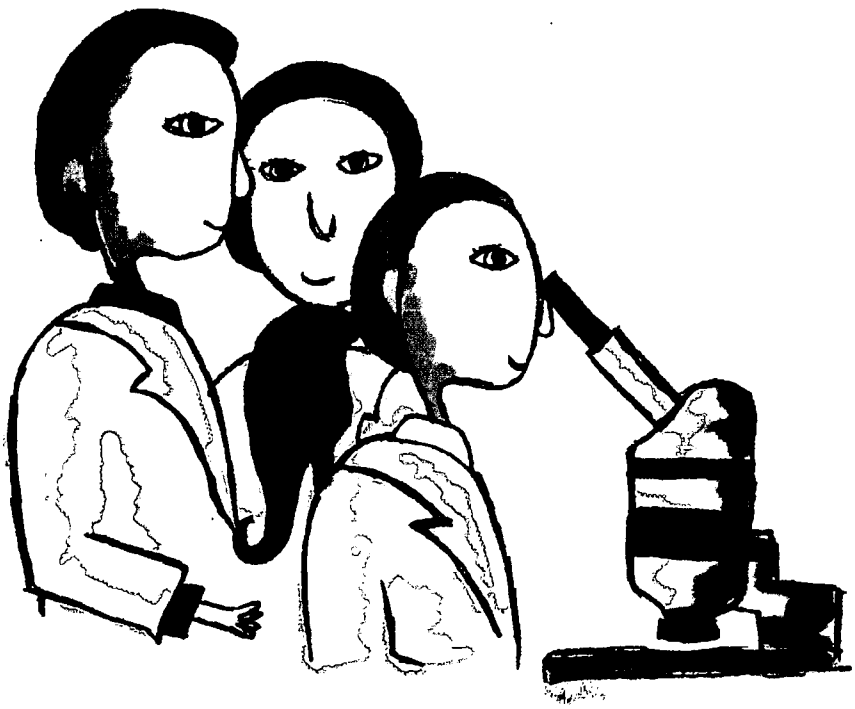
Other molecular motors include protein machines that tote DNA-laden chromosomes or protein cargo throughout the cell. The enzyme that copies DNA does its job through what scientists call a "sliding clamp" mechanism. As a growing DNA strand, a future gene winds through an enzyme called DNA polymerase like a thread through a needle. The energy source for this and all biological motor-driven processes is ATP.

It's a Gas!

Tediously long car trips elicit multiple rounds of word games like "20 Questions," in which players take turns thinking of a secret object and having their opponent ask more and more detailed questions to identify it. In this game, the first question is always, "Animal, Vegetable, or Mineral?" Virtually everything imaginable falls into one of those three categories.

Chemists could play such a game, in which the mystery item is a molecule—any molecule. In this game, the first question would always be, "Solid, Liquid, or Gas?" Looking outside the window, it's easy to think of entries for each of these categories: Stones are solids, dewdrops are liquids, and the atmosphere is a blend of many different gases. But there's a trick: In theory, any molecule could in fact be all three, if the conditions were right. In pure form, whether a molecule is solid, liquid, or gas depends on its environment, namely the ambient temperature and the atmospheric pressure. Water is an easy example. Everybody knows that below 32 degrees Fahrenheit, water is a solid, and above 32 degrees, water is a liquid. Put a tea kettle on the stove and witness water turn into a gas.

Our bodies, too, harbor an assortment of solids, liquids, and gases. But of these three physical states, which chemists call "phases," everything that lives is largely liquid—water is the universal solvent of life. Fingernails, hair, and bones are solids, indeed, but only the dead parts. Living cells resident in bone and its vital bone marrow thrive in a watery environment. Gases can also be found throughout the body; some examples include the oxygen we breathe in and the carbon dioxide we breathe out. But inside the body, even these gases



Stuck in a Corner?

The stereotypical image of a scientist as a faceless white coat hunched over a microscope in the corner of a lab has never been accurate, but it's even more wrong today. While plenty of scientists spend a lot of time in their own workspaces, they rely heavily on interaction with other scientists to share ideas and validate concepts—at scientific conferences, at the coffee maker, or, increasingly, via e-mail. Although a scientist in his or her own lab may crack away for years at a very small piece of a big puzzle—say, how a particular enzyme works—he or she spends much of the time communicating with other scientists to further the understanding of molecular secrets.

are dissolved in liquids—mainly blood, which itself is mostly water.

One gas, nitric oxide (whose chemical symbol is "NO"), serves the body in a host of useful ways. Scientists were rather surprised not many years ago when they discovered that the gas NO is a chemical messenger. Tiny and hard to study in the laboratory, NO eluded scientists for many years. Other molecular messengers—such as neurotransmitters and larger proteins—can be relatively easily extracted from body fluids and studied in a test tube, where they can remain intact for minutes or even hours at body temperatures. NO, on the other hand, vanishes in seconds. While this property makes it horrendously difficult to study, such volatility renders NO a molecule with extraordinary versatility. In a snap, NO can open blood vessels, help pass electrical signals between nerves, or fight infections.

But in addition to being a friend, NO can also be a foe—too much or too little of this gas can be harmful. Blood vessels that have been widened too much can lead to potentially deadly shock, a condition in which blood pressure plunges so low that vital organs cannot get enough blood to survive. An overactive immune response—fired up by NO—can produce a painful syndrome called inflammatory bowel disease. With all this at stake, the body works hard to stringently control production of this powerful gas.

CHEMICAL BIOLOGY
in Action

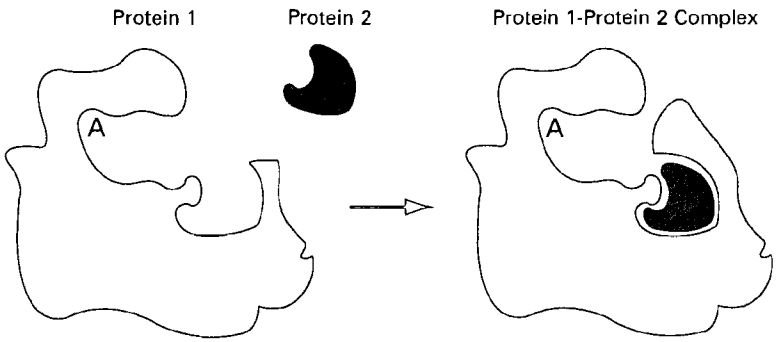
T.L. Poulos, H. Li, C.S. Raman

△ Protein crystals of nitric oxide synthase revealed its three-dimensional structure.

Just Say NO

The molecule that manufactures NO is an enzyme called nitric oxide synthase (NOS). Owing to nitric oxide's many different functions in the body, three different versions of NOS exist, specialized for the cardiovascular, immune, and nervous systems. In recent years, scientists have achieved a major victory in beginning to understand how NOS works. Thomas Poulos of the University of California, Irvine determined the structure, or three-dimensional shape, of one form of NOS. Since intimate associations between an enzyme and its substrate rely on a snug fit, probing the three-dimensional shape of an enzyme or other protein can enable scientists to begin to understand how the protein works, predict what other molecules it might fit, and design drugs to boost or block its activity. After obtaining a sample of NOS protein from the laboratory of Bettie Sue Masters of the University of Texas Health Science Center in San Antonio, Poulos obtained a "picture" of NOS by bombarding a tiny crystal arrangement of the protein with high-energy X-rays, then piecing together the protein's shape by tracing the directions in which the energy was scattered throughout the crystal. This work, years in the making, paints a portrait of NOS consisting of two identical units. In a cell, the two units of NOS assemble

head-to-head, creating a new landscape upon which substrates and helper molecules convene to complete the task at hand: creating nitric oxide from an amino acid called arginine. In the case of NOS, the helpers include iron and a tiny molecule called a "cofactor." Enzymes like NOS are lost without these helpers.



Pulling Into Dock

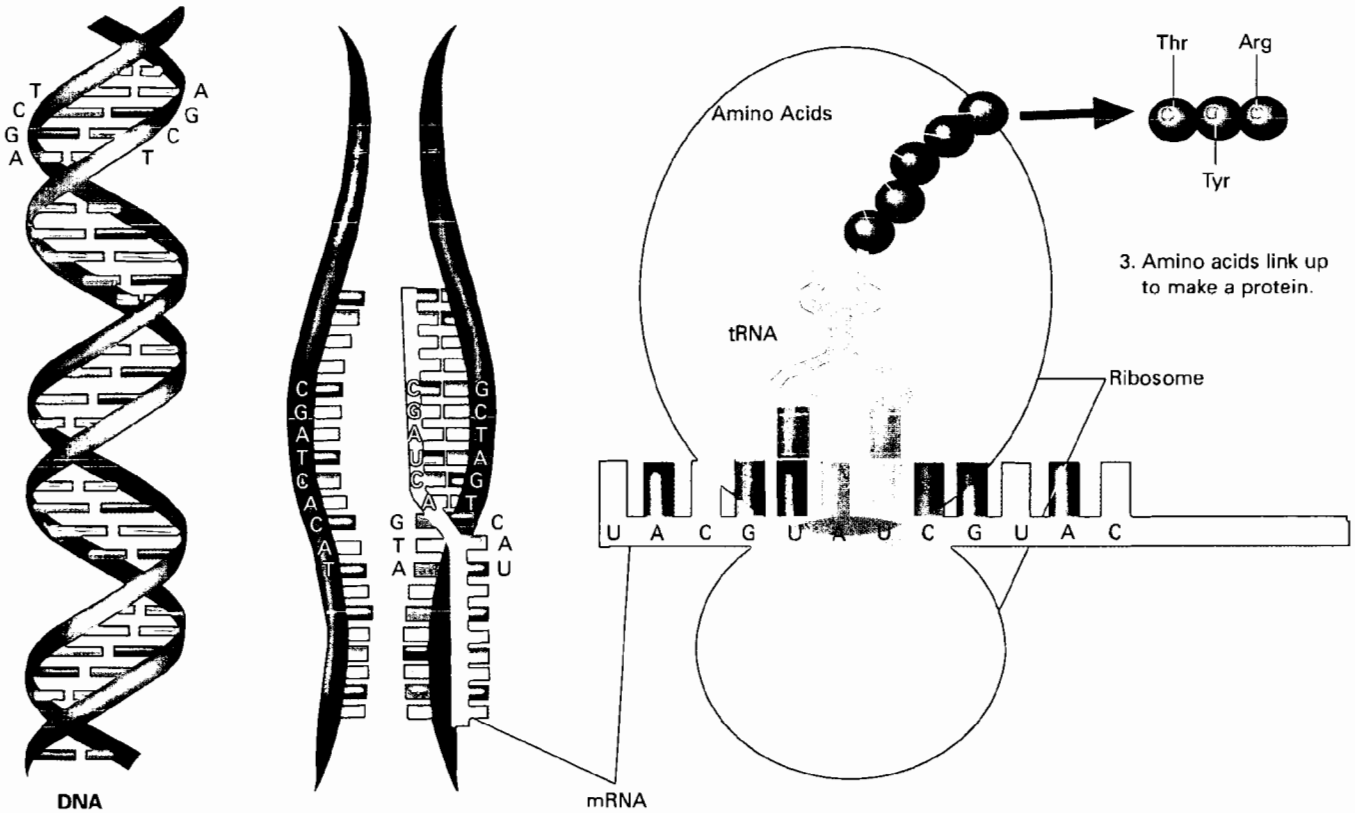
Like a ship nestling into its berth, many proteins require the help of one or more other proteins to perform their jobs well. However, unlike ships, proteins docked together often change their shape as a result of such an encounter. The differently shaped protein is newly and exquisitely able to capture a substrate and carry out a chemical reaction. Akin to rearranging seats in a room to accommodate more guests, the re-shaping of proteins (called conformational changes) can make extra room for substrates and products to fit. Such shape changes also change the electrical "ambience" of an enzyme's innards, revealing differently charged portions of the molecule that can have a big impact on molecular interactions.

Folic Acid Saves the Day

In baking, some ingredients are simply not optional—forget the baking powder, forget the muffins. Just as baking powder is essential for some recipes, helper molecules called cofactors are necessary ingredients for many biochemical reactions.

Take folic acid (one of the B vitamins), for example. Scientists have known for decades that folic acid can protect against certain birth defects—such as spina bifida—that develop during the first few weeks after conception. For this reason, the Food and Drug Administration recommends that every woman of child-bearing age supplement her diet with 400 micrograms of the vitamin. Scientists figured out that folic acid does its molecular good deeds by lowering levels of a potentially harmful compound called homocysteine, which is also a risk factor for heart attacks and strokes. As it turns out, folic acid performs this task by speeding up the conversion of homocysteine to methionine, a nontoxic amino acid that the body needs.

Folic acid does this by improving the fit between an enzyme and its cofactor. The enzyme in this case is known shorthand as MTHFR, and the cofactor, a molecule called FAD, is also vitamin-derived (from vitamin B2) and is essential for converting homocysteine to methionine. Martha Ludwig and Rowena Matthews, both of the University of Michigan, determined that by locking FAD onto MTHFR, folic acid performs this protective role in the body.



1. Enzymes "copy" DNA to make messenger RNA (mRNA).

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

3. Amino acids link up to make a protein.

Making a Protein From Scratch

Tucked away inside the DNA sequence of all of your genes are the instructions for how to construct a unique individual. Our genetic identity is "coded" in the sense that four building blocks, called nucleotides, string together to spell out a biochemical message—the manufacturing instructions for a protein. DNA's four nucleotides, abbreviated A, T, G, and C, can only match-up in specific pairs: A links to T and G links to C. An intermediate in this process, called mRNA (messenger ribonucleic acid), is made from the DNA template and serves as a link to molecular machines called ribosomes. Inside every cell, ribosomes read mRNA sequences and hook together protein building blocks called amino acids in the order specified by the code: Groups of three nucleotides in mRNA code for each of 20 amino acids. Connector molecules called tRNA (transfer RNA) aid in this process. Ultimately, the string of amino acids folds upon itself, adopting the unique shape that is the signature of that particular protein.

Building Blocks

So the case is made that enzymes, and all proteins, are extremely important in the body. Where do these important molecules come from? Do they last forever?

Proteins are synthesized continually throughout life. Stockpiles of proteins are not passed on from generation to generation, but their molecular instruction guides—our genetic material, DNA—are. After reading the DNA "letters" in our genes, specialized molecular machines (groups of enzymes working side by side inside the cell) copy the DNA, then other machines use this genetic template to churn out proteins. To do this, enzymes mix and match a set of 20 different amino acids, the building blocks of proteins. Hooking together these amino acids, the body constructs thousands of different protein types. Theoretically, millions of proteins could be formed through all the possible linkages between amino acids. It is not surprising, then, that every one of these amino acids must be readily available at all times for protein synthesis.

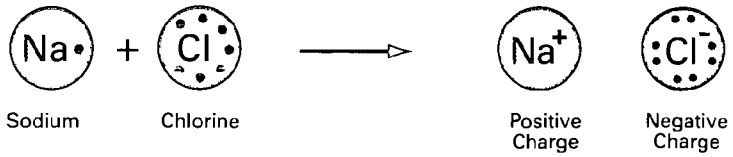
Dire consequences may result if one or more of these amino acids is either absent or overabundant. For instance, a genetic disorder called phenylketonuria (PKU) is caused by the body's inability to get rid of extra phenylalanine, an amino acid abbreviated "Phe." PKU is an "autosomal recessive" disorder, meaning that the only way to get the disease is if both of your parents carry a version of a gene linked with this disease. If only one parent has the gene linked to PKU, his or her children cannot develop the disease. Children who have PKU are born without the enzyme that breaks down the Phe amino acid. Extremely high levels of Phe accumulate and are very toxic, especially to the brain. As a result, PKU causes mental retardation. Yet Phe is an essential amino acid—your body cannot do without it. Both diet and genes contribute to causing PKU, and so any means to control the supply of Phe in the body can prevent the disease.

A thin silver lining to the PKU story is that the disorder can be diagnosed simply—in fact, since the 1960s, nearly every baby born in the United States has received a tiny needle stick in his or her heel to retrieve a droplet of blood to test for levels of the Phe-chewing enzyme. If caught early enough and treated in the first year of life, PKU can be controlled. In 150 million infants tested since the early 1970s, 10,000 cases of PKU have been detected and treated. At present, doctors treat children with PKU by prescribing a life-long restrictive diet; certain foods, such as milk and diet sodas containing the artificial sweetener aspartame (NutraSweet®), are rich sources of Phe. The diet is rigid, requiring children to avoid those and many other foods, such as meat and fish, dairy products, bread, nuts, and even some vegetables. As a result, people with PKU have to take a special Phe-free vitamin/mineral supplement to ensure that they receive adequate amounts of all of the other essential amino acids bountiful in those foods. People used to think that once a child with PKU reached the teens, he or she could go off the diet, which can be expensive because of the

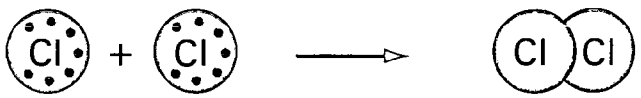
supplement. However, current guidelines recommend that people with PKU remain on the restrictive diet throughout life.

To get around the difficulty and inconvenience of maintaining a highly specialized diet and taking a dietary supplement for life, a better solution might be to provide the Phe-digesting enzyme to people whose bodies lack it. But while replacing the missing enzyme that breaks down Phe (abbreviated "PAH") may seem a simple plan, this is much easier said than done. The PAH enzyme has many parts and cofactors. What's more, delivering the enzyme requires a liver transplant, a procedure that itself carries significant risks. An alternative approach would be to supply people with PKU with an enzyme that will get rid of Phe and that can be safely administered by mouth. Such an enzyme, called "PAL," abounds in Nature—plants, yeast, and a variety of other organisms have it, and scientists can produce it in the lab using genetic engineering strategies. Recently, researchers have succeeded in treating an experimental strain of mice who develop a PKU-like syndrome with lab-made PAL. Clinical studies in people will determine for sure whether this strategy offers hope for people with the disease.

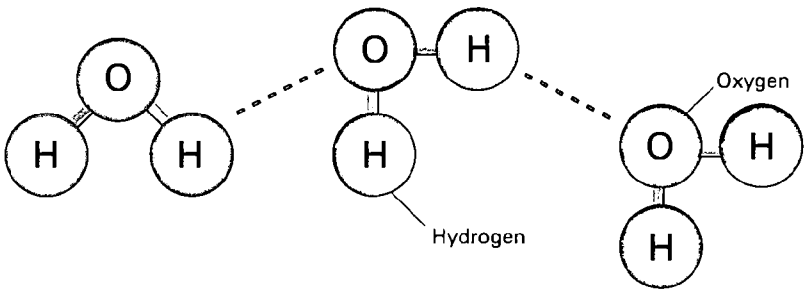
Ionic Bond (Sodium Chloride [table salt])



Covalent Bond (Chlorine Gas)



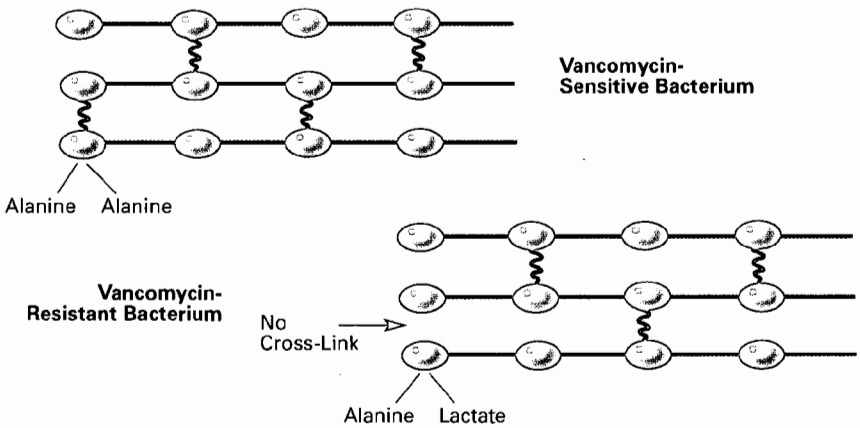
Hydrogen Bond (Water Molecules)



△ Three types of attractive forces hold atoms together to make molecules. Dots represent electrons taking part in chemical bonding.

A Special Bond

You may be surprised to learn that at the heart of chemistry is physics—the study of attracting and repelling forces that link up the building blocks of life. Chemical bonds are those physical forces that keep atoms together, and they come in a few varieties. Ionic bonds, in which positively charged atoms are attracted to negatively charged atoms, are the strongest of the bond types. Covalent bonds are more subtle, and occur when neighboring atoms (such as hydrogen) share electrons from within their respective halos of swirling particles. Chemists refer to both ionic and covalent bonds as "intramolecular" forces. Other important forces are called "intermolecular" forces—those holding different molecules together. These types of forces form the basis for liquids and solids, which are really just collections of molecules arranged in a precise pattern in space. Intermolecular forces are also called van der Waals forces, named for the Dutch physicist who first discovered them. Hydrogen bonds are a type of van der Waals force, and represent an important bond in biochemistry.



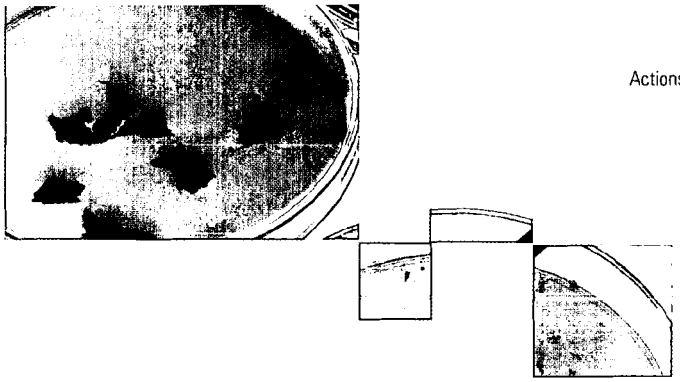
△ The cell wall of a bacterium killed by vancomycin contains a critical cross-link (left). The cell wall of a bacterium that is resistant to vancomycin is missing this cross-link (right).

A Killer's Strategy

Bacteria called enterococci possess enzymes that weave together alternating protein-sugar strands to create a tough cell wall. At the tip of one of these strands is a pair of amino acids (two alanines), the signature of which is recognized by the antibiotic drug vancomycin. The bacterium's resistance genes confer upon it the ability to reprogram the strand tip to have a slightly different chemical composition, and therefore a different shape. A single hydrogen bond is the hallmark of this change. The altered cell wall is far less appealing to the antibiotic, and the bacterium escapes unscathed.

From Mice to...Bacteria?

A favorite experimental tool of many scientists is the laboratory mouse, which can be bred "to order" with characteristics useful for addressing specific research questions. While rodents differ from people in important and obvious respects, believe it or not mice and rats share many of the same genes with humans. In some cases, upwards of 80 percent of the "letters" in a mouse gene may be identical to a similar one—its "homologue"—in humans. Nature is economical: Very important genes (those that code for key metabolic enzymes, for instance) are conserved throughout evolution, varying little between species. For researchers, that's a good thing. Mice and a slew of other so-called "model organisms"—such as bacteria, yeast, and even plants—are the workhorses of many biochemical laboratories. But in addition to these often striking similarities, there are significant differences in the biochemistry of model organisms, especially in the most primitive of species like bacteria. Scientists can exploit these differences to fight disease, targeting enzymes or other molecular parts that are common to microorganisms but are absent from your body.



CHEMICAL BIOLOGY
in Action

Chemistry to the Rescue

Arguably many of the most important medical advances this century relate to the development of powerful antibiotics and vaccines to treat infectious diseases caused by bacteria, viruses, and parasites. But those breakthroughs have come with a cost—the microbes have learned how to fight back, and with a vengeance. The misuse of antibiotics—these drugs are overprescribed by doctors and people often fail to finish a full prescription—is the most common reason why antibiotic resistance is coming so rapidly to the fore.

When you take an antibiotic, the drug treats infection by knocking out hundreds of strains of "sensitive" bacteria in your body. But it also leaves behind scores of so-called "resistant" strains—slightly altered versions of the sensitive variety. The resistant microbes, with no stops in place, repopulate themselves rapidly. To make matters worse, these lingering resistant organisms hang out not only in your body, but they can spread to your family and friends—worsening the problem for everyone.

Bacteria are not inherently malicious. In the human body, many different types of bacteria reside within the large intestine, where they perform vital roles in processing food. Trillions of microorganisms break down undigested carbohydrates, common components of vegetables and other foods like beans. In the wrong place, however, these normally innocuous bacteria—called enterococci—can do the body great harm. In disease, such microbes can seep from the relatively safe harbor of the intestines into other regions of the body, such as burned skin, the heart, or the urinary tract. There, the bacteria can multiply rampantly, especially when the immune system is already strained. Enterococci are stubbornly resistant to most antibiotic drugs. Until recently, an antibiotic called vancomycin fairly effectively put the brakes on enterococcal infections. However, in recent years the incidence of enterococcal resistance to vancomycin has been on a disturbing rise.

Fortunately, chemists are hot on the heels of enterococci. Christopher T. Walsh of Harvard Medical School has traced the roots of vancomycin resistance to a single, errant chemical link. Vancomycin normally kills enterococci by getting in the bacterium's way while it tries to manufacture a protective cell wall for itself. Vancomycin prevents the molecular "bricks" of this cell wall from melding together, leaving the bacterium susceptible to the harsh environment and destructive enzymes in the cells of its host's body. Walsh and his coworkers unearthed a set of just five genes that enable enterococci to get past the antibiotic drug vancomycin's action by using a slightly different method to build a cell wall. Walsh's detective work points to promising avenues for future antibiotic drug development, based on the strategy of interrupting enzymes that rearrange the cell wall precursors.

Computer Labs

Bioengineer Christophe Schilling works with computers, and he works in a lab. But his is not a garden variety computer lab. Schilling, who just completed his Ph.D. in bioengineering at the University of California, San Diego, studies bacterial cells—and the thousands of enzymatic reactions occurring inside them—without ever putting on a pair of lab gloves or pouring bacterial broth into a flask. Schilling's "*in silico*" (literally, "within silicon," a component of computer hardware) research relies on computers to study how enzymatic pathways talk to each other and work together. But while the technique promises to be inordinately powerful in predicting cellular performance under a vast set of conditions, Schilling admits that he'd be out of a job if so-called "wet" (laboratory-based) biochemists didn't keep busy in their labs figuring out what enzymes in the cell actually do. *The Chemistry of Health* asked Schilling about the potential of mapping a cell using computers:

CH: What don't we already know about what goes on inside living cells?

Schilling: Biologists are now forced to confront the issue of complexity in the cell—how a small change in one component can affect hundreds of things. The challenge facing the next generation of scientists is to understand cells as systems...how all the components interact and how the interactions define cellular function.

CH: Do you need a really powerful computer to do *in silico* experiments?

Schilling: No, I just use my laptop—but I'm working on relatively simple problems now using basic linear algebra. In the future, as we try to build models of more complex organisms—such as humans—and apply more intensive mathematical approaches, a supercomputer might be required. We aren't limited by our computational power at the moment, but rather by our lack of biological knowledge and the scarcity of adequate modeling approaches.

CH: What ingredients do you need to perform an *in silico* metabolism experiment?

Schilling: I start with a list of genes, then I look in textbooks and scientific articles to find out what reactions they catalyze and what's known about them—this provides a "parts catalog" of sorts. Then, I apply simple laws of physics and math principles—basically, describing networks of interacting enzymes as a set of mathematical equations. Out of that comes a prediction of what kinds of

In the future,

computer models will be used

to design experimental programs

in research and industry...

products the cell is capable of making under different environmental and genetic conditions.

CH: Will computers replace beakers and petri dishes?

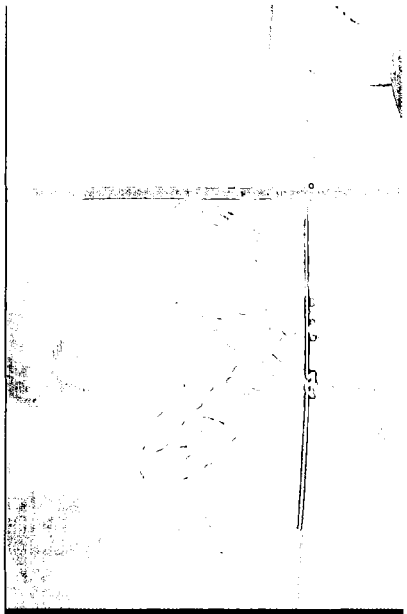
Schilling: No! Much of our knowledge of bacterial metabolism comes from biochemistry research in the 1960s—I rely heavily on this information. In the future, computer models will be used to design experimental programs in research and industry—yet at the same time the experimental results will be required to improve the computer models. So, you could say that they're in a partnership of sorts.

CH: How would you attract young people to study metabolism?

Schilling: I think you have to get people who are interdisciplinary—people who can gain appreciation for all aspects of the problem. It won't work with teams of different specialists just working together on their own subprojects in genetics, biochemistry, or computational biology.

CH: How did you get interested in metabolism and bioengineering research?

Schilling: In my junior year at Duke University, I was a biomedical/electrical engineering double-major and I saw a talk on automated DNA sequencing by Leroy Hood, a genetics researcher at the University of Washington. It was the first time I had seen engineering strategies of any sort being applied to a molecular problem. The next day, I dropped electrical engineering and picked up genetics.



Got It?

Describe one way bacteria become resistant to antibiotics.

What do biological motors use for fuel?

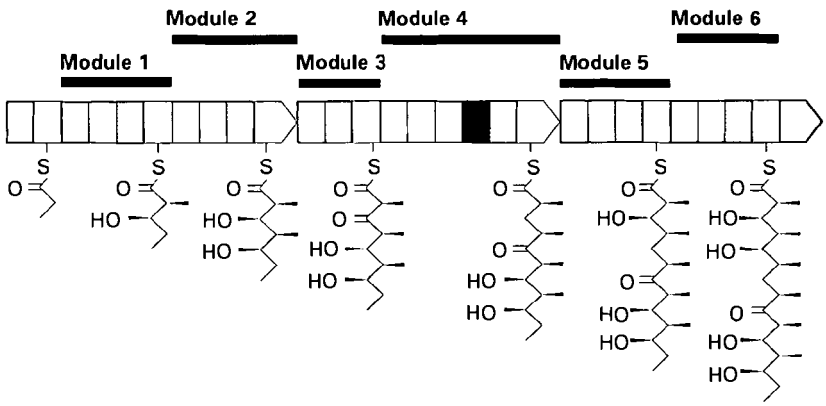
How does an enzyme speed up a biochemical reaction?

What are the three phases of matter?

In 20 years, do you think scientists will still study biology in a laboratory—or will they just do everything on a computer? Give a reason for your answer.

Harnessing Biology's Magic

Life scientists yearn to understand the natural world. They persist in trying to unravel the mysteries of biology because these mysteries are inherently intriguing. But more pressingly, scientists want to learn how biological systems work so that they can control them. Such control yields benefits to health and to the human enterprise in countless ways. Harnessing biology's magic underlies the extraordinary promise of biotechnology.



△ Erythromycin is made by enzyme modules, each of which adds two carbons to the growing chain of atoms.

Adapted with permission from Kosan Biosciences

Metabolic Factories Make Lots From Very Little

Certain types of soil bacteria make the antibiotic erythromycin—a complicated chemical structure containing 37 atoms of carbon, 13 atoms of oxygen, 67 atoms of hydrogen, and a single atom of nitrogen—beginning with only a couple of small and simple starting materials. The bacteria make this widely used antibiotic through a pathway consisting of a series of enzyme "modules," or mini-factories, each of which is itself made up of at least three different enzymes. In the case of erythromycin production, the job of each module is to progressively add two carbons to the growing chain of atoms destined to become erythromycin.

It's Biology, It's Chemistry... It's Engineering!

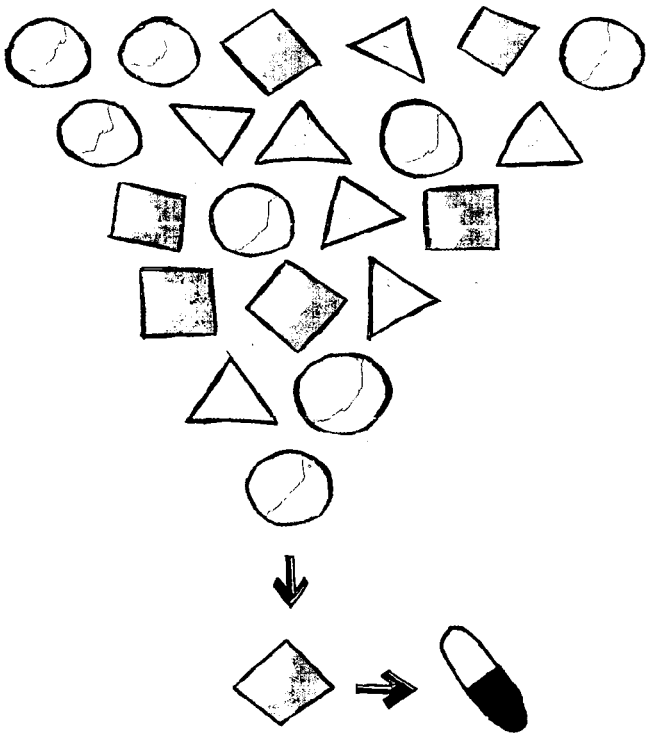
Metabolic engineering, that is. In this exciting field, biology and chemistry collide head-on. The goal is to use the tools of biology to produce chemical compounds that, in many cases, never before existed in Nature: so-called "unnatural" natural products. Metabolic engineers are in the business of using living systems to turn simple sugars and other small molecules into promising new antibiotic drugs—even agricultural and veterinary products.

Some metabolic engineers aren't even engineers, but rather biologists who picked up the requisite chemistry knowledge or chemists who learned the necessary biology. Many metabolic engineers actually are engineers by training. Whatever their background, the common thread is that metabolic engineers think about metabolism with an unconventional pair of eyes. These scientists see metabolic pathways as mini-chemical laboratories, capable of carrying out multiple chemical reactions in a single pot—the cell—without the need for time- and labor-intensive separation and purification steps.

Metabolic engineers work their magic by altering the metabolism of a bacterium, plant, or animal cell. To accomplish such a goal, the researchers must first pick apart the biochemical circuits these organisms routinely use to break down food and produce energy from it (called catabolic pathways), as well as those pathways that re-use the building blocks to make bigger

molecules (called anabolic pathways). Metabolic pathways are those involved in the production or breakdown of aptly named molecules called "metabolites."

More than a hundred metabolites currently represent mainstay medicines for people, as well as for animals. The antibiotics erythromycin and tetracycline, a cholesterol-lowering drug called lovastatin (Mevacor®), and a flea-busting pet medicine called avermectin are all "polyketides," a class of metabolites that soil bacteria manufacture naturally and abundantly. Since polyketides are made by a chain reaction of many enzymes, metabolic engineers experiment with mixing and matching the genes that encode these enzymes to purposefully alter the ultimate outcome of the series of reactions. By doing so, they can come up with entirely new molecules. Companies have been built upon this prospect, and they are mining Nature for the encrypted secrets that can enable microbes to yield medicines that are more powerful or have fewer side effects than those currently in use. Because these methods rely heavily on biology, they are in many cases considerably less toxic than traditional commercial production schemes, which often require the use of potentially hazardous chemicals to yield synthetic compounds.



Combinations, Combinations

Drug companies large and small are in the business of locating new compounds, called "leads," to test for their usefulness in treating disease. In general, the road to drug discovery involves two sequential steps: lead discovery and lead optimization. One popular method some companies use to discover could-be drugs is combinatorial chemistry, a process in which chemists create and then sift through immense collections of compounds ("libraries"). Such screening libraries consist of a diverse, randomly assembled array of thousands of different molecules made from a few starting chemical building blocks. While such approaches can create a bewildering number of possibilities, the lead molecules that are identified through such a scheme may require extensive laboratory tinkering to transform them into body-friendly molecules that work well as drugs.

Microbes Go Blue

Tooling away in his microbiology lab studying how the bacterium *Escherichia coli* (*E. coli*, a common microbe) eats chemicals called hydrocarbons, David Gibson noticed a surprising thing: Some of the bacterial spots in his petri dishes had turned a brilliant blue. Looking in his notebook, Gibson realized that those particular specimens were the very ones that he had just spruced up with a new gene—one that coded for an enzyme called toluene dioxygenase. He carefully analyzed the blue pigment produced by the new strain of bacteria and reasoned that the color had been produced when the enzyme converted a simple nutrient called indole into indigo, the world's largest-selling dye and the one that makes blue jeans blue. Coincidentally, the year was 1983, exactly 100 years after 19th-century chemists had devised a method to chemically synthesize the dye, but one that relies on the use of hazardous starting materials (cyanide, for one) and that also generates toxic byproducts. Scientists at Amgen, a company in Thousand Oaks, California, discovered that a very similar enzyme, called napthalene dioxygenase, also turns indole into indigo. Genencor International of Palo Alto, California tried to introduce the biological method to the $200 million indigo market, but ran into trouble. Despite the biotechnical innovation and environmentally friendly nature of getting bacteria to make indigo, as it turns out, the chemical synthesis of this dye is far less expensive, quashing commercial schemes to produce indigo biologically.

Endless Possibilities

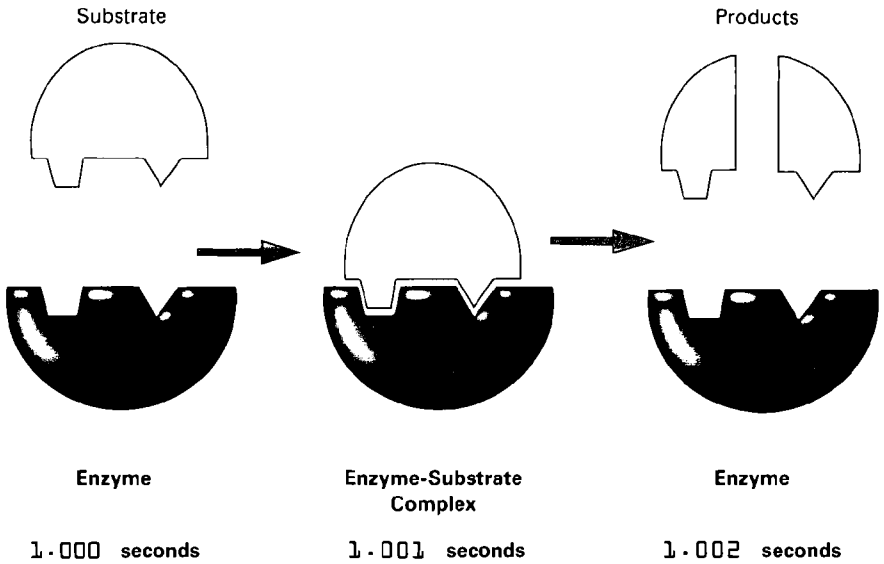
One of the most challenging aspects of the search for new drugs is combing through reams of possibilities—finding that perfect needle in a towering haystack. An enormous number of new molecules can be generated by a variety of means, but the tough part is finding the good ones. A promising approach chemists are using to develop potential new drugs is "combinatorial chemistry," a sort of "needle-finding" technique in which chemists generate breathtaking numbers (millions) of compounds and then attach each one to a miniature plastic bead. The result is an extensive collection, or a "library," of many beads, each with a unique molecule attached. Each bead, then, holds a potentially good drug—a "needle" in a huge haystack of possibilities. Scientists need to be creative in finding ways to distinguish molecules that look very similar to each other but that might act in very different ways. Often, chemists do this by color-coding the process—the "best" molecule advertises itself by turning red or blue, for instance, when hooked by a drug-target chemical detection system.

Chemistry for a Greener World

While strategies like metabolic engineering offer great promise for spawning new medicines, other areas of chemistry aim to clean up the Earth, improving people's health by ridding the air and waters of pollutants.

Terrence Collins of Carnegie Mellon University in Pittsburgh has developed a class of molecules, called "oxidation catalysts," that reduce the amount of chlorine required for industrial bleaching processes. The catalysts, crafted from nontoxic components, may find use in the laundry and paper industries and could also someday be used to treat drinking water by cleansing it of harmful parasites. Collins' catalysts work by jump-starting a natural whitening agent (hydrogen peroxide) that is either present in, or can be easily added to, water-based solutions. A key plus to these green catalysts is that their "shelf life" can be pre-set. This feature, something Collins calls "dial-a-lifetime," permits scientists to control how long the catalysts stick around before they self-destruct.

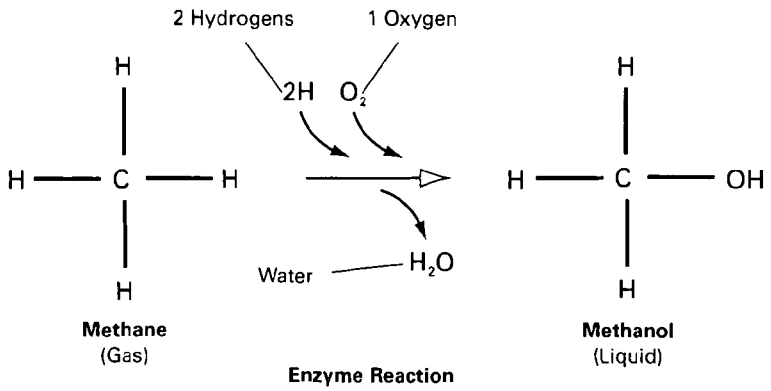
Innovative chemical strategies can help reduce pollution from manufacturing processes, but they might also help mop up after environmental damage has already occurred. To chemists, breaking down small, stubbornly inert molecules such as methane—a single carbon atom framed by four hydrogens—is a technical tour de force. But to a certain variety of bacteria that dwell in hot springs in Bath, England, chewing up methane is a breeze. As miniature apprentices, the hot springs bacteria can provide a valuable service to scientists working to clear the air of methane, which is second only to carbon dioxide as a contributor to the "greenhouse effect" that has been implicated as one source of global warming. In the United States, the most significant sources of methane gas are landfills and agricultural livestock manure.



△ Enzymes convert substrates into products very quickly.

Speeding Along

All chemical reactions involve the conversion of starting materials (called substrates) into products. Catalysts are molecules that make reactions go much faster than they would on their own. By definition, catalysts are facilitators—they themselves are not used up in the reaction and can be re-used. In industrial reactions—say, the manufacture of ammonia—catalysts can be a mix of simple molecules such as iron, potassium, oxygen, and aluminum. Your body's catalysts are enzymes. Some enzymes make the reactions taking place in your body occur up to a trillion times faster than they would without any help! Enzymes are therefore essential to life, since your body cannot afford to wait days, weeks, or years to receive the important products of biochemical reactions.



△ The enzyme methane monooxygenase converts methane into methanol, producing water as a byproduct.

Researchers and biotechnologists would love to be able to use environmentally friendly biological catalysts to convert methane into methanol. Chemist Stephen Lippard of the Massachusetts Institute of Technology has made major strides in this area by intensively studying the hot springs bacteria to find the magic ingredient—an enzyme—that they use to eat methane.

Lippard and his collaborators figured out what this enzyme, called methane monooxygenase (MMO), looks like and how it likely works. As it turns out, MMO is a curiously complicated molecular machine made up of three separate parts. Together, the three parts manage to transform the tiny methane molecule into methanol in a reaction with oxygen that replaces one hydrogen atom of methane with an oxygen and a hydrogen. This chemical reaction makes methanol, with water as a byproduct. The fact that a bacterial enzyme can do this is important. While methane is stubbornly difficult to break apart in the laboratory, its chemical cousin methanol can be processed rather easily. Moreover, methanol (a liquid) can be transported much more easily than methane, which is a gas that is harder to keep contained.

Tiny Bits of Help

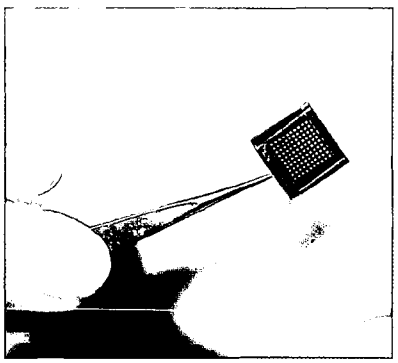
Many other scientists are finding ways to use the bacterial work force. Some chemists are using enzymes from bacteria to break down agents of biological warfare. Sarin, the deadly nerve gas sprayed in 1995 into the Tokyo subway system by the cult Aum Shinrikyo, is one example. One of a class of molecules called organophosphates, sarin trips vital nerve circuitry in the bodies of people or animals who come in contact with it; very small quantities can kill a sarin-exposed victim in as little as 5 minutes.

Fortunately, however, certain types of bacteria manufacture an enzyme called phosphotriesterase (PTE) that inactivates sarin and other organophosphate molecules like it, some of which are found in certain insecticides but are hundreds of times less toxic to people. Certain organophosphates, such as the common insecticide malathion, kill insects because, unlike animals, bugs lack an enzyme that breaks down this chemical. For many years Frank Raushel of Texas A&M University has studied the PTE enzyme, and recently he and his colleague Hazel Holden of the University of Wisconsin, Madison cleared a substantial hurdle: They identified the three-dimensional structure—a "molecular snapshot"—of what this enzyme looks like. This information will help scientists better understand how the enzyme works—and could reveal how to engineer one that works even better.

Metals Can Be Good for You...

Enzymes like PTE rely upon a special kind of molecular assistance to do their jobs efficiently. Metals such as iron, zinc, and copper all perform vital roles in some of the enzymatic reactions that fuel the body's metabolism. Iron, for instance, helps the protein hemoglobin transport oxygen to organs in the body. Many metals act to stabilize the shapes of enzymes. But the body's handling of metals—some of which can be highly toxic in excessive amounts—is a tricky business. In some cases, cells exert exquisitely tight control, assuring that only one or two free metal atoms are present inside an individual cell.

Copper is a case in point. Crab and lobster are more than perennial summer favorites—they are also a good dietary source of this metal. Yes, the stuff of pennies is crucial for life—copper is an important helper to many cellular enzymes, including one called superoxide dismutase (SOD), which sops up dangerous "free radicals" that accumulate inside cells. Defects in SOD have been linked to some inherited forms of amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. Although copper is necessary for life, it is a potentially toxic substance that—in the wrong cellular locale—can damage other molecules, and in some cases even cause disease. A team of scientists—Valeria Culotta of The Johns Hopkins University in Baltimore and Thomas O'Halloran and Amy Rosenzweig, both of Northwestern University in Chicago—recently deciphered the three-dimensional structure of a yeast copper "chaperone" protein. This protein transports copper to the SOD enzyme and protects the metal from unwanted cellular interactions along the way. In ALS, researchers suspect, defective SOD—when energized with the copper it needs to function—runs amuck and causes cellular damage. Scientists predict that they will soon be able to catch the copper chaperone-SOD duo in the act of trading off copper, offering drug designers a crystal-clear glimpse of how to cripple this molecular embrace in patients with Lou Gehrig's disease.



Marsha Miller

△ An artificial "tongue" can be used to "taste" chemicals.

An Electronic Tongue

It's a far cry from the real thing, but a new artificial "tongue" promises to do a lot more than taste hamburgers and lick stamps. Chemist Eric Anslyn of the University of Texas at Austin and his colleagues have developed a prototype "tongue" biosensor for sampling liquids: a tiny silicon wafer embedded with detection beads that turn color in the presence of specific chemicals. Right now, Anslyn's electronic tongue can only differentiate between acids, simple sugars, and certain electrically charged molecules. In theory, though, many more chemical micro-detectors could be added to the chip, enabling the device to pick out several different components of a solution poured over it. Indeed, an electronic tongue might be a really good thing, considering some of the solutions it might be used to "taste"—blood, urine, and polluted water, for instance. Of course, the system might also be used to assure quality control in much more palatable substances, such as wine or soft drinks.

...or Metals Can Be Bad for You

While it's clear that the body would not work properly without a prescribed amount of a select group of metals, some metals are indeed toxic to the body. Even for the metals your body needs, too much is not a good thing. Since metals are elements (the building blocks of all chemical compounds), as basic components of the Earth they cannot be broken down (like proteins and fats can, for instance). Thus your body takes great care to shepherd these potentially toxic materials to their proper destinations inside cells. As with copper, many other metals are escorted around by protective, chaperone-like molecules.

Some toxic metals, in contrast, aren't good in any amount. They can hinder important enzymes, preventing them from doing their jobs. Lead from the environment, for instance, can trip up the body's synthesis of a vital component of hemoglobin called heme, disabling the blood's oxygen transport system. Some metals can get trapped inside cellular compartments called organelles and pose trouble for normal cell functioning. Certain forms of mercury can be deadly, causing irreversible damage in the brain. Scientists think that some highly toxic metals, such as arsenic, can also cause cancer in the skin and lungs.

METALS IN HEALTH AND DISEASE

METAL (Chemical Symbol)	WHERE IS IT?	WHAT DOES IT DO?	HOW DO I GET IT?
"Healthy" Metals			
Iron (Fe)	Binds to enzymes throughout the body (e.g., hemoglobin, nitric oxide synthase)	Helps body transport oxygen and certain chemical messengers	Meats (highest in beef, pork, liver), baked or lima beans, molasses, spinach
Copper (Cu)	Binds to enzymes throughout the body (e.g., superoxide dismutase)	Defends body against damage from free radicals	Shellfish (crab, lobster), dried beans, nuts
Zinc (Zn)	Binds to enzymes throughout the body, to DNA, and to some hormones (e.g., insulin)	Plays role in sexual maturation and regulation of hormones, helps some proteins stick tightly to DNA	Shellfish (oysters), chick peas, baked beans, whole grains, nuts
Sodium (Na) Potassium (K)	Throughout the body (Na outside cells, K inside cells)	Helps communicate electrical signals in nerves, heart	Na: Table salt and baking soda K: Bananas, oranges, avocados
Calcium (Ca)	Bones, muscle	Muscle and nerve function; blood clotting	Dairy products, broccoli, figs, sardines
Cobalt (Co)	Forms the core of vitamin B12	Necessary ingredient for making red blood cells	Meats, dairy products, leafy green vegetables
"Unhealthy" Metals			
Arsenic (As)	Rocks, soil	Can cause cancer, death	Toxic
Lead (Pb)	Old paint (before 1973)	Can cause cancer, neurological damage, death	Toxic
Mercury (Hg)	Contaminated fish (especially from the Great Lakes region of the United States)	Binds to sulfur-containing molecules in organelles; can cause neurological damage, death	Toxic

Future Factories

The Chemistry of Health asked Mary Lidstrom, Professor of Chemical Engineering and Microbiology at the University of Washington, "What's new for you on the biotechnology horizon?" Bioremediation isn't necessarily her pressing interest, says Lidstrom, explaining that engineers at companies are well on their way to getting bacteria—especially the kind she studies—to clean up the environment. To her, the real excitement is in getting bacteria to manufacture novel materials cheaply and efficiently, using nontoxic starting materials and generating nontoxic waste products. In her own lab, Lidstrom spends much of her time trying to convince bacteria to do things they weren't meant to do.

And bacteria—

they have such amazing metabolism.

They can do almost anything.

CH: What does the future hold for the kind of biotechnology you're working on?

Lidstrom: The greatest challenge is for the chemical industry to move away from petrochemicals. Our goal is to turn bacteria into chemical factories.

CH: How would that help matters?

Lidstrom: You could use simple sugars like glucose, or other potentially renewable resources—such as methanol—as starting materials.

CH: What challenges do biotechnologists working in this area face?

Lidstrom: The problem is that we can't do this economically right now—the challenge is how to redesign these bacteria. Nature didn't make them to do this.

CH: What turned you on to science?

Lidstrom: I grew up on a cattle ranch in Oregon, where I was around biology all the time. I have always been fascinated with how things work and why—how does light shining on a leaf open it up? And I had great science teachers to nurture my interests.

CH: Why microbiology?

Lidstrom: There's no blood! And bacteria—they have such amazing metabolism. They can do almost anything.

Got It?

What are the substrates used by the enzyme methane monooxygenase? What products does this enzyme make?

What advantages do combinatorial chemistry methods have over the more traditional ways chemists have used to screen for new drugs?

Name an antibiotic manufactured by soil bacteria.

Describe two ways your body uses metals to function properly.

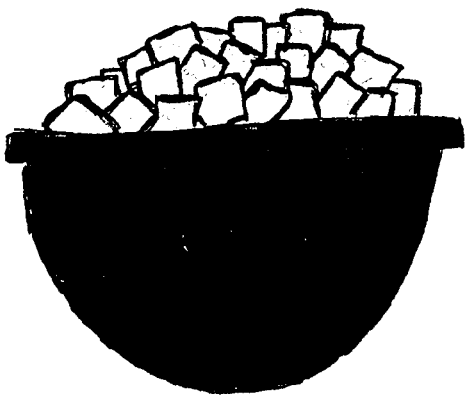
Discuss some of the plusses to using living organisms to produce medicines or other consumer products.

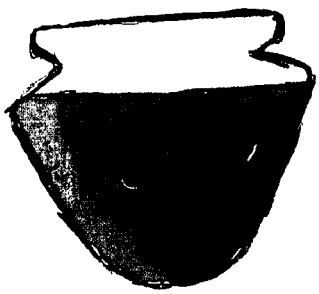
CHAPTER 3

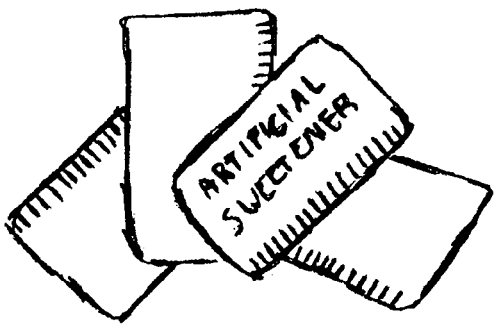
Sugars and Fats: Are We What We Eat?

To a great degree, the old adage holds true: We are what we eat. Our diets—everything from broccoli to butter to bread (a mix of proteins, fats, and sugars)—contain the biochemical ingredients for life. Ultimately, sugars (called carbohydrates) and fats (called lipids) are your body's chief sources of fuel.

But wait—tempting culinary concoctions like velvety caramel or cookie-dough ice cream aren't exactly what scientists are talking about when they refer to sugars or fats. The proteins, fats, and sugars you eat actually contain varying mixtures of all three of these types of molecules, plus water. Your digestive system teases apart a towering swirl of frozen custard, for instance, into its constituent "biopolymer" parts (proteins, lipids, and carbohydrates). These biopolymers are further digested into even smaller pieces: proteins into amino acids; carbohydrates into smaller sugars called simple sugars (like glucose); and fats into two breakdown products, called glycerol and fatty acids. Your body then transforms most of these breakdown products into just a few common biochemical intermediates. These are the simple molecules fueling the metabolic engines that produce the energy you need to eat and breathe.





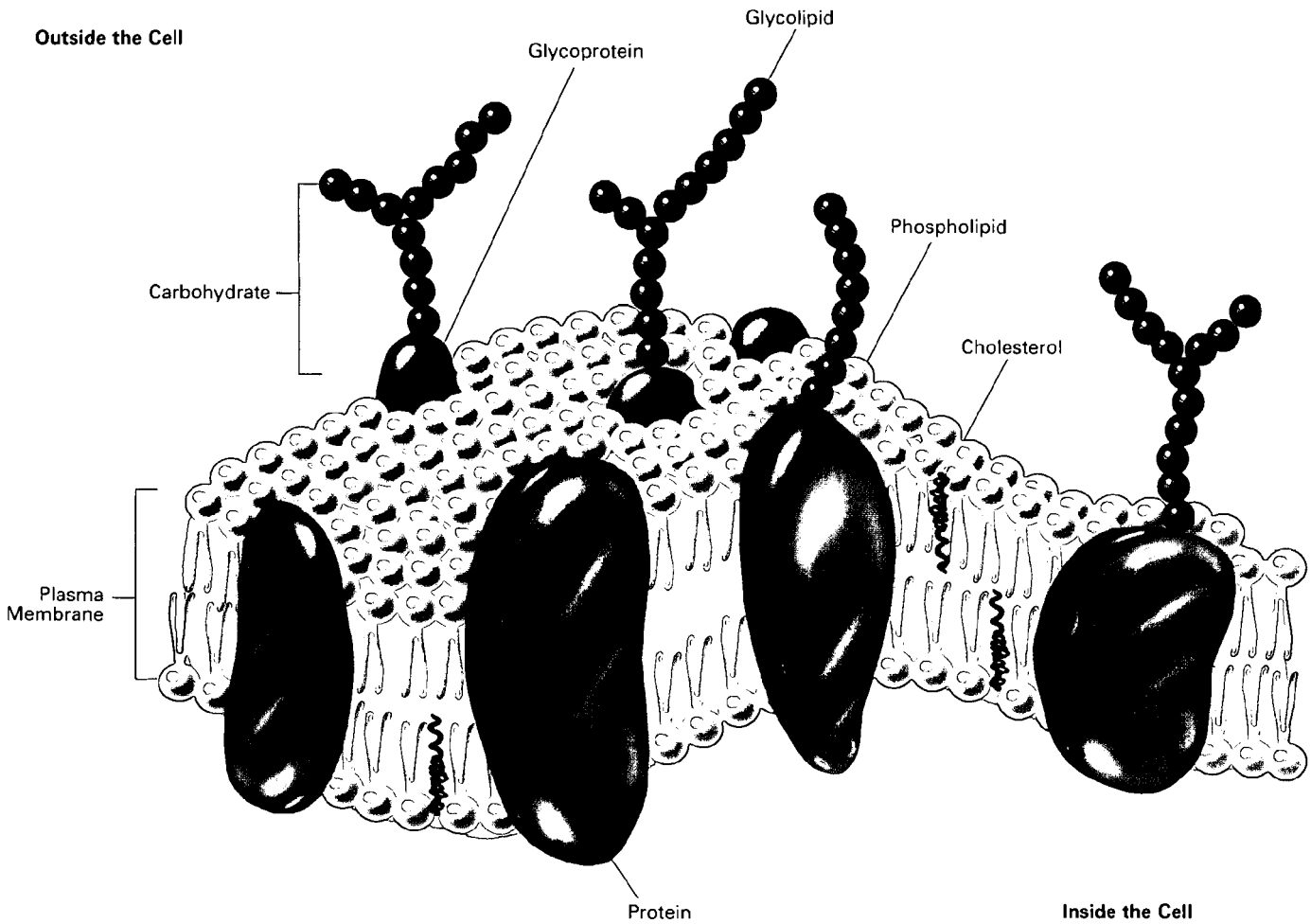


Form and Function

Sugars and fats are also key structural components in cells. It is true that fat has gained a certain notoriety, signifying the consequence of too many French fries that end up in extra pounds. But fats are essential ingredients that are constantly being produced, recycled, and incorporated into crucial fixtures such as the cell's lining and protective barrier, the plasma membrane. Fat and a fat-derived substance called cholesterol constitute important structural components of the plasma membrane—a greasy envelope of lipids and sugars with proteins threaded through—that encases and protects the DNA and myriad signaling and structural proteins nestled inside. Yet the plasma membrane is not just a simple barricade; rather, the construction of this interactive sheath is a true feat of cellular engineering, orchestrated by the orderly arrangement of ball-and-stick molecules called glycolipids (lipid chains adorned with sugars) and phospholipids (lipids marked with charged cellular tags called phosphate groups). When aligned, these fat-containing molecular creations resemble a double array of matchsticks lined up perfectly end-to-end. The components can line up so flawlessly due to the simple chemical rule that oil and water don't mix. A double-thickness plasma membrane more or less automatically forms when the matchstick "end" (the lipid part) of each glycolipid or phospholipid gravitates toward oil (other, similar lipid matchstick ends) and the matchstick "head" (the sugar or phosphate part) drifts naturally toward the watery environment typical of the areas inside and between cells. Varying amounts of cholesterol,

How Much Sweeter It Is

By far, the majority of molecules people taste as "sweet" are carbohydrates. Besides table sugar (sucrose), many other sweet molecules do exist. Surely everyone is familiar, for instance, with the pink or blue artificial sweetener packets joining sugar as staples on restaurant and coffee shop tabletops. Sweet 'N Low® and Equal®, which contain the chemicals saccharin and aspartame, respectively, are roughly 200 times as sweet as table sugar. Saccharin, believe it or not, is a chemical derived from petroleum. Aspartame is a tiny molecule constructed from two of the body's natural amino acids, phenylalanine and aspartate. But drawbacks such as aftertaste and lack of heat stability have prompted food scientists to pursue alternative sugar substitutes. Among the latest finds is a protein, called brazzein, extracted from a fruit native to Africa. To date, scientists have discovered only a half-dozen proteins—not sugars—that our tongues perceive as sweet. Of these, brazzein is the smallest and among the sweetest—more than a thousand times sweeter than sucrose. Food industry researchers are hot on brazzein's trail, as the protein seems to leave no unpleasant aftertaste and can withstand unusually high temperatures. The molecule is amazingly stable to heat: It retains its sweetness even after being "cooked" for 2 hours at temperatures greater than 200 degrees Fahrenheit. In a surprising twist, scientists who recently unscrambled the three-dimensional structure of the brazzein molecule say it resembles plant proteins involved in defense against microbial pathogens and some arthropod toxins, such as those secreted by scorpions.



△ The plasma membrane is a cell's protective barrier.

also a matchstick-shaped molecule, account for the fluidity, or flexibility, of any given plasma membrane. "Sticks" of cholesterol slide in between phospholipids and glycolipids and influence interactions between them—making the entire membrane more liquid or solid, depending on the exact location and amount of the cholesterol molecules present.

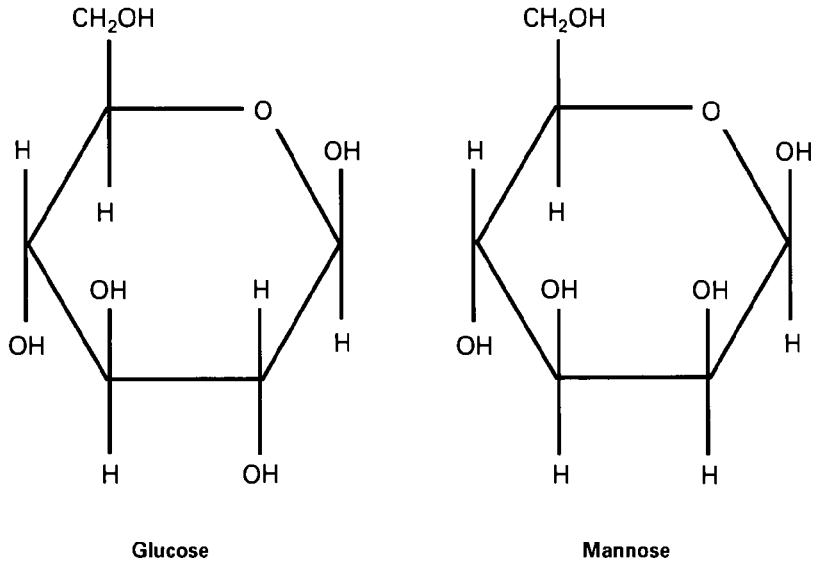
Long chains of water-insoluble lipids are constructed from building blocks called fatty acids, which are also stowed away as a source of fuel in fat cells. The chemical bonds linking fatty acid units together in glycolipids and phospholipids determine how rigid or floppy the lipid chains will turn out to be. This, in turn, affects the shape of the cell structures they form.

In many cases, lipids are much more than passive molecular bystanders—they serve as active participants in cell function. Besides influencing the physical state—the fluidity, shape, and structure—of the membranes of all types of cells, lipids perform other important cellular tasks, such as carrying messages. Sugar and phosphate chemical tags target glycolipids and phospholipids for a journey throughout the cell interior, where they participate in the relay of cell signals—including those that tell a cell to grow and divide, or not.

Fats That Protect Bacteria Can Harm People

The outer surfaces of the cells of some types of bacteria, such as *E. coli* or *Salmonella*, are coated with fat. This lipid-rich shield, a component common to all bacteria of one particular class called "gram-negative" bacteria, serves a barrier function and prevents the escape of important microbial enzymes. An integral part of this bacterial barrier is a lipid-and-sugar-containing substance called lipopolysaccharide (LPS). A key constituent of LPS is a molecule called lipid A, which scientists also call "endotoxin." This molecule can be very toxic to humans who encounter it. During severe infections, large amounts of lipid A shed by gram-negative bacteria trigger the body's immune system to overreact, commanding an army of immune cells to mount an attack. The resulting overproduction of immune chemicals can damage blood vessels and lead to a deadly condition called septic shock, in which blood pressure plunges to dangerously low levels and key organs such as the heart and kidney quickly become starved of oxygen from the blood. For obvious reasons, lipid A is an important target for chemists interested in developing antibiotic drugs.

Scientists have already determined that depriving bacteria of lipid A—either by taking away the cells' ability to make it or by wiping it out with a drug—kills the bacteria that produce it. Biochemist Christian Raetz of Duke University has extensively studied the pathways that bacteria use to make lipid A. In the process, Raetz and his colleagues have identified certain compounds that stifle the production of lipid A, some of which may lead to the discovery of new antibiotic drugs. Ironically enough, Raetz has found some precursors to the synthesis of lipid A, as well as some lipid A look-alike molecules, that block the lipid A-provoked inflammation that leads to septic shock. One of these compounds is currently undergoing testing in Phase II clinical trials, the stage in the testing of potential new drugs in which researchers determine if the compound is effective. (To progress to Phase II clinical testing, researchers have to first prove, in Phase I trials, that the compound is safe for use in people.)



△ The chemical structures of the sugars glucose and mannose are very similar.

Sugar-Coated Proteins

Sugars attached to proteins (glycoproteins) are another key ingredient of cell membranes. Just as the sugar portions of glycolipids are oriented toward the watery cell exterior, so too are the sugar components of glycoproteins. Jutting out from the cell, these sugary "decorations" serve an identifying role, sort of like cellular address labels. Signaling molecules coursing through body fluids encounter specific patterns of sugars, which either grant them entry or refuse access. In this way, glycoproteins play a gatekeeper role in human cells. By virtue of "marking" cell surfaces, glycoproteins also help organs and tissues form, by directing "like" cells to meld together properly. Sugar coatings also help roving cells move along blood vessels and other cellular surfaces inside the body, providing "traction" via their ability to latch on to cell surface receptors.

Sweet Therapy

In medical research studies, the "sugar pill" is usually the so-called placebo: a "dummy" pill that scientists administer to half of a test group of patients to evaluate how well the "real" pill works. In an interesting twist, biochemist Hudson Freeze of the Burnham Institute in La Jolla, California and his colleagues in Germany are using sugar pills themselves to combat a rare, inherited childhood disease. Given the many crucial roles sugars play in the body, it is not surprising that when the body doesn't manufacture sugars properly, dire consequences follow. Usually, diseases caused by a body-wide lack of certain carbohydrate-containing proteins plague the central nervous system (usually, the brain) and result in severe mental retardation, but other very serious symptoms, such as bleeding problems caused by defective blood proteins, are also a hallmark of some carbohydrate deficiencies. Upon analyzing the cells of a child with CDG (a group of diseases collectively called Congenital Disorders of Glycosylation), Freeze, who for years had studied sugar metabolism in a primitive organism called a slime mold, quickly noted a conspicuous shortage of one sugar in particular, called mannose. He worked out a plan to try supplementing the child's diet with the missing sugar. As a result of receiving this inexpensive treatment, the child—who, it turns out, lacks the enzyme that converts another sugar, glucose, into mannose—has been able to resume a normal life. Larger clinical trials verifying the usefulness of dietary mannose supplements for treating CDG patients are currently under way.

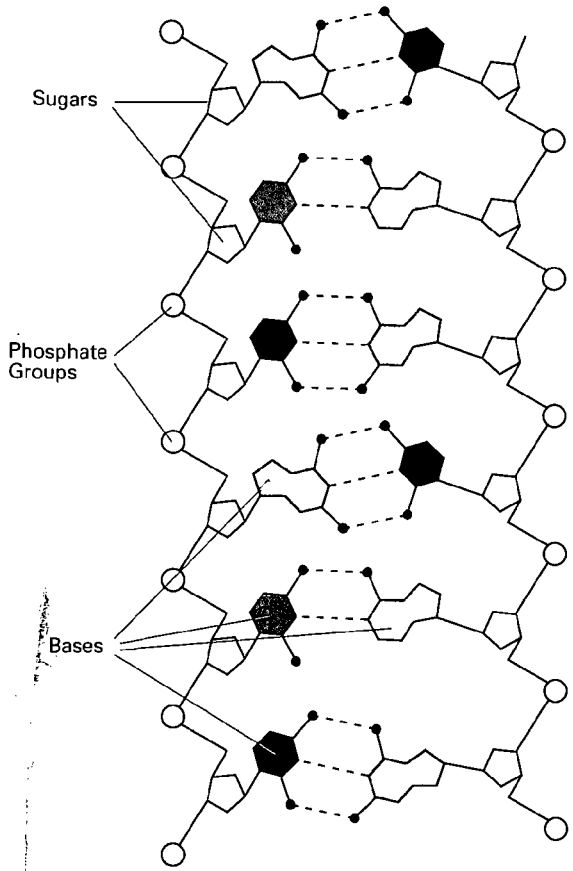
CHEMICAL BIOLOGY
in Action

Sticky Situations

A class of immune system cells called white blood cells are a case in point. Studding the exterior of these cells are protein molecules called L-selectins. These sugar-grabbing proteins help white blood cells perform their tasks, such as to travel to the site of an impending infection to fend off microorganisms. The body's process of recruiting immune cells to combat injury or infection, however, has its own shortcomings—in the act of responding to such crises, immune cells spill their toxic contents and inevitably damage normal cells in the process. The result can be inflammation and pain.

Developing means to quash inflammation is therefore an important goal, and indeed is the target of an ongoing, multibillion-dollar pharmaceutical effort. Chemist Laura Kiessling of the University of Wisconsin, Madison had a hunch that forcing L-selectin molecules on immune cells to cluster together might send a signal to the cells' clean-up crews to clip the molecules from the cell surface. By doing so, the cells would lose critical docking sites that normally render the cells capable of sticking to each other—a key step in setting off an inflammatory response. Her hunch was correct: A few members of a new class of synthetic sugar molecules called "neoglycopolymers" can perform this trick, causing L-selectin molecules on meandering cells first to cluster and then to fall off cell surfaces. Neoglycopolymers are simple to make and halt inflammatory processes in a distinctly different way than do existing anti-inflammatory drugs, such as aspirin or ibuprofen. While these medicines block signaling molecules inside the cell, neoglycopolymers prevent cells from touching each other in the first place. Kiessling's research is yielding valuable insights into cellular processes that hinge upon cell migration—not only inflammation, but also the spread of cancer throughout the body, and perhaps even the way in which bacteria infect humans.

In addition to blocking the sticky interactions that draw cell surfaces together, scientists are also interested in changing cellular landscapes altogether. To that end, Carolyn Bertozzi of the University of California, Berkeley has gotten into the business of "remodeling" cell surfaces. Like Kiessling, Bertozzi is a chemist interested in intercepting biological maneuvers that underlie human disease processes such as infection, inflammation, and the unchecked spread of cancer cells. Bertozzi set about her goal by figuring out a way to trick a cell's own metabolic machinery into redecorating its surface with unnatural molecules—such as ones on cancer cells that might be especially attractive to cell-killing agents, or ones on heart cells that might be attractive to artificial materials like pacemakers and other medical implants. The method Bertozzi dreamed up is beautifully simple in design. Her experiments have shown that she can feed cells a novel synthetic sugar that is just a little bit different from a natural cell surface sugar and get the cell to build a chain of such sugars and send it to the surface for display. Bertozzi can coax different cell types to ingest and display varying amounts of the unnatural sugars, providing the cell with brand-new surface features. The kicker is, in many instances the cells don't even seem to notice!



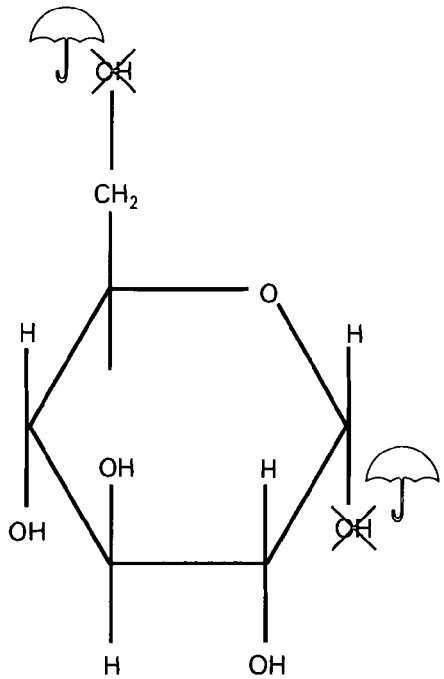
△ Sugars are part of the DNA double helix.

A Complicated Recipe

Many drugs currently in the development pipeline are proteins. The golden era of genetic engineering has enabled scientists to make proteins from DNA in just a few easy steps. But the going hasn't been so easy with sugars. Chemists have long struggled with the problem of being able to tailor-make sugar molecules in the laboratory, and finally some scientists are nearing the light at the end of the tunnel. An ability to make all types of sugars on demand will undoubtedly tap the innumerable resources these molecules harbor—as drugs, as cellular "handles" for drugs to hang onto, and as basic research tools to probe hidden facets of cells. In practical terms, the ability to make sugars and sugar-derived molecules in the lab will allow chemists to spend less time agonizing over how to make the sugars and more time on studying the many roles these complicated molecules play in the body.

A Supporting Role

Throughout your body, sugars help communicate messages by serving as molecular routing slips like the ones that direct pieces of mail to their correct destination. Sugars also play important structural roles within and between cells. Sugars form the scaffolding for the alphabet of life, DNA. The two threadlike strands of DNA "zip" together by virtue of a biochemical concept called complementarity. The four "letters" of the DNA alphabet—the "bases" A, T, G, and C—spell out the sequence of your genes, sort of like words. Because of each base's shape, Gs stick only to Cs and As attach only to Ts. The double helix of DNA, therefore, is a consequence of these base-specific chemical attractions. Bolstering the bases in place is a scaffolding of sugars that is "glued" together via molecules called phosphates. In plants, bacteria, fungi, and some arthropods, the supportive structural role played by carbohydrates is dramatic: Sugars literally hold the cell together by helping to form and maintain a tough cell wall.

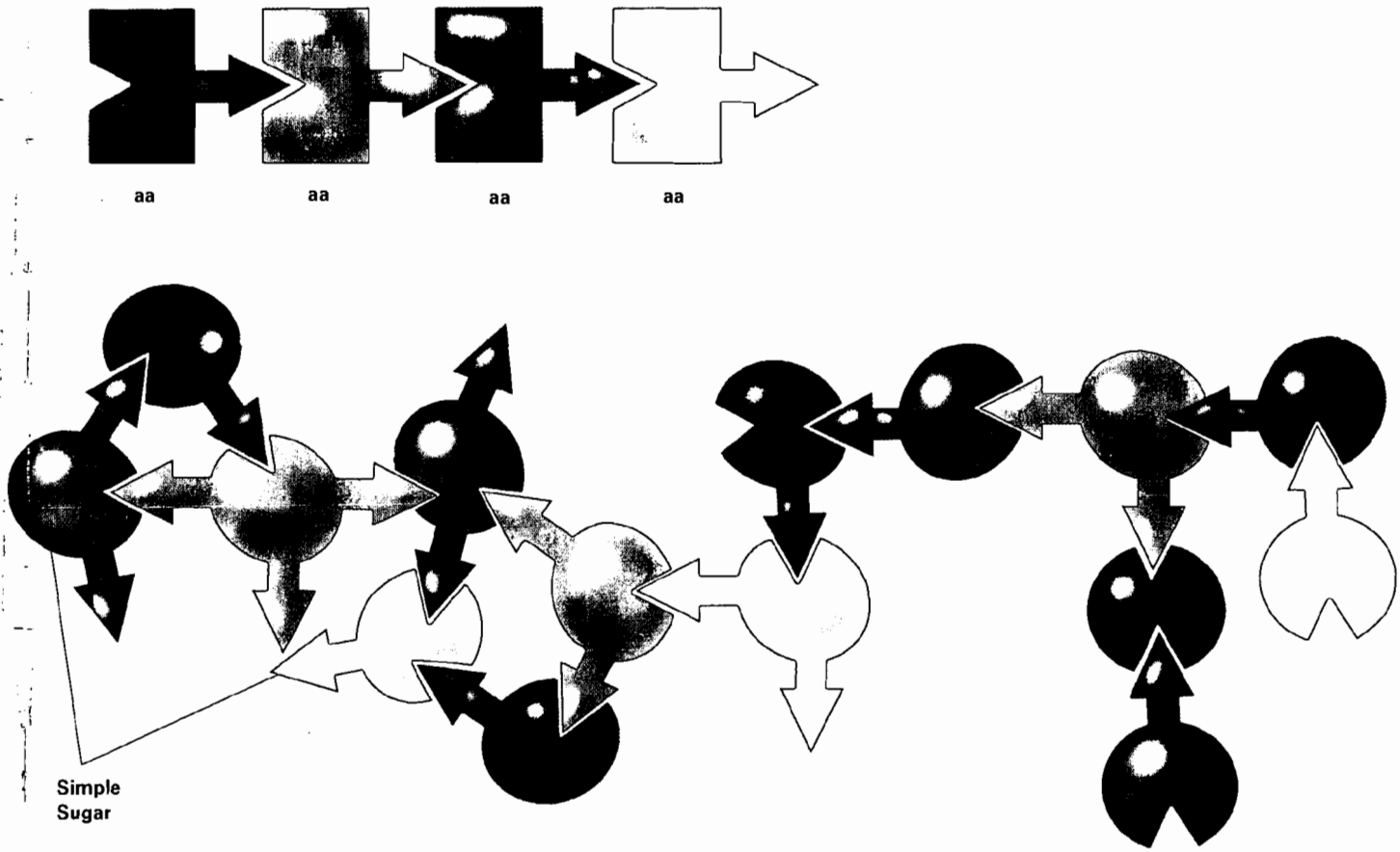


◁ So-called "protecting groups "(☂) help chemists prevent unwanted chemical reactions.

One especially exciting avenue is the potential for scientists to make from scratch the various sugars that reside on the surfaces of bacteria and viruses. The ability to mimic such sugars will grant scientists the capacity to design new vaccines to control these disease-causing microorganisms.

Why is making proteins so easy and making sugars so hard? The answer lies in the fundamental structure of each. Proteins are chains of amino acids that can only fit together one way: head-to-tail, sort of like beads on a string. On the other hand, oligosaccharides—long, and often branched, chains of sugars—can fit together in many different ways, and chemists have a tough time forcing the construction one way instead of another.

Just two of the building blocks of an oligosaccharide chain can chemically snap together in dozens of ways. Another constraint is the fact that chemists often want to make branched structures, as opposed to linear "beads on a string." Traditionally, chemists attach chemical masks (so-called "protecting groups") to prevent the simple-sugar building blocks from forming unwanted linkages. This way, by blocking every potential attachment site but one—the wanted one—a chemist can ensure that only that particular link will be made. Afterward, the protecting groups can be removed, leaving only the sugar. This process of carefully separating chemical mixtures and applying and removing protecting groups can be very time-consuming.



△ (top) Amino acids (**aas**) link head-to-tail to make proteins. (bottom) Simple sugars link in many orientations to make oligosaccharides.

One-Pot Synthesis

Chi-Huey Wong of the Scripps Research Institute devised an inventive strategy to make some types of sugars in his lab—in a fraction of the time required by most other approaches. Wong's recipe for making oligosaccharides takes little time because it can all be done in one pot. The ingredients for "one-pot oligosaccharide synthesis" (as he calls it) are individual sugar building blocks with masking groups attached, plus a computer. At present, the process isn't simple—a considerable amount of groundwork is required to get his computer to guide the assembly of sugar pieces in a pre-defined order. Just as cooking a meal requires the chef to cut up all the vegetable and meat ingredients before cooking, before Wong added components to the "pot," he had to prepare all his chemical "ingredients." To do so, he first conducted a series of chemical reactions and assigned a computer to monitor these reactions, rank how fast each occurred, and keep track of all those reaction rates. Wong then instructed the computer to choose individual chain-building linkages by virtue of how fast, or "reactive," they were. At the moment, he has only a limited set of building blocks and reactions to start with, but Wong predicts that logging even more structures and reactivities into his computer will ultimately allow for the process to be completely automated by robots.

Wong's strategy is but one of many aimed at synthesizing sugars on demand. Other chemists are using a variety of techniques—virtually all of which rely upon the use of protecting groups. (The ones that don't rely on the use of protecting groups use enzymes, which are uniquely capable of selecting one, and only one, particular attachment site.) Some chemists, such as Daniel Kahne of Princeton University, are perfecting a technique to build sugar chains atop a solid support. The rationale for such an approach is that sugars exhibit unique shapes and properties when stuck to a surface compared to floating around in a solution. Studying some of those unique properties has obvious relevance to how sugars behave in real cells in real bodies, where they mostly exist on surfaces. Another plus to making, and studying, sugars on a solid surface is that the method is efficient and easily permits the use of combinatorial chemistry techniques that can randomly generate huge collections of surface-bound sugar arrays that are potentially useful as drug targets.

Putting Things In Order

Ram Sasisekharan, a biochemist at the Massachusetts Institute of Technology, constantly finds himself caught up in sticky situations. In fact, it's his choice to do so. As a scientist who ponders the scores of roles sugars act out in physiological systems, he spends much of his time devising ways to figure out how long, complicated tangles of carbohydrates are hooked together. Sasisekharan uses a brew of chemistry, physics, and math to determine the letter-by-letter sequence of sugary molecular chains called polysaccharides. Historically, Sasisekharan says, biologists have tried to "get rid of sugars" in the samples of proteins and DNA they analyze, because "they got in the way and were a nuisance." This is hardly the truth, he says, extolling the virtue inherent in studying sugar molecules—in his words, "the most information-dense molecules Mother Nature makes." According to Sasisekharan, sugars are orders of magnitude more complex than proteins or nucleic acids, which is a likely reason they've been the molecule scientists left behind. With a recent explosion of research on sugars and the important things they do in the body, that's unlikely to be the case for long. *The Chemistry of Health* asked Sasisekharan to fill in some of the exciting details.

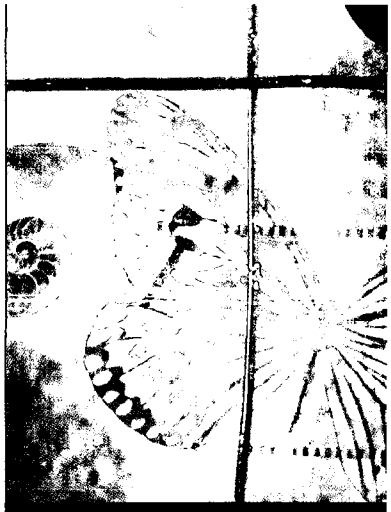
CH: What are some of the things sugars do that make them so interesting to study?

Sasisekharan: Sugars are like "clothes" cells wear. Which sugar "coat" a cell wears—for example a wool coat or a T-shirt—affects how that cell perceives and responds to its environment. The sequence of a sugar chain can influence the job a cell performs. I hope the day will come that we can tell cells what to wear—so that by having cells wear the right clothes at the right time, we can influence what cells do!

CH: You've recently discovered a way to decipher the sequence of long chains of sugars—how do you do it?

Sasisekharan: The sequencing method we developed really hinges on two key principles: mathematical coding and atomic-scale measurements of the weights of sugars. First, we start with

I see math as a form of communication
cutting up a problem into smaller, more manageable pieces
so you can put them all back together
in a logical way and solve the problem.



Got It?

cellular material that contains not only sugars, but also proteins and lots of other stuff. We're starting with a sugar chain called a glycosaminoglycan (GAG, for short). We know that there are 32 subtly different sugar building blocks to make this particular kind of sugar. In order to be able to distinguish the building blocks—and all their chemical markings—from one another, each has to be uniquely coded by a computer.

Next, we chop up the sugar several different ways, with enzymes and chemicals, producing a huge number of overlapping pieces. Then we weigh the tiny pieces with atomic-level accuracy, using a powerful technology called mass spectrometry. Finally, we feed all this information to a computer, and using the mathematical code we developed, the computer helps us figure out the solution. A lot like a jigsaw puzzle, there's only one way this "puzzle" can be properly assembled. We had a real "wow" moment when we saw that our computer program could generate a database of all the input material and just pop out the answer!

CH: Using math seems very important to the type of research you do—is that true?

Sasisekharan: Yes. Math is everywhere—it's just another system of logic we use to solve problems. Everybody thinks about problems in some logical way—like how to get from the kitchen to the garage. I see math as a form of communication cutting up a problem into smaller, more manageable pieces so you can put them all back together in a logical way and solve the problem.

CH: How do you see advances in carbohydrate chemistry advancing human health?

Sasisekharan: I think the greatest gains will be in diagnosis, in getting a handle on correlating disease states. The ability to study sugars in detail will enable scientists to be able to find all the possible cellular landscapes, and possibly what alters them. Said simply—why do cells wear different sugar coats at different times? Pinpointing exactly which sugars appear on the surface of cells is going to play an important role in how we understand development—the very fundamental principles of how cells position themselves to form tissues and organs.

CH: Why do you find studying science exciting?

Sasisekharan: Besides basic survival, I think a fundamental human instinct is curiosity. Innovation and invention have been instrumental for the survival of humankind...like Isaac Asimov said, "No way but onwards."

Why is it difficult for chemists to make carbohydrates from scratch?

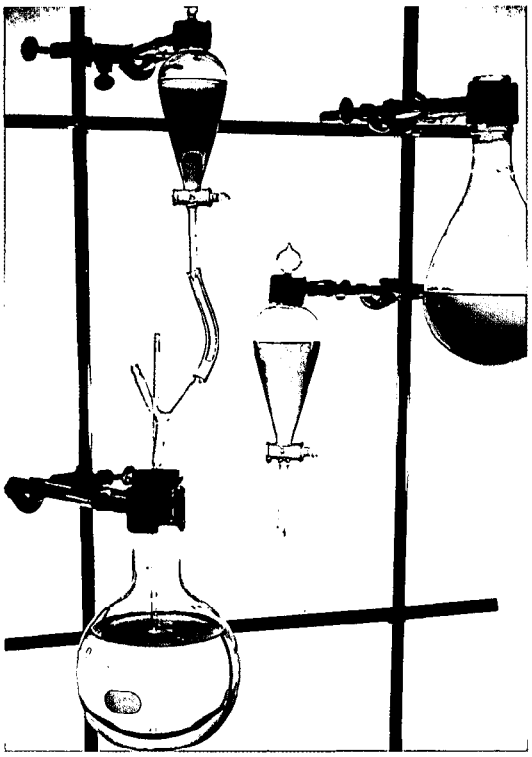
Cholesterol has an essential function in every cell in your body—what is it?

Describe two roles carbohydrates play in your body.

Can you think of some possible ways that carbohydrate chemistry research might lead to improvements in treating disease?

CHAPTER 4

A Chemist's Toolbox



△ Traditional chemistry lab equipment consists of glass beakers, clamps, and tubing.

To many, the word "chemist" conjures up images of wafts of steam spiraling out of glass laboratory beakers bubbling with scorching, brightly colored liquids. A vivid scene, perhaps, but a more accurate image of the toolbox of today's chemist might include equipment such as computers, microscopes, and large vats of fermenting bacteria.

The chemistry of yesteryear bears only a slight resemblance to today's endeavor. To be sure, the quest for knowledge—to understand how and why molecules combine and recombine in wondrous ways—remains the same. Yet chemistry, biology, and even physics are all fields of study that are becoming much less self-contained. Biologists use physics trickery with lasers to watch molecules move one at a time. Physicists craft unique radioisotopes that exist for only minutes or hours (as opposed to many that stick around for centuries) and that serve as perfect tools for researchers to track molecules in the bodies of animals and people. Biologists and an increasing number of chemists use living organisms—so-called model systems such as bacteria and yeast—to probe the molecular mysteries of health and disease.

Basic biomedical scientists—be they chemists, biologists, or biochemists—study health-related problems that may not, at the outset, have a clear connection to a specific disease. Drafting hypotheses and testing them, over and over again, is a lot of hard work. Many experiments "fail" in the sense that the scientist's hunch turns out to be wrong. But every "failure" is in itself a success: a key tidbit of information pointing the scientist's trained eye in a slightly new direction, where he or she can re-test an idea under a slightly different set of conditions. For most scientists, this ongoing process is addictive!

By using models, researchers can perform all this testing and re-testing with systems (such as microorganisms, plants, animals, or computers) that have a set of defined charateristics that don't change much from day to day, or from experiment to experiment. Remarkably, many creatures that are less highly evolved than humans use similar molecules and pathways to carry out their everyday lives. One example is amylase, an enzyme in your saliva that breaks down starch into smaller sugars. In breadmaking, amylase is "food" for yeast, which use this enzyme to help them produce carbon dioxide, the gas that makes dough rise. In many cases, if a particular enzyme or pathway is very similar in diverse organisms, there is a good chance that it's a very important molecule—often indispensable for life.

A Model Cell

A protective barrier called the plasma membrane is one of the most important regulatory locales in a cell, serving as the point of entry and exit for a bounty of large and small molecules that are carried to a cell via the bloodstream. To function properly, cells need a constant supply of nutrients, electrolytes, and structural materials. While some of these necessary components are manufactured in-house, many are obtained from outside the cell. The plasma membrane is also an important communications hub, filtering messages sent by other cells and the outside environment. Membranes are studded with proteins called channels and pores that thread their way from the outside to the inside of the cell, or the other way around. Scientists often study these proteins because they are a key target for drugs.

Scientists have devised molecules "smart" enough to self-assemble into miniature cells or cell parts—such as the plasma membrane. And some researchers are creating teeny, laboratory-made reaction vessels.

M. Reza Ghadiri of the Scripps Research Institute has invented a way to get laboratory-made rings and strings of amino acids to assemble themselves into tube-shaped channels and pores. To create the tubes, Ghadiri constructs rings of eight to ten amino acids. By altering the reaction conditions a little, such as fine-tuning the pH of the test-tube liquid, Ghadiri can get the rings to stack on top of each other, forming a tube. Such artificial versions of naturally occurring molecules

Thomas Eisner

△ Squash beetles are sophisticated chemistry labs.

Bug Labs

When it comes to using model organisms, chemist Jerrold Meinwald of Cornell University goes one step further than many scientists: He looks for critters that run their own chemical laboratories. Insects do virtually all of their communicating—with other insects, plants, and their environment in general—by chemical means, exuding a host of different materials, such as toxic venoms and sexual attractants, in the process. Meinwald and long-time Cornell collaborator Thomas Eisner discovered that one variety of insect, the squash beetle, undertakes the constant production of a bewildering array of chemical compounds—some with enormous molecular rings—starting with just a few small chemical building blocks. Even more amazing, these chemical secretions—which appear as "defensive droplets" on tiny hairs on the surface of the non-moving, immature form of the beetle—continually change themselves (by slight shifts of pliable bonds between connected atoms) to create still more molecules. In general, Meinwald suspects, many such insect-made concoctions serve as defense against predators, but most haven't been analyzed yet in the lab.

might be an extraordinarily useful tool for scientists to use to design—and ultimately deliver—drugs to the right spot in the body. By tweaking the dimensions of the amino acid ring-building blocks, for instance, Ghadiri can design channels to transport substances of varying sizes, ranging from three-atom water molecules to considerably larger molecules of sugars, like glucose. The designer molecules could also be used as antibiotic medicines, by virtue of the artificial channels' ability to poke holes in bacterial membranes—making them too leaky to hold their contents.

Jason Keiper

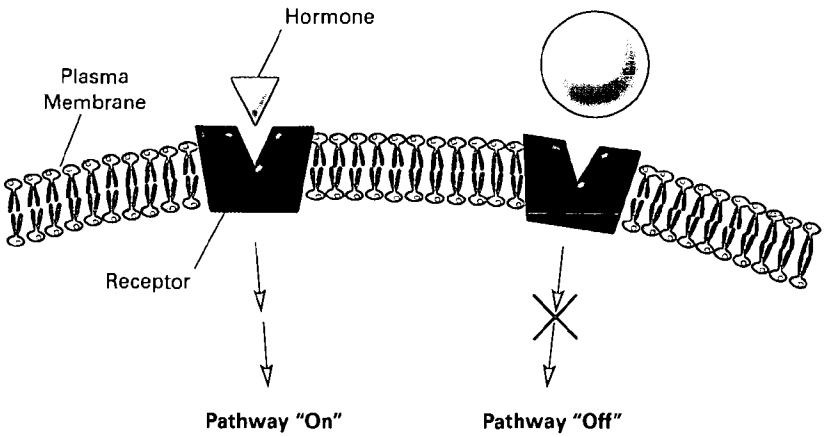
△ Two giant vesicles are about to fuse.

This Is Organic Chemistry?

A similar approach, being pursued by Fredric Menger of Emory University in Atlanta, is the design and production of "giant vesicles," which are sort of like artificial cells. Menger can make the vesicles—basically large, membrane-encased bubbles—about the same size as a cell, and with custom-made cellular properties. His innovative work is yet another example of how blurred the classic lines have become between chemistry and biology. Before Menger's graduate students can begin to study cell function—traditionally a biological pursuit—they must pass muster as expert synthetic organic chemists. Menger asserts that such a skill—the mastery of using chemistry to make from scratch a multitude of biological mimics—comes in very handy when asking questions about fundamental cellular processes.

For most of his vesicle experiments, Menger drops into water a greasy material (a lipid called DDAB, didodecyldimethylammonium bromide). Almost instantaneously, the oily liquid balls up,

pinching itself off into spheres. Though seemingly tiny, by a chemist's standards they are gargantuan—nearly the size of a cell (something easily seen with a standard light microscope). If you're going to use the vesicles to ask "cellular" questions, says Menger, it is essential to make the spheres approximately that size (so the angle of curvature of the "membrane" most closely resembles that of a cell). But the real advantage of making the lipid balls so big is that Menger can peer into a microscope and watch what they're doing—in real time—as he dumps other chemicals or hormones on them or subjects them to quick shifts in temperature. Menger hopes these unusual chemistry experiments will shed light on very biological problems, such as how tumor cells stick together, how severely disrupted membranes (such as in burns or wounds) heal themselves, and even how sperm fertilize eggs. And, since cell membranes are a common port of entry for a variety of drugs, the work may also lead to better drug delivery schemes.



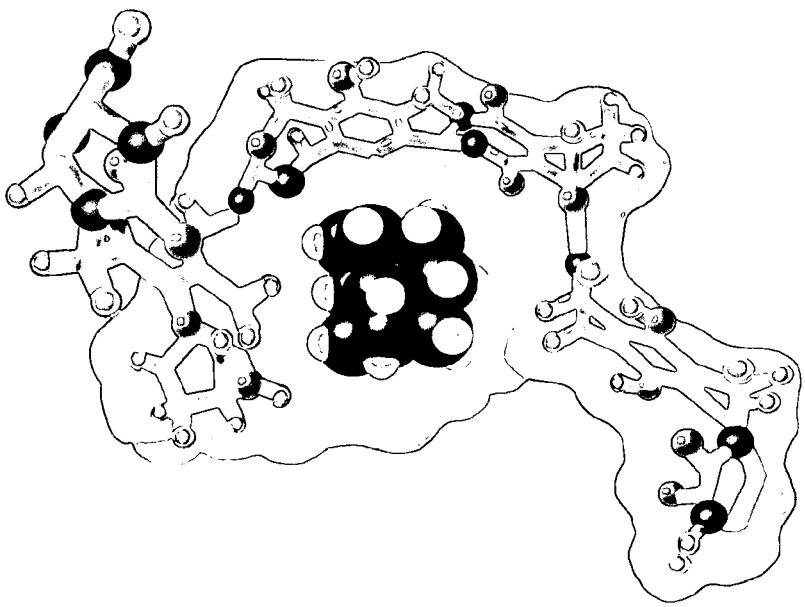
Who's Hosting This Party, Anyway?

Eons of natural selection have arranged perfect fits for biological teammates such as receptors and the proteins they recognize: enzymes and their substrates, for instance, or two twists of matching DNA strands. Starting from scratch in the laboratory, however, chemists must work hard to create an appropriate suitor for a known molecule or for a brand-new one that doesn't even exist in Nature. A field of research called "host-guest" chemistry aims to devise ways to study—and even create—interactions between two molecules (the host and the guest), mimicking or blocking some naturally occurring function. Often, the guests are known biological entities. One example might be a receptor for a hormone. In your body, such receptors are linked to other receptors through biochemical pathways, so activating one sets off an unstoppable cascade of reactions causing some physiological response, such as a change in your blood pressure. To interrupt such pathways—those revved up in heart disease or cancer, for instance—scientists are trying to develop synthetic hosts that can attach themselves tightly to their guest molecule and keep them from talking to other proteins (their real-life hosts). Such a strategy has the potential to trip up an entire signaling pathway. Chemists use computer models along with as much detailed knowledge as they can find about molecules' behaviors and shapes to custom-manufacture new molecular mimics.

A Room Without Much View

Mimicking cell parts to study chemical reactions in biological places is an important area of chemistry research today. In so doing, scientists can easily make ever-so-slight alterations that may not even exist in Nature and then test the physiological outcome of such changes. In addition to manufacturing cell-like components, some chemists have gotten into the business of creating tailor-made, sub-microscopic spaces for reactions to take place. Such spaces aren't very roomy, but they do provide a really snug fit for just a couple of molecules of a defined shape. Julius Rebek of the Scripps Research Institute is an expert at making such "molecular cages," which in some cases could make it easier for scientists to study biochemical reactions in the lab.

The clever thing is that Rebek spends little time constructing these molecular cages—they do it themselves. Rebek supplies the scaffolding—typically, enjoined rings of atoms that can be prepared from fairly uncomplicated chemical recipes. Then, chemical attractive forces "glue" the pieces of the cage together, in much the same way as the seams of a softball are stitched together. The cages are ideal reaction centers. Rebek traps other chemicals inside the cages, so these molecules are forced to touch each other and then react. As the reaction proceeds, the products are also trapped inside, and they can be extracted later. The process is a lot like what happens with enzyme-catalyzed reactions, in which the key job of the enzyme is in positioning the reacting chemicals side by side in close proximity. In addition to acting like enzymes, molecular cages—which can be formed repeatedly and reversibly—may find use as biological sensing devices, designed to detect only molecules that have a certain unique shape.

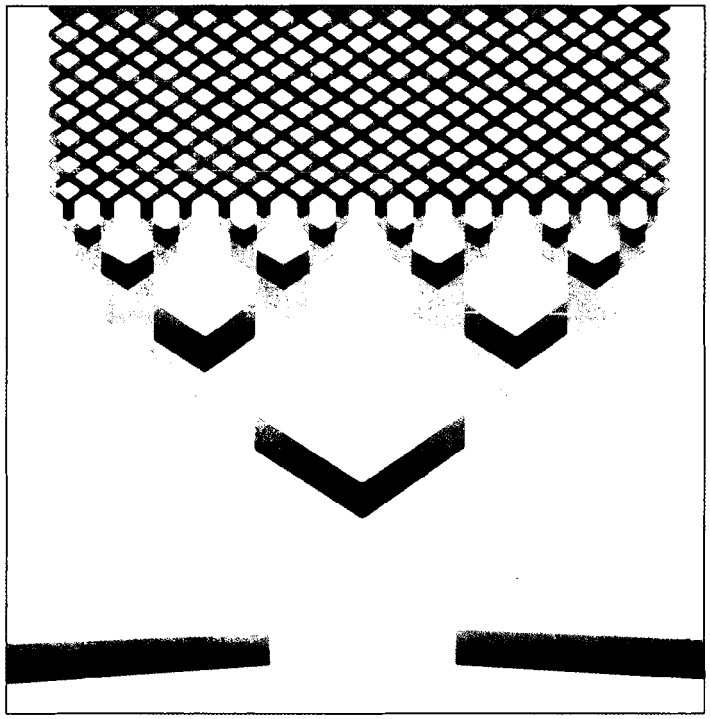


△ Two flaps of this "softball" molecular cage open up to expose a molecule called adamantane (in center) to other incoming reactants.

Reproduced with permission from Julius Rebek, Javier Santamaria, and Michael Pique (Scripps Research Institute)

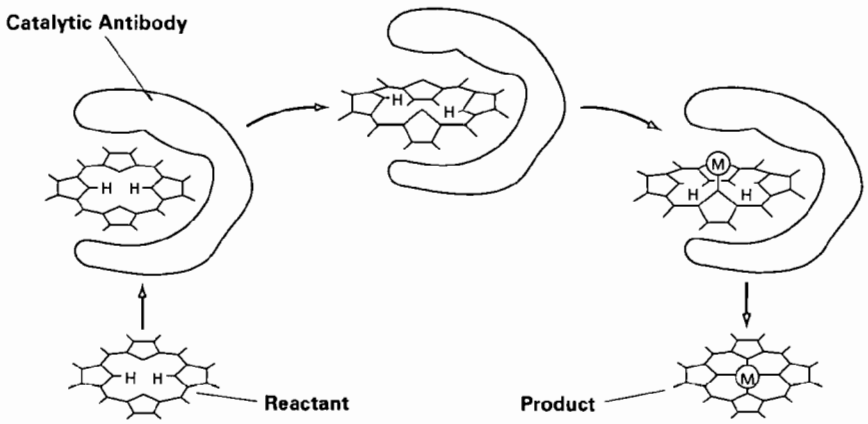
Pass the Chip, Please

But don't bother with the sour cream and onion dip. Because this isn't the potato variety, but rather the kind of chip that's made from silicon, plastic, and glass...the kind that fits easily between the tips of two fingers...the kind that contains a laboratory full of instruments! It's true—Purdue University chemist Fred Regnier has succeeded in creating such a "laboratory-on-a-chip" that contains expansive networks of miniature tubes and Lilliputian separation columns, all etched onto a dime-sized silicon wafer, via the same techniques used routinely to manufacture computer chips. Voltage applied to alternate ends of the chip channels a liquid sample throughout the tubing, where it then encounters various mini-instruments, such as dust particle-sized reaction vessels and single, hair-thin chromatography columns (chambers that separate components of a mixture). The tiny chip-labs use far less starting material, requiring a millionth the amount of liquid compared to typically sized instruments—a quantity that equates to just a fraction of a drop. And besides conserving workspace, the chips also save time by permitting several experiments to be conducted at once rather than separately. Such properties could someday also make this technology ideal for measuring multiple components of a solution—cholesterol, sugar, and electrolytes in blood, for instance—in a doctor's office.



Courtesy of Fred Regnier

△ This lab-on-a-chip contains an expansive network of miniature tubes and columns, each the size of a tiny fraction of a drop of water.



△ Catalytic antibodies can act like enzymes, converting reactants into products.

Adapted with permission from *Trends in Cell Biology* 1999, 9, M24-M28. Copyright 1999 Elsevier Science.

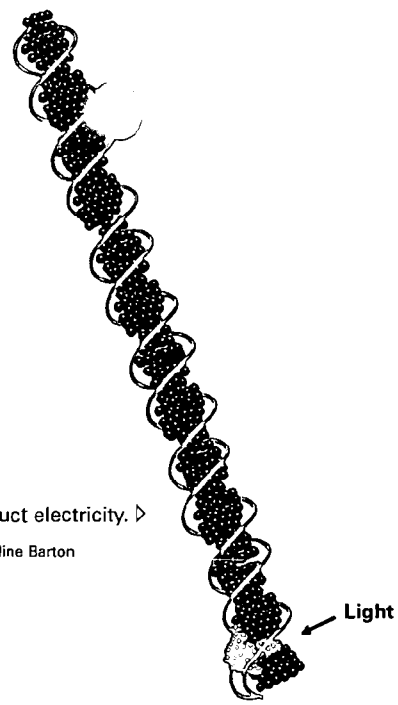
Hard-Working Antibodies

The first thing most people think of when they hear the word antibody is "something that floats around in my body and helps me fend off a cold or the flu." In your body, that's indeed the main task for antibodies. Tailor-made by your immune system, antibodies "heal" you by first identifying—then supervising the destruction of—the bugs that make you sick. Even better, the next time the same pesky molecule comes around, you have the antibodies on hand, just waiting to do away with it. Perhaps the most remarkable thing about antibodies is how versatile they are. Any foreign molecule, really, can touch off the production of a specific antibody that will match it. Tree pollen. Bacterially produced toxins. DNA. Stop for a minute and think how clever the immune system must be to have the capacity to whip up a perfectly targeted antibody for such a wide variety of different molecules with which we come into contact. Chemists have harnessed the extraordinary power of our antibody-producing immune systems to probe fundamental problems in chemistry. Antibodies, for example, have been prepared against molecular complexes that occur in the middle of a chemical reaction. Such complexes—what chemists call "transition states" are like a molecular snapshot of what happens during the most important part of a chemical reaction. So-called "catalytic antibodies" can be prepared that actually influence—by speeding up or even freezing in time—an interesting chemical reaction that a scientist wants to study.

Other scientists are developing similar chips to be used as drug delivery devices. Such a "pharmacy-on-a-chip," dreamed up by chemist/engineer Robert Langer of the Massachusetts Institute of Technology, is still in the development stages. Langer's chip—also a dime-sized wafer of silicon—has a few dozen tiny reservoirs carved into it. The "sample wells," as such reservoirs are called, hold a volume smaller than that of a salt grain. The wells are lined with a gold membrane and filled with various solutions (in the testing phase, the researchers poured in fluorescent compounds that would be easily detectable upon release). The reservoirs are then sealed off with glass. Langer and his co-workers formulate a solution that mimics body fluid (in terms of pH and electrolyte content), submerse the chip in this liquid, and rush electrical current across electrodes laced atop the wells. Then, chemistry happens! Gold particles team up with chloride molecules in the solution and form what chemists call a salt: a duo of alternately charged molecules. Result: The gold membrane well covering collapses and the well's contents—say, a drug—spill out into the solution.

The Many Faces of DNA

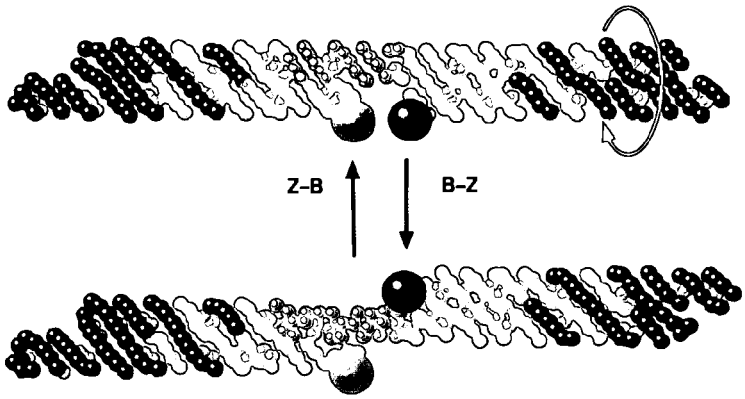
DNA — it's not just for heredity anymore. Deoxyribonucleic acid, whose primary function is passing on genes from parents to offspring, is at heart a collection of molecules—a *chemical.* Scientists are capitalizing on some of the unique features of this versatile substance, and in this way, DNA is acquiring a host of new uses. In the future, electronic devices wired with DNA have the potential to work faster and to fit into a tiny fraction of the space today's larger machines require. DNA-based mini-machines also promise to be extremely efficient, consuming less power and producing less heat than the equipment currently in routine use. Many properties of DNA—its size, structure, and the rules that govern how it is copied—may make it superior to current materials for a variety of purposes. Here's a sampling:



DNA can conduct electricity. ▷
Courtesy of Jacqueline Barton

Electrical Mini-Wires

Scientists have known for half a century that the DNA in our bodies—and in microbes, plants, and animals—has a special structure (called a double helix) that looks a lot like an upward spiraling staircase. The two halves of the staircase are complementary—they stick to each other much like the opposite strands of VELCRO®. Each "banister" of the staircase consists of ringed sugar molecules held together by chemical units called phosphate groups, and the "steps" in between are also flat—they are stacks of ringed molecules called nucleotides. These steps are the letters in the code of life, and make up each gene's alphabetical sequence. Because of the orderly arrangement of the whole thing, strands of DNA have defined electrical properties. Stacks of ringed molecules exhibit orderly displays of electrons and form what scientists have creatively dubbed "pi-ways." (So-called pi-orbitals are electron-occupied shells that hover above atoms and are particularly common surrounding the types of bonds in ringed molecules). Scientists have found that electrons can literally hop along these routes. Why would anybody care that DNA can conduct electricity? Damage to DNA, suspect scientists such as Jacqueline Barton of the California Institute of Technology, might be caused—or perhaps even fixed—by electron transfer through DNA. More practically speaking, DNA wires could be very useful components of miniature machines.



△ Rotation between two naturally occurring shapes of DNA (B and Z) causes this tiny robotic arm to move back and forth.

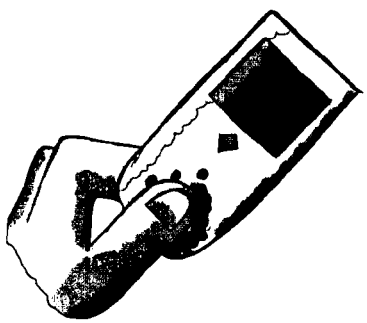
Courtesy of Nadrian Seeman

Mini-Robots

Some of the factories of the future will be far smaller than those of today. That's because such manufacturing plants will have on staff teeny robots, not humans, to perform routine and repetitive tasks. Nadrian Seeman of New York University has used laboratory-prepared strands of DNA to construct the first DNA-based nanomechanical device. (The prefix "nano" signifies one-billionth, so that an object that is 1 nanometer is one-billionth of a meter long). Seeman started with a synthetic DNA molecule he calls "DX" DNA, whose shape is very rigid. This property makes it an ideal robotic arm. Seeman used enzymes that link up the building blocks of DNA to fit together three different DNA pieces, each looped off at the end. The junctions of the mini-machine's parts are twists and turns that naturally occur in DNA. Seeman's tiny nanodevice is much too small to see, even with a microscope. So, as a means to measure the distances between the connecting DNA parts, and to be sure that the entire device is constructed as planned, Seeman labels each of the parts with a fluorescent tag and looks for telltale glows that occur when molecules are close together (or that don't occur when they are farther apart).

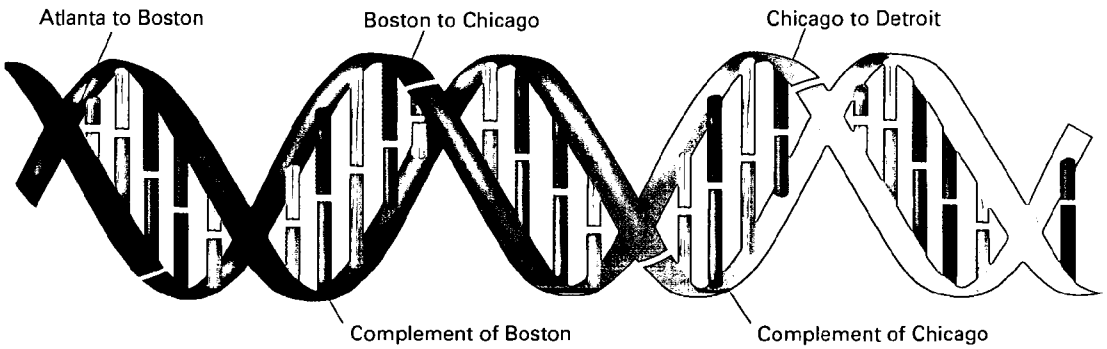
Biosensors

In the very near future, DNA will find use as a versatile material from which scientists can craft biosensors, devices that detect the presence of something biological—say, a minute amount of DNA in a virus—and then output a signal. DNA biosensors can theoretically be used for medical diagnostics (for instance, detecting a misspelling in a disease-causing gene), forensic science, agriculture, or even environmental clean-up efforts. A significant advantage of DNA-based sensing devices is that no external monitoring is needed. How do they work? DNA biosensors are complicated mini-machines—consisting of sensing elements ("probes" that match up in sequence with the DNA to be detected), microlasers, and a signal generator, all in one. At the heart of DNA biosensor function is the fact that two strands of DNA "stick" to each other by virtue of chemical attractive forces. On such a sensor, only an exact fit—that is, two strands that match up at every nucleotide position—gives rise to a fluorescent signal (a "glow") that is then transmitted to a signal generator. Ideally, the sensor would be a tiny square of a chip that could be immersed in a test fluid—blood, for instance—to pick up traces of disease-causing bacteria or viruses.



Computers

Scientists crafted the first prototype DNA computer in 1994. These tiny PC-wannabees aren't mainstream yet, but they may present technologists and biologists alike with a powerful tool for solving bewilderingly complicated problems. If you think about it, computers made of DNA make sense. Mother Nature picked DNA as the carrier of life for good reason. DNA is both stable and predictable—intact strands of the genetic material have been unearthed in specimens thousands of years old. A set of mathematical rules defines how DNA is transmitted across generations. And to top it off, DNA is self-replicating—it can copy itself! Take a famously hard-to-solve math problem called the "Hamiltonian Path Problem," in which given several points—cities, for instance—the goal is to find the shortest trip from the start city to the end city, but the rules state that you can only travel through each intervening city once. Seems easy, but conventional computers have a miserable time finding the answer, because the only way they know how to solve the problem is to try all the possibilities, one by one. In fact, with 100 or so cities, a supercomputer is needed, and with 1,000 cities, no existing computer can solve this problem! DNA-based computers, on the other hand, would find such a problem a breeze, since they could test all the possibilities at once, in parallel. How might they do that? Scientists made "cities" out of synthetic strands of DNA that they made in the lab (much like a gene, each DNA-city had a different combination of the four different nucleotides). Next, the researchers made connector strands. The lengths of these connectors, which linked the end of each DNA-city with the start of another (several cities could be hooked together in this way), were sized according to the distance between the cities. The scientists then mixed everything together, and all of the matching DNA-cities came together in all possible combinations. Voila! The shortest string of DNA to come out is the answer to the problem.



△ A DNA computer can solve extremely difficult math problems.
Adapted with permission from Tomo Narashima

Life on the Edge

Life on the edge can be most interesting. To chemist Barbara Imperiali of the Massachusetts Institute of Technology, the borderline between chemistry and biology is indeed an intellectually challenging frontier, and one likely to deliver significant gains in human health. Using a chemistry toolkit, Imperiali is one of many of today's chemists seeking to solve biological mysteries. One problem Imperiali has chosen to tackle is how certain sugar-studded proteins get around compartmentalized cells (those—like human cells—that contain a nucleus and other organelles) which, she describes, "have a need for serious traffic control!" Imperiali focuses on cell pathways responsible for tacking sugars onto proteins, and on those proteins themselves. Using innovative design strategies, she's developing "artificial proteins" from building blocks not used by Mother Nature. She's also pushing the limits of technology in developing exquisitely sensitive biosensors that can detect trace amounts of metals in biological fluids. *The Chemistry of Health* asked her what kinds of tools she needs to make these sorts of experiments possible.

CH: What are some of the most exciting technologies at the chemistry-biology interface?

Imperiali: There isn't really any single technique that stands out. Technology has been making enormous leaps and bounds in the last two to three decades. We're in a position now to bring all the tools together to investigate complex biological systems in great detail.

CH: What technologies are indispensable for the kind of work you do?

Imperiali: NMR (nuclear magnetic resonance) spectroscopy, for sure. This is a technique for looking at the structure and movement of molecules in a water-based solution. It's one way we test if the proteins we've designed actually do what we think they do. NMR is also very valuable in medicine these days, where it's known as MRI and is being used to image whole people.

No one in my family was a scientist.
I just found it fascinating.
I liked biology,
but I loved the precision
that chemistry can offer.

Another great method is fluorescence, a technology that's extremely sensitive in detecting vanishingly small amounts of biological samples and can even be used to follow proteins around inside living cells!

Another fantastic technique is mass spectrometry. With "mass spec," as it's called, we can instantly determine the composition of tiny amounts of sample—with other methods, 10,000 times as much material might be required to analyze some samples.

CH: How are chemistry labs different today from 10 or 20 years ago?

Imperiali: When I was a graduate student, a desk, a bench, and a chemical hood was "my territory." Now, students have a desk, but they move around the lab to different stations to do their experiments. There's also a lot more intermixing of labs. That happens a lot—it's absolutely the thing to do when you're trying to tackle interdisciplinary problems.

CH: What got you interested in science to begin with?

Imperiali: No one in my family was a scientist. I just found it fascinating. I liked biology, but I loved the precision that chemistry can offer. I was excited about looking at individual molecules and understanding biological function, molecule by molecule.

CH: Would you advise a young person interested in science to pursue a chemistry research career?

Imperiali: Absolutely, but I also tell them that they should choose something that they really enjoy. Otherwise, it won't be worth it. I try to tell them to learn how to think rather than to learn a specific skill.

Got It?

How do molecular cages resemble enzymes?

Give three examples of how scientists are using miniature biological chips in research today.

List a few examples of model organisms.

How do researchers use host-guest chemistry to study biology?

Discuss why it is important for chemists to work together with biologists, physicists, and other types of scientists.

CHAPTER 5

The Healing Power of Chemistry

That medicine came from *where?* Scientists are hunting in some very unusual—indeed, some even downright unpleasant—places for new drugs. Take chemist Jim Gloer of the University of Iowa, who is on the prowl for new antibiotics produced by a type of fungus that thrives in animal dung. Yes, you heard it right: animal poop. These unenviable organisms, called coprophiles—literally, "feces-loving"—are a rarely studied microbial breed, but offer tremendous promise for finding useful drugs. Oddly enough, such fungi are fiercely territorial, spitting out chemicals that are toxic to neighboring (and thereby competing) species of fungi. That is precisely what biomedical researchers look for—chemicals that will poison bothersome types of fungi that can be deadly in people infected with them.

That's an important goal. Due in part to the disease and part to the treatment, illnesses like AIDS and cancer often set the stage for the body to become overwhelmingly infected by microbes that otherwise would be rejected at the door. Such "opportunistic" infections are most often caused by just a few notorious types of fungi. Unfortunately, not many drugs are currently available to thwart these microbial menaces without causing severe side effects. A key advantage of Gloer's strategy is that his approach to finding anti-fungus compounds isn't a random one (as many antimicrobial drug screens typically are). By selecting compounds that he already knows can eradicate other fungi, Gloer is starting with a batch of molecules that all possess exactly the type of cell-killing activity he's looking for.

Russell Barrow

△ Fungus is alive and well in possum dung.

Looking to Sea

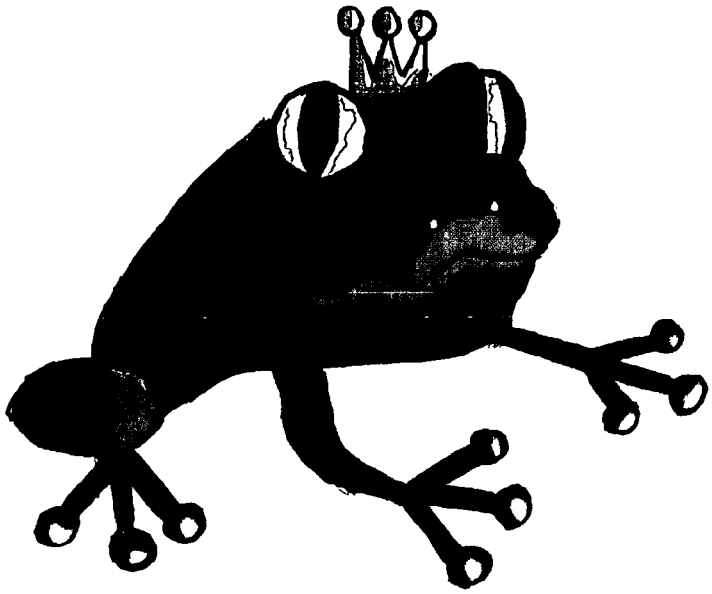
The vast, largely unexplored seas are another promising source for medicines. Scientists are plumbing the oceans' depths to discover novel molecules in organisms such as marine sponges, snails, and a wealth of other sea-worthy creatures. It may seem surprising that, in general, fast swimmers and successful predators are not what the researchers are after. On the contrary, scientists have come to appreciate the extraordinary chemical richness lying in wait inside the tastiest, most brightly colored "couch potatoes" of the seas—the so-called filter feeders that stick to rocks and coral. Precisely because they can't move—or because they stand out in a crowd due to their surface coloring—these animals are sophisticated chemistry labs. For protection, and to compete for food and other resources, such animals engage in chemical warfare day in and day out. Scientists have discovered that some of these potent chemicals show tremendous promise for treating cancer and other diseases. Certain

compounds have passed initial muster—showing promise in test-tube and animal studies—and have now progressed to clinical trials in humans. But while there are many promising could-be medicines out yonder in the world's oceans, an imposing obstacle is getting enough of them. Researchers are finding one way around this dilemma by devising ways to make the compounds in their labs, but there are significant obstacles to efficiently synthesizing usable quantities of many of these chemicals. Aquaculture (water "farming") is an innovative strategy coming into practice, in which researchers cultivate in small, specialized ponds large amounts of the organisms that produce compounds that exist in vanishingly small quantities in Nature.

It so happens that marine organisms harbor another hidden resource when it comes to finding potential drugs. Looking more closely, chemists are discovering that tiny, one-celled sea plants called microalgae that hitch a ride on larger marine organisms are also great producers of interesting chemicals. Terrestrial plants have been a source for drugs for thousands of years, so perhaps it shouldn't come as a big surprise that sea plants are turning up compounds with exciting potential uses as drugs to fight cancer, heart disease, and many types of infections. Miniature plant-like organisms called cyanobacteria that live in a variety of wet environments—fresh or salt water, or even damp soil—are also surfacing as excellent sources of powerful cancer and bacterial cell killers. Dick Moore of the University of Hawaii at Manoa has successfully used a strategy to sleuth compounds specifically effective against slow-gowing and hard-to-treat "solid" tumors (those that accumulate as lumps of tumor cells in various organs and account for most cancer deaths in the United States). One such compound he has found, called cryptophycin-8, can tear apart the cellular scaffolding in a broad spectrum of solid tumors implanted in mice, including "multidrug resistant" ones that are no longer susceptible to standard cancer drugs. Moore has found another cyanobacteria-derived molecule, called majusculamide C, that works in a similar fashion but hones in on fungus cells, making it potentially useful for treating fungus-provoked diseases in humans as well as in agricultural crops.

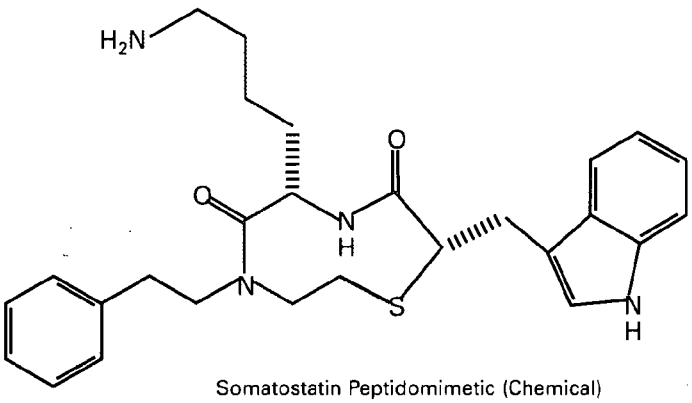
By land or by sea, tradition has it that chemists first find interesting Nature-made chemicals that show promise in fighting disease, then the scientists

learn how to make them synthetically. Ultimately, many of the best drugs have been born of medicinal chemists' fiddling with natural compounds in order to retain useful, therapeutic portions of the molecules, while stripping away parts that cause unwanted side effects.

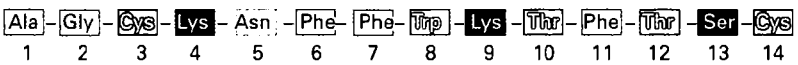


A Princely Role

Everyone knows that frogs don't really turn into princes, but scientists suspect that frog skin might turn into useful medicines. In the late 1980s, while working in a lab at the National Institutes of Health in Bethesda, Maryland, biologist Michael Zasloff wondered why frogs with surgical wounds usually healed perfectly without getting infections, despite living in a relatively dirty lab aquarium. Zasloff turned his attention to this quizzical observation and went on to isolate a peptide—a string of amino acids—called magainin (coined after the Hebrew word for shield) that frogs produce in response to skin injury. Intrigued by the finding, Zasloff went on to found a company called Magainin Pharmaceuticals, Inc. in Plymouth Meeting, Pennsylvania that investigates the potential medicinal value that may be lurking in the skin of amphibians and other animals big and small. Zasloff is quick to note that nobody has a clue how a giant squid or an octopus—which have neither antibodies nor white blood cells called lymphocytes—avoids becoming consumed by microbes! Over the years, he and his colleagues have uncovered many frog-made peptides that possess potent microbe-killing properties. Such a chemical defense system operates by virtue of the peptides' ability to poke holes in the cell membranes that serve to protect bacteria from the outside world. In addition to the peptides, scientists including Zasloff have found hundreds of other types of molecules called alkaloids in amphibian skin. When inside cells, many alkaloids home in on structures called ion channels—tunnel-like assemblies through which important electrolytes pass. These are key cellular fixtures, as they police the entry and exit of charged molecules across cellular membranes. As such, they also happen to be important drug targets. Some channels, for instance, initiate a cascade of molecular events that tell the cell to "feel" pain. Researchers have discovered that one particular molecule isolated from frog skin, called epibatidine, shows powerful painkilling activity in animal models, possibly due to the compound's ability to latch onto such channels. Interestingly, scientists think that many of the alkaloid "drugs" in frog skin come from the bug meals they eat—spiders and other arthropods in particular.



Somatostatin Peptidomimetic (Chemical)



Somatostatin Peptide (Hormone)

◁ Peptidomimetics (top) are chemical substitutes for hormones, such as the 14-amino acid peptide hormone somatostatin (bottom).

Making Medicines

A key role played by chemists is learning how to mimic effectively Nature's bountiful manufacturing processes. Once in a while, such a strategy—when it pans out—can tell a story of "research-to-riches." Robert Holton, an organic chemist at Florida State University, discovered a way to produce commercially useful amounts of Taxol®, the number-one selling cancer drug worldwide. This drug, which doctors use (often in combination with other cancer drugs) to treat

Acts Like a Protein, But It's Not

Designing drugs is a tricky business. Lots of could-be medicines look good on paper, but a drug can only do its intended job of treating a symptom or fighting a disease if it gets to the right place in the body to do its job. That's tough, since many modern medicines are look-alike versions of the body's natural molecules—small pieces of proteins called peptides that are meant to nestle into other protein targets like receptors. The problem is that the body's digestive tract chews up proteins, and peptides, as a normal part of metabolism (getting energy from food). So what's a medicine designer to do? Many have opted to seek out molecules called "peptidomimetics," which possess many of the useful properties of peptides (in that they mimic important biologic targets) but differ from peptides in other significant ways. Medicinal chemists in the business of designing drugs try to make mimics that are absorbed into the body, stand up to digestive enzymes, and stick around long enough in the bloodstream to get to the tissues and organs where they need to go. Drugs such as these are already used in clinical practice to treat infections, heart disease, and cancer. A key factor in making the look-alikes useful, however, is tricking the body into thinking they're natural molecules, and not drugs. That's important, because to get to their molecular "job sites," peptidomimetic drugs often hitch a ride via the body's natural molecular transportation systems.

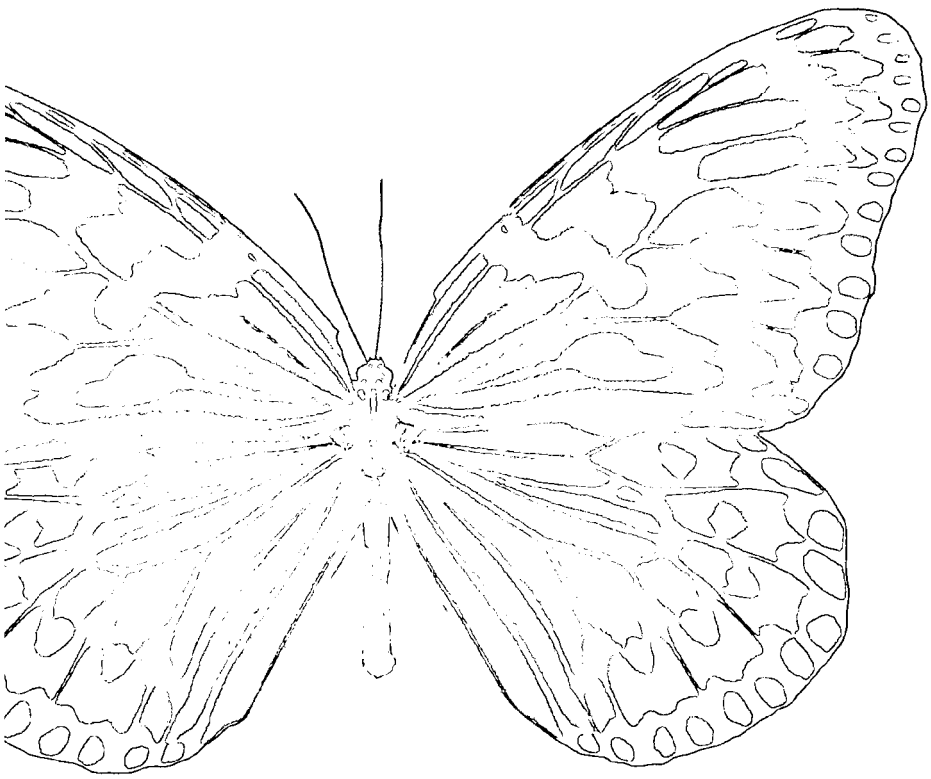
ovarian and breast cancer, was first discovered in the 1960s. Scientists found Taxol in the bark of the Pacific yew tree, which grows in the Northwestern United States. But there was a problem. The Pacific yew is a slow-growing, environmentally threatened species. Holton helped pave the way to Taxol's current success with a practical approach: He figured out a way to make the drug from a more readily available ingredient that is abundant in the more plentiful European yew tree. Holton licensed his "semi-synthetic" technology to the pharmaceutical company Bristol-Myers Squibb, and since 1992, when the FDA approved the lab-made form of Taxol, Holton has earned more than $50 million in royalties. A few years later, he went on to lead the first group of scientists to make Taxol completely from scratch—a process that's not yet commercially viable. Rather than resting on his laurels, Holton poured many of his rewards straight back into research by founding the MDS Research Foundation in 1995. In turn, this nonprofit organization licensed Holton's technology from Florida State University and started a company called Taxolog to create new Taxol-like molecules (called taxanes) that are more effective at treating cancer. Through such an arrangement, profits from new anti-tumor agents will be recycled back into basic research in synthetic chemistry.

CHEMICAL BIOLOGY
in Action

Library Research Pays Off

Chemists Gary Glick and Jonathan Ellman never intended to work on the same problem, but now they do, and the collaboration is paying off impressively. Two clever minds can be better than one—out of these scientists' partnership has emerged at least one promising new drug to treat a devastating autoimmune disease called systemic lupus erythematosus, often called "lupus" for short. According to the Lupus Foundation of America, this disease affects up to 2 million Americans, some of whom bear a characteristic rash across the bridge of their nose dubbed the "butterfly rash," because of its shape. Lupus ravages the body's immune system by coaxing the kidneys to attack their own DNA. Current treatments are ineffective and have serious, use-limiting side effects. Glick and Ellman sought to identify a drug to treat lupus by harnessing the power of combinatorial chemistry to rapidly leaf through thousands of molecules. The team started with a huge catalog of molecular structures and searched for compounds that could kill the cells responsible for causing lupus (the so-called autoimmune lymphocytes), while sparing normal immune cells. This type of drug discovery effort is only possible with the advent of combinatorial chemistry, because very large numbers of compounds (libraries) have to be tested before scientists can pluck out molecules with the desired properties. Glick and Ellman's search led

them to one interesting candidate molecule that stops lupus in mice prone to developing the disease. An especially exciting feature of the newfound molecule is that after the lupus-prone mice take it, they suffer none of the serious side effects common to all current anti-lupus drugs on the market. Glick and Ellman are setting out to test the compound in humans.



Getting It Left or Getting It Right?

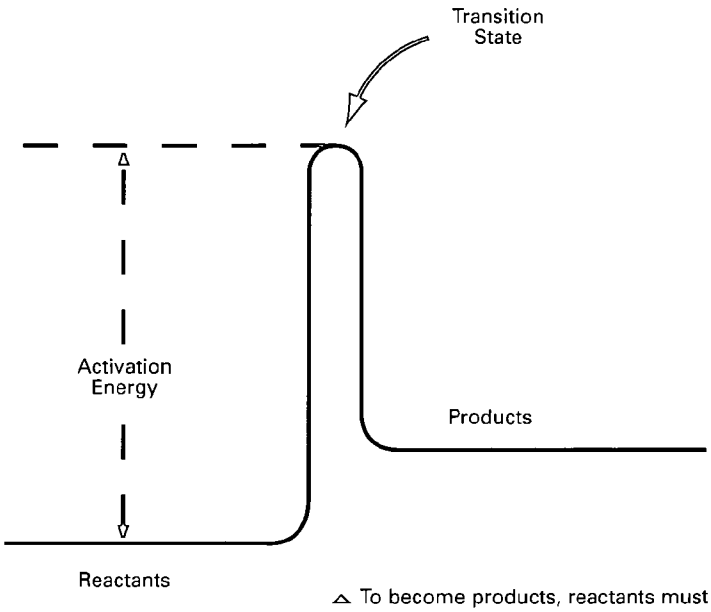
Making chemicals in the lab isn't quite the same thing as cooking up a pot of spaghetti, in which you simply boil the pasta, heat up the sauce, and voila! It's not so easy to make molecules from a laboratory recipe. The thing is, many small molecules—created by scientists or by Nature—come in two, mirror-image forms, a "left" and a "right." The molecules that make up sugars and DNA conform to this principle, called "chirality," which is actually rooted in the laws of physics. Chemical bonds—the physical forces that attract or repel atoms in molecules—rotate in space two ways, giving rise to two complementary, mirror-image molecular forms. These are sort of like a left hand and a right hand—put them together and they match up, but they'll never align when placed atop each other. Put another way, a right hand will never fit into a left-handed glove.

Why should any of this matter when it comes to drugs? Well—take the case of a small-molecule drug that does its job in the body by nestling snugly into a particular cavity of a certain protein receptor. The left-handed version of this drug might fit perfectly into the correct space inside the receptor, whereas its right-handed counterpart

couldn't squeeze in, no matter what. And in some instances, both "hands" of a drug (each called an "enantiomer") fit into a biological spot, but one might help treat a symptom while the other causes the body harm!

A terrible tragedy occurred when this happened with a drug called thalidomide, which was used in the 1960s to treat morning sickness in pregnant women. Scientists found out too late that one of thalidomide's two hands caused horrific birth defects. What's more, researchers discovered that removing the "bad" hand from a dose of thalidomide didn't take care of the problem—the body can itself make the harmful hand from the "good" one.

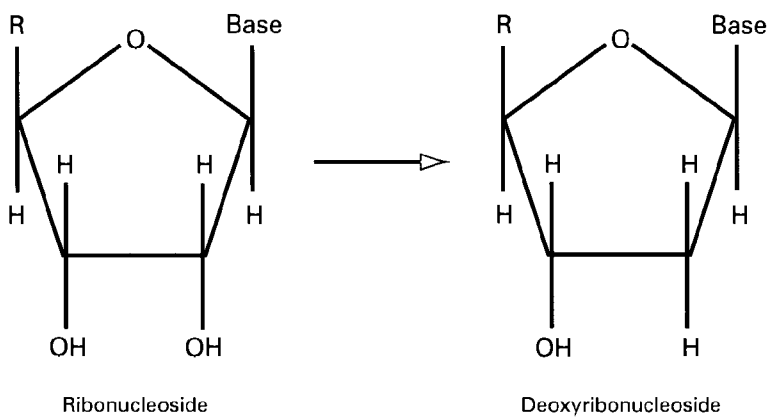
Another two-faced drug in this regard was a popular allergy medicine called Seldane®, which the Food and Drug Administration removed from the market in 1997 because in combination with a certain antibiotic it caused life-threatening heart rhythm problems. Scientists determined that neither enantiomer of a breakdown product of Seldane—now marketed as a medicine called Allegra®—interacts the same way with the antibiotic, and Allegra is now used by millions of Americans.



△ To become products, reactants must overcome an energy hill.

In the Middle

When thinking about chemical reactions, it's tempting to focus on two things only: what goes in (the starting materials, or reactants) and what comes out (the product or products). Sometimes left out is all the exciting stuff that happens in the middle. Think of a chemical reaction as being like two valleys with a mountain in the middle. To become products (one valley), reactants (the other valley) must overcome something chemists call the "energy of activation," or energy hill. In this mountain range analogy, the energy hill is the highest point of the peak between the two valleys. In molecular terms, this point in space and time is called the transition state, and it represents a freeze-frame arrangement of bonds broken or enjoined, which only lasts one thousand-billionth of a second. In a sense, the transition state is the precise point at which a seesaw tips over to the other side. Despite their fleeting existence, transition states are highly sought after by chemists who wish to purposefully alter reactions one way or another by knowing the details of this pivotal micro-moment.



△ By removing an oxygen (O), the enzyme ribonucleotide reductase creates deoxyribonucleosides, the building blocks of DNA.

To manufacture products quickly and cost-effectively, traditionally pharmaceutical companies have chemically cooked up medicines that contain equal portions of the left and right hands. That is because it is usually much less efficient and more expensive to produce only one hand of a drug. Over time, however, chemists in industry and elsewhere have come to realize the importance of making single-handed compounds. There are those especially troubling cases in which one enantiomer is toxic. But in the vast majority of cases, most drugs produced as left- and right-handed mixtures are only half as strong as they could be, because one hand does nothing more than dilute

A Dead-End Job

For more than 20 years, chemist JoAnne Stubbe of the Massachusetts Institute of Technology has been picking apart every step of one biochemical pathway vital to synthesizing the building blocks of DNA. In particular, she has focused her energies on an important enzyme in this pathway, called ribonucleotide reductase or "RNR." In the course of her studies, Stubbe has sleuthed the way RNR grabs its substrate—arming her with strategic knowledge she has used to design look-alike molecules that fit into the enzyme's shape, but don't make it work. Compounds such as these, called "suicide substrates," completely freeze up the enzyme they're targeting. They trick the enzyme into thinking that it is doing its job, but in fact no job gets done. Cancer cells—which divide as fast as they can—are super-synthesizers of DNA, and are crippled by any drug that interferes with this process. Stubbe and her industry colleagues have shepherded one such RNR suicide substrate through test-tube and animal studies, and into testing in people. Clinical trials with this potential cancer drug are currently under way in the United States and Japan.

the medicine produced. Chemist Eric Jacobsen of Harvard University spent years perfecting a laboratory tool—a "chiral catalyst"—that can purposefully produce one and only one enantiomer of a particular type of molecule, eliminating the waste inherent in the process of making a left- and right-handed mix, or in separating the two enantiomers from each other after manufacturing. The pharmaceutical company Merck recognized the value of Jacobsen's tool and has used it successfully for the production of a widely used AIDS drug called Crixivan®. Other scientists, such as K. Barry Sharpless of the Scripps Research Institute, have tailor-made chemical reactions that produce a single enantiomer. The method is sort of like stripping the "random" part out of a coin toss so that the quarter always comes up heads. Sharpless' reactions, which give rise to one-handed chemical intermediates, have been important for the production of a variety of medically useful chemicals, including certain antibiotics, heart medicines, and antidepressants.

By paying more attention to getting it "right" (or "left," as the case may be) today's chemists have enormous opportunity for improving existing medicines—by eliminating dose-related side effects, for instance—as well as for streamlining the process of making the most effective new medicines.

Losing Medicines

Finding or making effective new drugs is a challenge in and of itself. But complicating matters further, sometimes perfectly good drugs simply stop working. More often than not, these are antibiotics—drugs used to treat bacterial or fungal infections. It is true that major strides have been made in the past century in scientists' quest to treat infectious diseases caused by bacteria, viruses, and other microbes such as parasites. Humans' increased lifespan during the past hundred years is due largely to the fact that we succumb to infection far less frequently today than people did 50 or 100 years ago. But this success has come with a price—many antibiotic drugs that once stamped out bacteria effortlessly now work much less effectively, if at all. In the blip of evolutionary time in which such advances have been made and put into routine medical practice, microbes are making a comeback. They are getting "smart" and devising ways to evade poisons (our drugs). Drug-resistant organisms pose a serious health threat.

Fortunately, many chemists and biologists have risen to the occasion and are working hard to outwit microbes that develop resistance. Many new forms of antibiotic drugs are currently in the pipeline; most are being specifically tailored to minimize the chance that bacteria will become resistant to them.

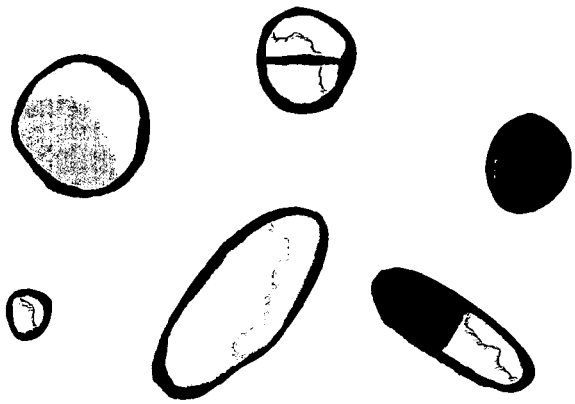
CHEMICAL BIOLOGY
in Action

The Shape of Things to Come

One of the beauties of science is sharing the wealth. Sometimes a collision of discoveries in completely different areas of science gives birth to important breakthroughs. By blending advances from the worlds of chiral (so-called "handed") chemistry and structural biology (in which scientists determine the three-dimensional shape of biological molecules), Arun Ghosh of the University of Illinois at Chicago has unearthed some promising potential drugs to fight AIDS. Ghosh and his colleagues pored over the results of other scientists studying the three-dimensional structure of an enzyme, called HIV protease, that is key to this deadly virus' livelihood. By using K. Barry Sharpless' method to fix the outcome of chemical reactions to produce "single-handed" molecules, Ghosh painstakingly designed sturdy compounds that attach themselves very tightly to an important pocket of this critical viral protein. In so doing, Ghosh landed a battery of potential drugs that in some cases are 50 times more potent than widely used protease inhibitor drugs that are a standard component of AIDS therapy in people. Ghosh has custom-designed new compounds, which are currently undergoing testing in animals, to overcome two soft spots inherent to HIV protease inhibitors currently on the market. Since the body's digestive enzymes easily chew up the chemical bonds that hold proteins together (so-called peptide bonds), Ghosh has focused on molecules that look like mini-proteins but aren't recognized as such by enzymes that break down proteins. Ghosh is attacking the resistance problem by crafting compounds that grip the HIV virus' protease enzyme in many different regions, since scientists suspect that drug resistance is often triggered by a critical lack of chemical bonds clamping the viral protease to a drug.

Making Good Medicines Better

Acetylsalicylic acid—more commonly known as aspirin—is a very old drug. It is also a very effective drug, available without a presciption for a wide variety of uses. Aspirin is an inexpensive medicine used to treat pain and swelling caused by minor skin wounds or sunburns, and as a protectant against heart disease. Yet despite its reputation as a "wonder drug," scientists still don't know exactly how aspirin works so well in so many ways. Charles Serhan of Brigham and Women's Hospital in Boston is one biological chemist who is trying to figure aspirin out. Aspirin isn't a complete black box—scientists already know that the drug works to alleviate pain by blocking biochemical circuits that produce two of the body's natural compounds, called prostaglandins and thromboxanes. Based on this, many researchers have assumed that aspirin's knack for halting inflammation—the painful irritation and swelling that are born of our own immune system's chemical weaponry—is caused by the drug working through that same biochemical pathway. Serhan's work sheds new light on the issue and may even lead the way to better anti-inflammatory medicines. After he discovered that aspirin treats inflammation by prompting the body to manufacture its own anti-inflammatory compound (a molecule called 15-epi-lipoxin A4), Serhan set about to make synthetic look-alikes of this molecule. In recent animal studies, at least one of the synthetic mimics worked 100 times better than aspirin and other stronger anti-inflammatory medicines available by prescription only. Serhan's research paves the way toward finding more selective treatment strategies that bring about less of the unwanted side effects produced by aspirin and many other drugs currently used to treat inflammation.



Medicines Just for You

Your diet, environment, and lifestyle can all influence how you respond to medicines. But another key factor is your genes. The study of how people respond differently to medicines due to their genetic inheritance is called "pharmacogenetics." The term has been pieced together from the words pharmacology (the study of how drugs work in the body) and genetics (the study of how traits are inherited). An ultimate goal of this type of medical research is to understand how a person's unique genetic make-up determines how well a medicine works in his or her body, as well as what side effects he or she might be prone to developing. In the future, advances discovered through such research will provide information to guide doctors in getting the right amount of the right medicine to a person—the practice of "personalized medicine."

Tools for New Medicines

Robert Grubbs, a chemist at the California Institute of Technology, is changing the way people make things. All kinds of things—bike helmets, corrosion-resistant pipes...and medicines! Grubbs introduced a new twist to a brand of chemistry called "olefin metathesis" that underlies the production of a wide variety of materials. Reactions that use this chemistry hinge on one key element to pull off such a feat: an extremely versatile catalyst that uses a metal called ruthenium. As molecules that make reactions happen, catalysts are vital drivers of the chemical transformations that produce the things we use and the drugs we take. Grubbs' catalyst is currently being used to manufacture a wide assortment of things biological, and promises to be a big help to pharmaceutical industry chemists, who are faced with the task of synthesizing complicated chemical structures day in and day out. *The Chemistry of Health* asked Grubbs to fill in some of the details.

CH: How can the same chemical process produce bullet-proof vests, insect repellents, and medicines?

Grubbs: The ruthenium catalyst we've developed opens up carbon-carbon double bonds and then attaches the pieces back together—in predictable, or even novel, ways. Essentially, the catalyst zips together chains of molecules into rings, which are a common component of all kinds of materials. But it also works to unzip the rings. It's very useful because there are double bonds everywhere.

CH: Why did the chemistry community need a new catalyst?

Grubbs: The old catalysts didn't allow you to do things very efficiently, and required chemists to use protecting groups. Metals such as ruthenium give chemists the flexibility to make things with a wide variety of starting materials, and under many different conditions. It just makes everything easier.

Originally I wanted to be an agricultural chemist,

but dealing with all the animal matter

wasn't much fun.

Organic chemistry

was something I discovered I liked to do.

CH: Did you set about to find the catalyst?

Grubbs: No, although it was always a dream of mine. It's funny—15 years ago, I was asked to give a talk predicting the future in this area of chemistry. I argued—strongly at the time—that recommending support for such research shouldn't be in the report, since it would be so misleading to the community. I've been surprised that it's worked out so well.

CH: What first got you interested in science?

Grubbs: I suppose a science teacher in junior high. But things have changed somewhat. Originally I wanted to be an agricultural chemist, but dealing with all the animal matter wasn't much fun. Organic chemistry was something I discovered I liked to do.

CH: What keeps you coming back to the lab every day?

Grubbs: I keep getting surprised all the time.

Got It?

What is the function of a chiral catalyst?

How might synthetic chemistry practices help the environment?

Describe the difference between peptides and peptidomimetics.

Name one reason why filter-feeding marine organisms secrete chemicals into the water.

Discuss some of the possible advantages and disadvantages of personalized medicine.

Chemistry for the Future

As chemists, biologists, physicists, and other scientists continue to unveil Nature's secrets, a flood of facts accumulates with stunning momentum. Each answer is a new beginning—fodder for new experiments. Many researchers assert that there's never been a more exciting time to be a scientist. After much effort was spent in the last century finding individual puzzle pieces, scientists can now revel in the process of fitting the pieces together.

Not that everything's been figured out—not by a long shot. The science of today beckons researchers to think big—to integrate singular items, and even single pathways—into the grander scheme of what it is that makes entire organisms tick with such precision.

Perhaps ironically, as science grows larger in scope and broader in focus, some of the most promising tools to synthesize the hows, whats, and wheres of human biology are exceedingly tiny. Micromachines, tiny biosensors, and miniature molecular reaction vessels will undoubtedly be standard items in a chemist's toolbox in 10 or 20 years.

Unravelling—and making sense of—the genetic instructions that spell life for organisms as diverse as flies, plants, worms, and people has sparked a most exciting revolution. Every minute of every day, scientists all over the world work feverishly, weaving a compelling tale of the chemistry that underlies our health.

It's all very exciting, but the progress mandates still more work. Much more work!

Among the questions still awaiting answers are these:

- How do the 6-foot long stretches of DNA in every cell in our bodies know how to keep our biochemical factories running smoothly?
- Who will find a way to outwit resistant bacteria?
- When will someone figure out how to fight disease by manipulating the intricate sugar coatings on our cells?
- Who will invent the tools that will revolutionize chemistry labs of the future?
- What unexpected places hold treasure troves for new medicines?

Curious minds of the future will sleuth these and other problems and change the world. Will one of those minds be yours?

Glossary

Alkaloids | A class of over 3,000 nitrogen-containing chemicals (such as caffeine and cocaine) that are produced by plants but have effects in humans and animals.

Amino acids | A class of 20 chemical units that are the building blocks of peptides and proteins.

Amylase | An enzyme found in saliva that breaks down starch into simple sugars.

Anabolic | A type of reaction or series of reactions in which complex molecules are synthesized from simpler ones; the opposite of catabolic.

Aquaculture | The underwater cultivation of animals and plants for food or for other purposes.

-ase | A suffix common to many, but not all, enzymes.

Atom | The smallest particle of matter that maintains the property of an element in the periodic table; atoms are composed of subatomic particles called electrons, neutrons, and protons, which themselves are composed of even tinier subatomic particles such as quarks.

ATP | Adenosine triphosphate; the energy currency of metabolism in all organisms.

ATP synthase | An enzyme in mitochondria that produces ATP by adding a phosphate group to the molecule ADP.

Base | A nitrogen-containing building block of DNA; the two types are the purines adenine (A) and guanine (G), and the pyrimidines thymine (T) and cytosine (C).

Bi- | A prefix meaning two.

Biochemistry | The scientific study of the chemistry of living cells, tissues, organs, and organisms.

Biochip | An electronic device containing organic materials.

Biopolymer | In a living organism, any large molecule (such as a protein, nucleic acid, lipid, or polysaccharide) made from smaller parts.

Biosensor | A system or device that detects a chemical or chemicals in a biological material.

Biotechnology | The industrial use of living organisms or biological methods derived through basic research; examples range from genetic engineering to making cheese or bread.

Bond | Physical forces holding together two atoms in a molecule.

Carbohydrate | A chemical compound made up of a chain or ring of carbon atoms to which hydrogen and oxygen atoms are attached in a defined ratio (2:1); includes simple sugars like glucose and complex sugars like chitin (the exoskeleton of crabs).

Carbohydrate biology | A branch of chemistry dedicated to the study of the many types of carbohydrate molecules.

Catabolic | A type of reaction or series of reactions in which complex molecules are broken down into simpler ones; the opposite of anabolic.

Catalyst | A substance that speeds up a chemical or biochemical reaction that would have occurred anyway (without help), but at a much slower rate; enzymes are biological catalysts.

Catalytic antibody | An antibody that speeds up a chemical reaction; also called "abzymes," these antibodies use a molecule called a hapten to mimic the middle, "transition" state of a reaction.

Chaperone | Any of a class of proteins that helps proteins fold or escorts proteins or other molecules throughout the cell.

Chirality | The ability of a chemical substance to exist in two mirror-image forms, each of which rotates polarized light in opposite directions.

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

Clinical trial | A scientific study in which physician-researchers study the effects of potential medicines on people; usually conducted in three phases (I, II, and III) that determine safety, whether the treatment works, and if it's better than current therapies, respectively.

Cofactor | A helper molecule (either inorganic, such as a metal ion, or organic, such as a vitamin) required by an enzyme.

Combinatorial chemistry | The random assembly of various chemical units into large so-called "libraries" of new synthetic compounds.

Coprophile | A feces-loving organism.

Covalent bond | A force that holds together two or more atoms, formed when electrons travel between the atoms' nuclei (and are thus "shared").

Cyanobacteria | A type of bacteria living in damp soil or rocks, or fresh or salt water, that performs photosynthesis, a process in which light, energy, water, and carbon dioxide are converted into oxygen and carbohydrates (sugars).

Di- | A prefix meaning two.

DNA (deoxyribonucleic acid) | A double-stranded molecule that encodes genetic information; composed of four nucleotides containing the bases adenine (A), cytosine (C), guanine (G), and thymine (T).

DNA polymerase | An enzyme that copies, and sometimes repairs, DNA.

Double bond | A type of covalent bond in which a pair of atoms shares two pairs of electrons.

Electrolyte | A charged molecule (such as a sodium or potassium ion) that is present in body fluids.

Element | A component of the periodic table; a pure substance that cannot be separated into simpler substances by chemical means.

Enantiomer | One of two "mirror images" of a chiral molecule.

Endotoxin | Any of a class of lipids found in the outer membranes of gram-negative bacteria; in people, the toxins cause diarrhea and/or septic shock.

Enterocci | Intestinal bacteria that are often resistant to the antibiotic vancomycin.

Enzyme | A molecule that acts as a catalyst, speeding up biochemical reactions.

Fluorescence | The property of giving off light at a particular wavelength ("emission wavelength") when illuminated by light of a different wavelength ("excitation wavelength").

Forensic science | The application of scientific knowledge to questions of civil and criminal law.

Genetic engineering | The manipulation of an organism's genes—introducing, eliminating, or changing them—using modern molecular biology techniques.

Glycolipid | A lipid covalently linked to a sugar.

Glycoprotein | A protein covalently linked to a sugar.

Glycosaminoglycan | A large molecule found on the surface of membrane-encased cells that consists of a network of long, branched chains of sugars and smaller, nitrogen-containing molecules.

Hexa- | A prefix meaning six.

Host-guest chemistry | A branch of chemistry in which researchers study the interactions between two molecules (natural or synthetic) with the goal of either mimicking or blocking a biological effect caused by the molecules' interaction.

Inflammation | The body's reaction to noxious stimuli or foreign particles, resulting in swelling, redness, and pain.

Hydrocarbon | An organic molecule consisting of hydrogen and carbon atoms only.

-ine | A suffix common to many of the amino acids.

Inorganic | Describing a substance not derived from a living organism and/or not composed of carbon and hydrogen (a hydrocarbon).

In silico | Literally "within silicon"; refers to modeling research conducted with computers only.

Ion | An electrically charged atom.

Ionic bond | A force that holds together two electrically charged atoms (called ions).

Lipid | A fatty, waxy, or oily compound that will not dissolve in water; it contains hydrogen, carbon, and oxygen, but proportionally far less oxygen than carbohydrates.

Lipid A | A key component of lipopolysaccharide.

Lipo- | A prefix meaning "lipid," or fat.

Lipopolysaccharide | An integral part of the outer cell membrane of certain types of bacteria (so-called "gram-negative" strains).

Mass spectrometry | A technique used to determine the composition and abundance of the atoms in a molecular substance, starting with a very small amount of sample.

Metabolic engineering | The targeted and purposeful alteration (using genetic engineering techniques) of an organism's metabolic pathways in order to better understand how the pathways work or to redesign them to produce a different set of products.

Metabolism | A set of 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.

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.

Nano- | A prefix meaning one-billionth.

Nanotechnology | A branch of science and engineering devoted to the design and production of extremely small electronic devices and circuits built from individual atoms and molecules.

Neoglycopolymer | A glycoprotein mimic; a synthetic molecule consisting of polymers with carbohydrates attached.

Nuclear magnetic resonance spectroscopy | A technique used to study the physical, chemical, and biological properties of matter; in this method, scientists subject a molecule to a strong magnet and watch what happens to the atoms that make up the molecule, which provides information about the molecule's composition.

Nucleic acid | A large molecule composed of units of nucleotides; includes both RNA and DNA.

Nucleotide | A subunit of RNA or DNA containing a base, a phosphate, and a sugar; thousands of nucleotides link up to form a molecule of DNA or RNA.

Olefin metathesis | A chemical reaction in which all of the double bonds in a hydrocarbon molecule are broken and then rearranged.

Oligosaccharide | A molecule made up of several simple sugars linked together.

Organic | Carbon-containing.

Organic chemistry | A branch of chemistry dedicated to the study of the structures, synthesis, and reactions of carbon-containing compounds.

Organophosphate | A class of toxic organic molecules containing phosphate, and often fluoride, that are used as insecticides and nerve gases (such as sarin); many of these molecules block the action of an enzyme (acetylcholinesterase) that recycles an important brain chemical called acetylcholine.

-ose | A suffix common to many carbohydrates.

Oxo- or oxy- | Prefixes meaning oxygen-containing.

Peptide | A molecule consisting of a chain of amino acids; a small protein fragment.

Peptide bond | The chemical link joining amino acids in peptides and proteins.

Peptidomimetic | A chemical compound that mimics the ability of a peptide to recognize certain physiological molecules, such as proteins and DNA.

Pharmacogenetics | The study of how people's genetic make-up affects their response to medicines.

Phenylketonuria | A genetic disorder in which the body cannot break down the amino acid phenylalanine; abbreviated PKU.

Phosphate group | A chemical unit consisting of an atom of phosphate bound to four oxygen atoms; often attached to other biological molecules, such as proteins, sugars, and lipids.

Phospho- | A prefix meaning phosphate-containing.

Phospholipid | A lipid made up of glycerol and fatty acids, with a phosphate group attached.

Phosphotriesterase | A bacterially produced enzyme that breaks down organophosphates like sarin.

Physiology | The study of how living organisms function.

Plasma membrane | The membrane that separates the contents of a cell from its outside environment; it consists of a double layer of phospholipids with embedded proteins.

Polymer | A large molecule formed by combining many similar, smaller molecules.

Polysaccharide | Any of a class of carbohydrates consisting of chains of simple sugars.

Product | A substance formed as the result of a chemical reaction.

Protecting group | A removable chemical unit used by synthetic chemists to purposefully cover up certain regions of a molecule so they do not react with other compounds during a reaction.

Protein | A large molecule composed of one or more chains of amino acids in a specific order and folded shape determined by the sequence of nucleotides in the gene encoding the protein.

Protein synthesis | The process in which the genetic code carried by messenger RNA directs cellular organelles called ribosomes to produce proteins from amino acids.

Reaction rate | A measure of how fast a chemical reaction occurs.

Ribonucleotide reductase | The enzyme in all organisms that catalyzes the conversion of nucleosides to deoxynucleosides.

RNA | Ribonucleic acid; a chemical found in cells that serves as an intermediate in the synthesis of proteins; the three major types are called messenger RNA (mRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA).

Structural biology | A branch of biology dedicated to the study of the three-dimensional structures of proteins and other molecules to help understand the function of these molecules in the cell.

Substrate | A molecule acted upon by an enzyme.

Suicide substrate | An enzyme substrate that itself is not toxic but that produces a toxic metabolic product.

Superoxide dismutase | A copper- and zinc-containing enzyme present in all oxygen-using organisms that scavenges free radicals and converts them into hydrogen peroxide and oxygen.

Synthetic chemistry | A branch of chemistry in which chemists devise ways to make specific compounds of interest and/or develop new chemical reactions for this purpose.

Toxin | A poisonous substance.

Transition state | The activated form of a molecule that has partly undergone a chemical reaction.

Tri- | A prefix meaning three.

van der Waals force | A weak physical force that holds together two molecules or two different parts of the same molecule.

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