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inside

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On the Cover

Photo of Gene Robinson: *Bill Wiegand*

Photo of Serrine Lau: *Margaret Hartshorn*

Editor's Note

The debate has raged forever. Nature or nurture?

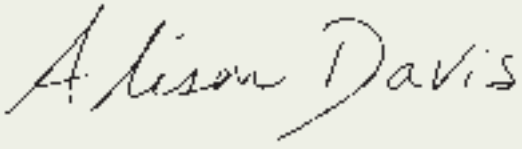
Are your looks, your health, your smarts, and your behaviors inherited? Or are they learned?

You probably know the answer already: It's both. The genes we inherit from our parents help to make us who we are, but how and where we live, whether we exercise or smoke, and various other factors have important effects.

What you may not know, however, is that genes and the environment interact. Scientists like Serrine Lau are discovering that chemical exposure can influence disease risk, but the risk is likely to differ based on a person's unique genetic makeup (see story on page 9).

And researchers are finding out that social interactions also probably have an effect on how the body works, through controlling the activity of certain genes. On page 3, read about how honeybee scientist Gene Robinson is looking for clues about social influences on genes by studying the behavior of hive societies.

Yes, scientists have read the human genetic code. What more can we learn from studying how nature edits the code? Lots—stay tuned for the sequel.



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A Sting of I

Love

BILL WIEGAND

"I realized that I really loved the bees."

By Alison Davis

Gene Robinson was sick of picking grapefruit.

Robinson was 18 years old, volunteering on a kibbutz in Israel, and he decided to look for something else to do. Along with grapefruit, this kibbutz was also a commercial honey producer. How about working with bees instead?

"Why not?" Robinson wondered at the time. Can't be much worse than picking grapefruit, he thought, and he ventured over to the hives.

It was love at first sight, recalls Robinson, who is now a biologist at the University of Illinois at Urbana-Champaign. In less than 2 weeks he developed a lifelong infatuation with the honeybee.

Order in Chaos

Robinson knew nothing about the honeybee, or about bees in general, but between the stings and the swarms he realized that things were not what they seemed.

He saw chaos in the hive. Bees were coming and going, without apparent order or meaning. But like so many closets that are a complete mess to someone else, if you know where everything is, it's not a mess at all. There is order amid the chaos, and Robinson saw it.

Thirty years after his introduction to the honeybee, Robinson still studies the insects. In fact, he does it for a living: Robinson runs a research lab dedicated to studying the biology behind social behavior in, you guessed it, bees.

"I realized that I really loved the bees—not so much the industry aspects—but the science, the questions," says Robinson.

Gene Robinson is an entomologist at the University of Illinois at Urbana-Champaign. Robinson studies honeybee behavior.

"How is their society organized? How are they able to do everything that they do?"

Today, Robinson admits that his early questions about bees were somewhat simplistic and not very testable. But over time, Robinson has developed a sophisticated research endeavor to uncover brain molecules that drive the behavior of these incredible creatures.

Robinson had spent so much time observing honeybees in their natural environment that he knew that the very social

way these insects live has to be a necessary part of their existence. He knew that the order of the hive is part of the bees' social construct.

But how could he figure out exactly what was going on?

BILL WIEGAND

Honeybees are a versatile experimental system since they can be studied in the lab or in the wild.

From Kibbutz to Cornell

Time, experience, and hard work landed Robinson at Cornell University in Ithaca, New York, where he pursued a Ph.D. in entomology (the study of insects). Before long, Robinson settled into a research project investigating how hormones and nerve circuitry influence social behavior in honeybees.

Gene Robinson looked to the honeybee brain (photo) to find genes involved in bee behavior.

The fact that honeybee societies exhibit complex behavior—not just knee-jerk reactions to their environment—means these insects have a pretty high level of functioning, says Robinson, adding that honeybees cannot survive without the social structure of a hive.

"Many people think of insects as simple, little robots that respond to stimuli," Robinson says. Instead, he notes, because their behavior is controlled in part by hormones, insects like bees have a lot in common with larger and more complex organisms like vertebrates (animals with backbones).

Robinson knew that in order to dig deeply into the topic of learning about how certain bee behaviors could be hard-wired, one of the first places to look was in the brain. Honeybees do have brains (see photo below), albeit not nearly as sophisticated as ours. There is no evidence, for example, that bees are conscious or that they think about the future.

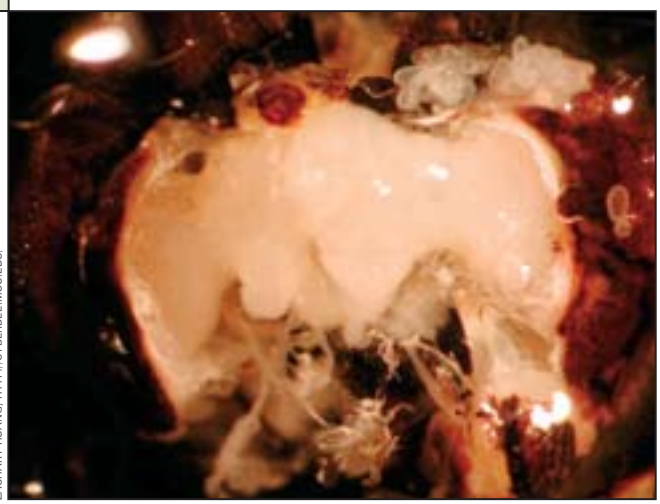
Robinson suspected that there must be an underlying molecular logic—the coordinated actions of genes in the brain—to account, at least in part, for social behavior in beehives. He decided to find the brain genes involved.

At the time, searching for the genetic underpinnings of social behavior was not exactly a mainstream idea.

In fact, Robinson remembers being very unsure about having such radical research ideas as a graduate student. He didn't have the confidence that often comes with time and experience, and he really wondered whether his ideas were too naïve.

"Sure, it's a new idea," Robinson recalls thinking, "and no one has ever done it. But maybe there's a good reason no one has ever done [these experiments]!"

Nevertheless, Robinson pressed on and sought support from advisors, among them John Hildebrand (then an insect scientist at Columbia University in New York City), who now runs a research lab at the University of Arizona



ZACHARY HUANG, HTTP://CYBERBEE.MSU.EDU/

in Tucson. Hildebrand had a passion for studying the sense of smell in moths, and he urged Robinson to pursue his ideas, wacky as they may have seemed.

Hive as Laboratory

Robinson found himself naturally drawn to just watching bees, but he also recognized the species as an extremely practical experimental system. You can study them in the lab, and you can study them in the wild. You can willfully alter the social structure of a hive community and see what happens.

The beehive, a society that rivals our own in complexity, exhibits a clear division of labor. Just as in our world, there are individuals with specialized job descriptions, such as caretakers, builders, and gatherers. One hive member, the queen, handles the job of reproduction.

While the queen bee lives for 2 to 5 years, the other females (the "worker" bees) and the male "drones" only live about 1 month. It takes about 3 weeks for a baby bee to mature into an adult hunter, called a forager.

What's interesting about bees is that rather than being stuck in a particular job, a hive adjusts its workforce according to need, such as the availability of food. A builder can switch to become a gatherer, or vice versa. Robinson's research has taught him that the changes in honeybee job descriptions are strongly influenced by the environment.

Robinson discovered that manipulating the social structure of the hive could alter the makeup of the hive workforce in a flash. By removing forager bees from the hive, all of a sudden the younger, "nurse" bees acquired foraging abilities at ages as young as 1 week old. Similarly, Robinson explains, given a shortage of nurse bees to care for the babies in the hive, some of the bees never grow up, instead becoming "Peter Pans" to care for the youngest hive dwellers.

"So there's social regulation for how fast a bee grows up," says Robinson, adding that some developmental changes associated with the growth of certain brain regions are known to be genetically determined.

Rhythm in the Genes

Robinson discovered that a gene called *period* was socially regulated in honeybee brains. This was the very first demonstration of social behavior affecting a gene that controls biological rhythms. The findings brought Robinson one step closer to his dream: understanding how genes orchestrate brain activity to give rise to social behavior.

Organisms as diverse as insects, mice, and humans act to some degree according to an underlying regularity. For many years, scientists have been fascinated with studying biological clocks, and an entire field is devoted to understanding so-called circadian rhythms (see sidebar, page 7).

In people and animals, circadian rhythms help control sleeping, eating, and other behaviors. Scientists have uncovered a genetic underpinning for circadian rhythms, and one of the pivotal molecular players is the *period* gene. Versions of the *period* gene have been found in almost all animal species.

To his surprise and delight, Robinson found that in forager bees, the *period* gene was ragingly active, whereas in nurse bees the activity of this gene limped along.

Makes sense, if you think about it: Nurse bees work around the clock, without rhythm. This is just the kind of behavior that suits the needs of babies who may get hungry any time of the day or night. The behavior of forager bees, on the other hand, is distinctly rhythmic as they hunt for nectar and pollen according to the availability of outside light, the ambient temperature, and other aspects of the bees' surroundings that tend to fluctuate rhythmically on a daily basis.

ZACHARY HUANG, HTTP://CYBERBEE.MSU.EDU/

This adult hunter bee is foraging on an aster flower.

A Sting of Love

Robinson had found a link between the complex, socially regulated foraging behavior of bees and the activity of a specific gene. He and others have since discovered that the activity of more bee genes coincides with foraging and other insect behaviors.

Put It to the Test

Robinson got busy teasing apart the molecular details of how a gene's activity could respond to social activity. In the case of the forager bees, what was it that caused the hive to reshape itself? What was the environmental trigger that forced bees in a hive deprived of foragers to turn up the volume of the *period* gene and acquire the ability to hunt for food?

Robinson came up with three ideas and tested each in the hives.

Maybe it's as simple as detecting a food shortage. With few foragers, the amount of food entering the hive goes down and young bees get into gear as they become hungry. Robinson refers to this potential scenario as "decentralized," since it doesn't involve any sort of top-down instructions from the queen bee.

Another similar, decentralized possibility might be that the young bees sense the absence of older bees, perhaps through some type of pheromone (or lack thereof) circulating throughout the hive. A pheromone is a chemical (a type of hormone) released by an insect or other animal through which it communicates with another individual of the same species through the sense of smell.

Finally, there could be a leader-follower type of response, in which some of the bees have special access to information—for example, environmental conditions—and these bees pass on the news to the rest of the hive. Robinson views this sort of scenario as "centralized," since it reflects a single bee (or a select few bees) putting out a call for change, sort of like having a command center within the hive.

Robinson interpreted the results of his experiments to conclude that there does not appear to be any sort of centralized control.

He likens the decentralized hive activity to how our own brain functions. Or the stock market. The actions of many individuals affect stock prices, even though it appears that there is a general, integrated response.

Honeybees also clearly respond adaptively as an integrated unit, but it's not as if one bee is sending out the orders.

ZACHARY HUANG, HTTP://CYBERBEE.MSU.EDU/

Honeybees acquire different job descriptions as they age. Normally, it takes about 3 weeks for a baby bee to mature into an adult hunter, called a forager (left). Undertaker bees (right) are usually around 14 days old, in the transition from nursing to foraging. This undertaker bee is carrying a dead bee out of the hive.

The queen does largely control the size of the bee population, but she isn't entirely running the show.

"There is no executive committee of [bees] that know more than the others," Robinson explains.

The story is far from over, says Robinson, but he now has a good sense that molecular signals, communicated via pheromones, are what's triggering the changes in hive behavior. Robinson has evidence, for example, that certain pheromones can directly cause changes in the activity of certain genes.

Nature or Nurture?

So what's the answer to the perennial biological question about the impact of nature versus nurture? Do genes or the environment make us unique? Are we born to be funny, or musical, or athletic? Or do practice and being in the right place at the right time matter more?

It's both, says Robinson, but even that's too simplistic a notion. He likes to take things a step further.

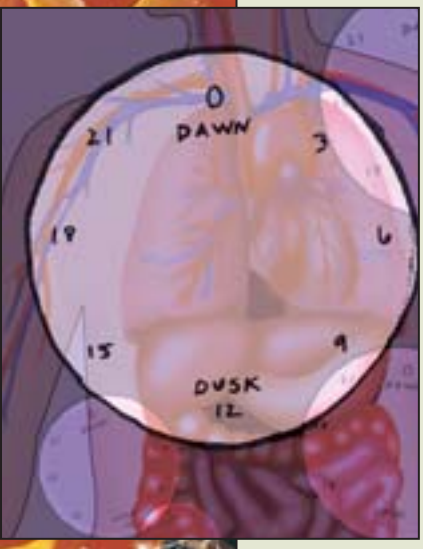
By interrupting the natural order of his "lab"—the honeybee hive—Robinson made the fascinating discovery that social environment does appear to be able to mold the function of genes, and vice versa. Robinson calls this new area of research "sociogenomics."

In his view, sociogenomics is "beyond nature and nurture." We're all born with one version of a human genome, Robinson says, but it's not carved in stone. Our genomes are influenced by both heredity *and* environment, and sculpted by our social interactions.

While the findings don't translate directly to humans—communities are social but certainly not exactly hives—Robinson's research provides a provocative new lens for seeing just what makes us who we are. ■

Dan Hogan and Jennifer White contributed to this article.

It's About Time



cir•ca•di•an (sur-**kay**-di-ăn) *adj.* of physiological activity occurring approximately every 24 hours.

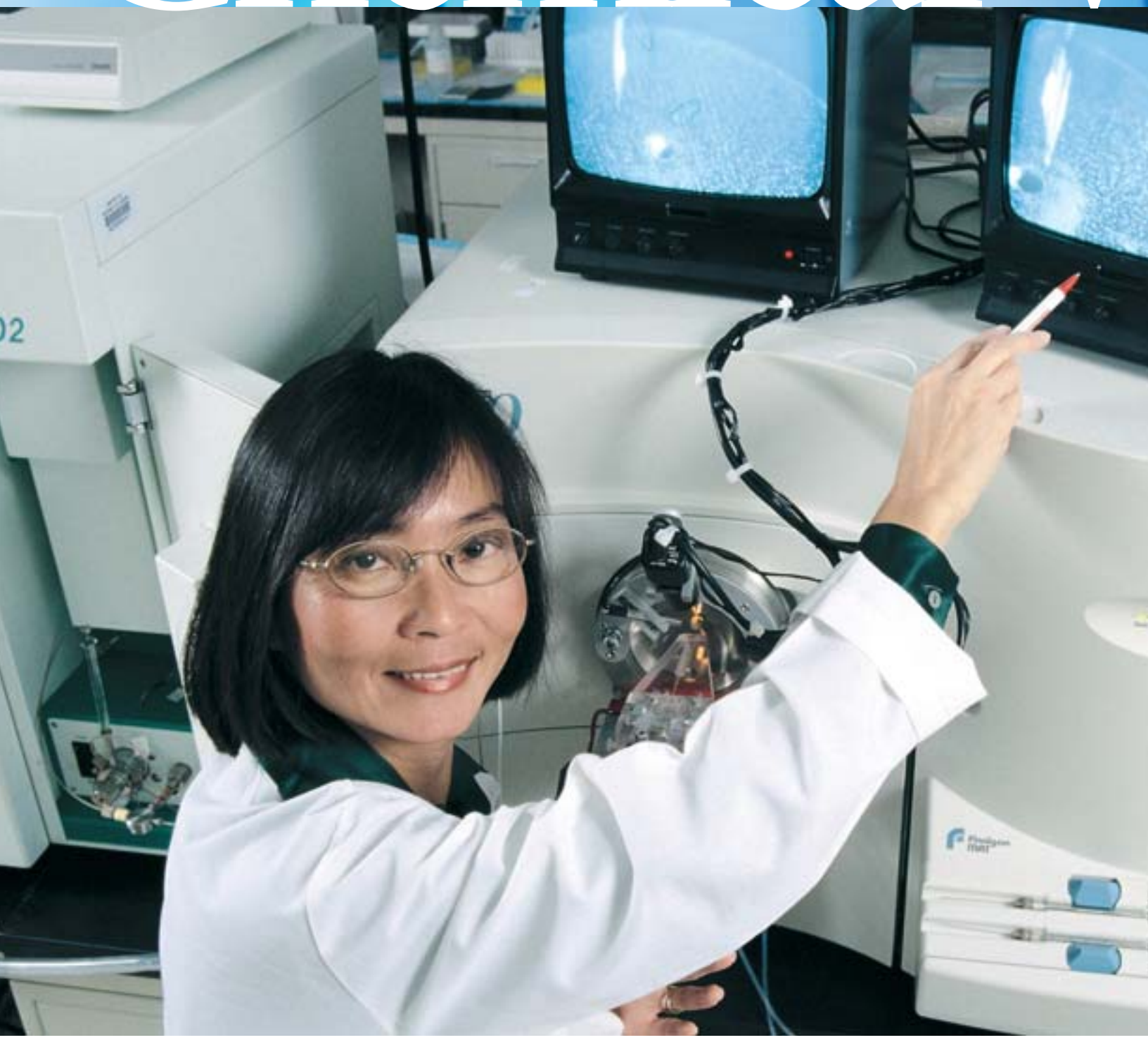
Why do most heart attacks occur in the morning? Why does a transcontinental flight make you feel so rotten? How do the swallows of Capistrano, California, know exactly when to fly south every year?

Like some animal behaviors, the human body also functions according to an internal rhythm. Inside your brain sits a master biological clock. This molecular timepiece, made up of cells, is housed in a sliver of tissue called the suprachiasmatic nucleus, or SCN. It sits quite close to the optic nerve, which controls vision, and light signals are thought to play a big role in keeping the body clock "on time." The SCN helps to coordinate the actions of billions of mini-clocks located throughout your entire body. This is one of the main ways your body controls sleepiness.

Scientists know that many body functions aside from sleep, including the regulation of temperature, hormone levels, digestive secretions, and blood pressure, all vary slightly—but regularly—throughout the day and night. These processes and many others are thought to be affected by our biological clock. A clock that's offset can make us feel downright awful: Jet lag is a perfect example. Or seasonal affective disorder, in which some people become depressed during the winter months when abundant sunlight is scarce.

Researchers, many working with insect model systems, are uncovering genes that are critical for keeping biological time. One of these, called *period* (see main story), has been linked to a variety of unexpected biological phenomena, including some behaviors.—*A.D.*

Chemical W



Vorld

"Don't just sit in the dark and wonder what comes next."

MARGARET HARTSHORN

Serrine Lau is a toxicologist at the University of Arizona in Tucson. Lau studies the role of genes in the body's response to chemical exposure.

By Alison Davis

Unlike a genie corked in a bottle, the genes in our cells are in constant contact with the environment. Every day, a sea of chemicals enters our bodies.

Scientist Serrine Lau studies interactions between those chemicals and our genes, looking for clues that can help predict—and protect against—disease.

Lau is a "toxicogeneticist" at the University of Arizona in Tucson. With a detective's doggedness, she investigates molecular "crime scenes," organs within the body that are prone to damage by poisonous chemicals.

Toxicologists are researchers who study how people process chemicals, so they can help guide disease prevention efforts. Toxicogenetics is a particular kind of toxicology research in which scientists like Lau strive to understand how subtle genetic differences can influence whether or not chemical exposures can endanger our health.

Lau loves toxicology research, in part because she feels it can provide a source of knowledge for making sound decisions about how to live in a world that is teeming with chemicals that can be healthful or harmful.

Her approach to science—and to life in general—is *not* "watch and wait."

"Don't just sit in the dark and wonder what comes next," Lau advises. Instead of panicking, "get more information."

Staying Tuned

When it comes to issues of chemical exposure, Lau thinks people need a rational approach for understanding environmental risks so they can be prepared. For example, it should be a no-brainer that if smoking cigarettes causes cancer, you shouldn't smoke them. Likewise, if you're prone to an itchy nightmare from touching poison ivy, you'd better be sure you know how to avoid contact with this environmental "poison."

Lau is now trying to unravel the molecular ins and outs of damage caused by a group of chemicals called polyphenols. These toxins are found in substances as varied as cigarette smoke, car exhaust, photo developing solutions, and some cosmetic depigmentation creams. According to Lau, other environmental sources of polyphenols and similar chemicals probably exist in our everyday surroundings but we simply don't know about them yet.

Every day, a sea of chemicals—synthetic or natural—can enter the body.

But before you start to freak out about poisons lurking in your midst, keep in mind that chemicals can be synthetic or natural, and they are not inherently bad.

By definition, a chemical is any substance produced by or used in a reaction involving changes in atoms or molecules. The reaction can be in a lab test tube or in your stomach. Therefore, the term "chemical" covers pretty much everything from corn syrup and caffeine to petroleum and nerve gas. Even organic foods grown without pesticides are swimming in natural chemicals.

Scientists do not know what all the chemicals in the environment are, nor how they might act in our bodies.

Medical research has shown that many chemicals are good for you. For example, scientists have discovered that pregnant women can significantly reduce the risk of certain types of birth defects simply by taking a daily dose of folic acid, which is a vitamin available in grocery stores and pharmacies. Food manufacturers routinely add this helpful, natural chemical to cereals, breads, and other grain products.

On the other hand, some chemicals in the environment are obvious nasties, such as the cancer-causing substances in cigarette smoke. But a lot remains to be learned about the vast majority of chemicals we come in contact with daily—in our foods, in our homes, on our clothing, and carried on the breeze.

As a toxicologist, Lau studies chemicals that are known to pose a serious health risk. In particular, she is interested in genetic differences that affect the processing of toxic polyphenols within the body.

Naturally, it is difficult to do these kinds of experiments in humans.

Good Model

So when Lau decided to study the complex interplay of genes and polyphenols, she first had to find an appropriate animal model.

Whereas studies of experimental medicines can be done in carefully planned clinical trials with patients who understand the potential risks and benefits, "obviously, you can't give harmful chemicals and pollutants to people," Lau says.

Toxicology researchers rely on animal systems to model metabolism, which is the sum of all the chemical and physical changes that take place within the body. Metabolism involves the breakdown of food to create energy and the recycling of body substances to form materials for making tissues and organs.

Researchers often use rodent model systems to study the effects of chemicals on metabolism.

The body processes foods, drugs, and other chemicals with the same physiological toolkit. However, metabolism differs among people because we all inherit a slightly different genetic makeup. These very small differences in our genes can profoundly affect the function of the proteins the genes encode. Several of these proteins participate in the processing of the substances that enter our bodies.

Many toxicologists use rodents to study metabolism. Although people don't have fur or tails, humans, mice, and rats share nearly 90 percent of the same genes. People and rodents therefore have many of the same enzymes—the molecules that break down food, drugs, and all kinds of chemicals.

Nonetheless, Lau says that one needs to be choosy when picking an animal model.

"You have to find out for each different type of chemical exposure," Lau says, "are we more like a rat, or a mouse, or a guinea pig?"

Lau hopes that finding the genes that increase susceptibility to toxins in animals will point to human versions of those same genes. This, in turn, may help scientists estimate the risk of chemical exposure in people.

Chemical Travels

How do drugs and chemicals make their way through the body? What tissues and organs does a chemical "visit" on its journey through our organs and tissues? Where are chemicals processed and expelled? These are all important, basic questions in toxicology experiments.

There are many ways substances can enter the body: through the mouth, nose, skin, or bloodstream. Most drugs and chemicals are processed primarily in the liver. This organ can either activate ("turn on") chemicals, or it can break them down so they are no longer active in the body. Regardless of how a chemical gets in and is metabolized, the body usually gets rid of it with help from the kidneys. This process is known as excretion.

When the body breaks down and excretes toxic chemicals, the byproducts of these chemical reactions can be harmless, or they can be even more toxic than the original substance. Because of their high level of exposure to chemicals, the liver and kidneys are often the most affected by cancer-causing substances. The bladder, the next stop for processed chemicals on their way out of the body, is also sometimes considered a "target organ" (like the liver and kidneys) for damage by some substances.

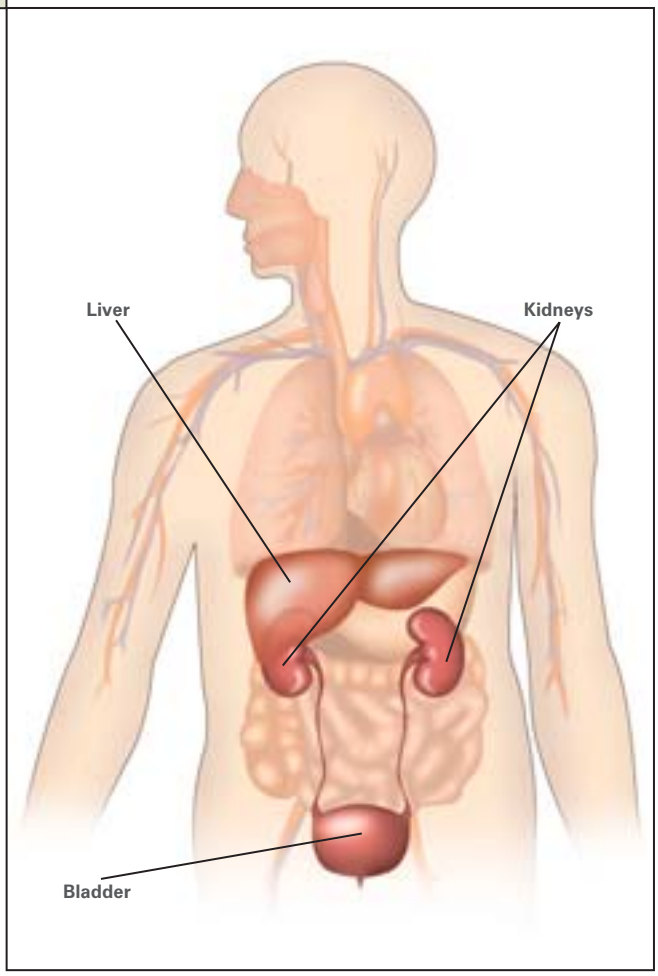
That is why, for example, smoking contributes to bladder cancer as well as cancer of the lungs, an organ that has direct exposure to the harmful chemicals in cigarette smoke.

Lau's experiments examine the susceptibility of rodents to kidney cancer caused by polyphenols. One such polyphenol, hydroquinone, is particularly poisonous. Hydroquinone is broken down inside the body into even more dangerous substances called quinone-thioethers.

For these studies, Lau uses Eker rats. This species of lab rat is especially prone to getting kidney tumors from exposure to quinone-thioethers.

In Eker rats, the kidneys—not the liver—do most of the processing of quinone-thioethers, creating toxic byproducts such as free radicals. These harmful breakdown products cause damage not necessarily by killing

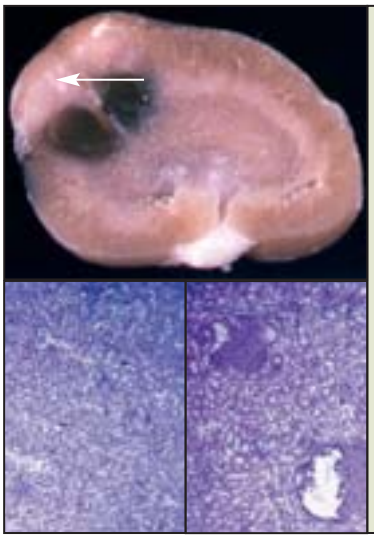
Body organs such as the liver and kidneys process chemicals and toxins. These "target" organs are susceptible to damage caused by these substances.



cells, but by tampering with the DNA that makes up genes. Messed-up genetic instructions can cause normal cells to turn into cancer cells that can assemble into tumors.

By comparing animals that are susceptible to quinone-thioether-induced kidney cancer with animals that are resistant to developing such cancers, Lau can home in on potential genetic triggers.

In one promising avenue of research, Lau and others have found that Eker rats and humans that are prone to quinone-thioether damage share defective versions of certain genes. One such gene directs the production of a tumor suppressor protein. As the name suggests, these protective proteins perform a healthy role in the body by preventing tumors from forming. If these molecular bodyguards are gone or defective, cells lose an important safeguard.



SERRINE LAU

Eker rats are especially prone to getting kidney tumors (arrow, top) from exposure to quinone-thioethers.

Compared to normal kidney tissue (bottom, left), cells in a kidney tumor (bottom, right) form a mass that hinders normal kidney function.

Lau's studies with rats show that quinone-thioethers turn off an important tumor suppressor gene. In some people who are highly susceptible to developing kidney cancer, the tumor suppressor gene produces a form of its protein that doesn't work right. Studies by other scientists have demonstrated that as kidney cancer worsens, this tumor suppressor protein loses its ability to function properly, presumably weakening kidney defenses.

Toxin Detectives

By continuing to look at molecular crime scenes in organs that process chemicals, Lau is searching for more pieces to add to the growing foundation of knowledge about cancer risk. To find clues, she examines the tissues of animals exposed to chemicals like quinone-thioethers, taking measurements of breakdown products.

In many labs, senior scientists like Lau leave this kind of hands-on experimental work to junior researchers, graduate students, and undergraduates. But Lau still does animal tissue dissections herself, surrounded by her lab team. She says the dissections present a perfect teaching exercise to explain the rationale behind every experiment and to give lab members the chance to make observations and ask questions.

During each dissection procedure, nothing is wasted, Lau says. Every tissue is either used for an experiment, donated to a fellow scientist down the hall studying a different organ system, or stored in the freezer for possible later use.

"Everyone calls us the 'squirrels' because we keep everything. But in 3 months you may get a new idea," she says, "and then you'll have the materials to perform the next experiment."

A Mind for Medical Mysteries

Lau was born and raised in Hong Kong. Neither of her parents was a scientist, but she has loved science ever since she can remember.

"It was always my favorite subject in high school and I was good at math," says Lau.

She also loved medicine, but Lau questioned whether she had the emotional fortitude to treat patients. Instead, she decided to pursue training in pharmacology, the study of how medicines affect the body, which led to her interest in toxicology.

Lau has never regretted those choices.

She thrives on solving the medical mysteries of health and disease. Lau especially enjoys research that addresses the entire organism, using animal models to learn how cells, organs, and tissues work together to run the body's metabolism.

Lau is convinced that important knowledge will come from those animal studies, since metabolism is quite similar among mammals. Experiments in rodents will speed the hunt for genetic fingerprints of susceptibility to drugs and toxins in people, she predicts.

"It's not such a bad thing that—when it comes to how our bodies process chemicals—we're not all that much different from a lab rat," Lau says. ■

The Weakest Link

According to the Pharmaceutical Research and Manufacturers of America, out of every 5,000 medicines tested in the lab, the vast majority fail in lab or animal studies. On average, only five of these potential medicines are tested in clinical trials. And only one of these five is eventually approved for use in patients.

Lots of money and time are spent on things that never work out.

The latest figures from Tufts University's Center for the Study of Drug Development say that a pharmaceutical company typically spends $802 million over the course of 10 to 15 years to bring a new medicine from the lab bench to pharmacy shelves.

Why does it cost so much and take so long to come up with a winning drug?

Many experts believe the weakest link in the drug development pipeline is the difficulty of predicting whether a substance will be toxic to the body.

The young but rapidly growing field of toxicogenomics holds the promise of improving this frustrating situation. Like scientists who study toxicogenetics, researchers who do toxicogenomics experiments look at interactions between genes and the environment, aiming to predict risks from chemical (or drug) exposure. However, rather than focusing on a single gene or a few genes, toxicogenomics scientists typically scan thousands of genes at once to look for telltale patterns of gene activity caused by drugs or environmental poisons.

Toxicogenomics approaches could weed out rogue molecules early on in the drug development process, leaving more time and money to focus on body-friendly molecules.

That would be a prescription for better health.—*A.D.*

Heard It From a Fly

Think those tiny, pesky flies circling the fruit bowl in your kitchen are simply a nuisance? Think again! Scientists continue to learn secrets about human health from basic research with simple organisms such as insects, worms, mice, and rats. Fruit flies have been a particular favorite for researchers investigating the role of heredity in the formation of tissues and organs. Both insects and people develop according to a genetically determined body plan, and scientists know that many of the genes involved in this process are very similar among animals.

Using fruit flies as a model system, NIGMS grantee **Grace Boekhoff-Falk** of the University of Wisconsin in Madison recently made a fundamental discovery about hearing. She and her co-workers discovered an insect gene nicknamed *spalt* that profoundly affects flies' ability to hear. The scientists found that experimental flies created to lack the *spalt* gene were deaf, as measured by direct tests of the flies' hearing organs located inside their antennae.

Boekhoff-Falk and her team also discovered that the *spalt* gene is nearly identical in flies and people. That means that what she learns about *spalt* in fruit flies may also apply to humans, and her work may help scientists find new approaches to diagnosing certain inherited hearing disorders.

Botulinum Toxin Vaccine

Botulinum toxin (BT) is the single most poisonous substance known, with very small amounts causing paralysis and death. Botulism, the illness caused by this bacterially produced toxin, typically results from eating contaminated food. Cases of botulism are rare, but concerns about the possible use of BT as a bioterrorism agent have brought a new urgency to research in this area. Of special interest is the effect of inhaling the toxin.

NIGMS grantee **Lance Simpson** of Jefferson Medical College in Philadelphia recently discovered how inhaled BT can cause poisoning by traveling from the airways to the bloodstream, where it does widespread damage to the body. Simpson also found that a piece of the BT protein called the heavy chain served as an effective inhaled vaccine in experimental mice. Simpson's work suggests ways to manufacture a human version of the vaccine against this potential bioterrorism weapon.

Although an antitoxin to neutralize BT circulating in the bloodstream is available, quantities of this remedy are too limited to rapidly treat large numbers of people. More importantly, an antitoxin works only in the bloodstream and it cannot enter poisoned nerve cells, reducing its usefulness. A safe and effective inhalation vaccine could get around these problems.

Tracking a Food-Borne Killer

Listeriosis is a serious infection caused by eating food contaminated with the bacterium *Listeria monocytogenes*. While listeriosis infections are rare, the *Listeria* bacterium is deadlier than other notorious microbes, such as *Salmonella* or *E. coli* O157:H7. Listeriosis infections can be caused by eating contaminated meat and dairy products or unwashed raw vegetables.

ELIZABETH WHITE

Food scientists had thought that *Listeria* outbreaks were unpredictable, occurring more or less at random across the country. But recent evidence from NIGMS grantee **Martin Wiedmann** of Cornell University in Ithaca, New York, suggests otherwise. This past summer, Wiedmann examined bacterial samples from listeriosis victims obtained throughout New York State over a 4-year period. Wiedmann used DNA fingerprinting techniques to classify the bacterial strains in individual infections.

Contrary to what he expected, Wiedmann discovered a pattern: The bacterial strains occurred in clusters, localized within certain geographic areas. A cluster means that several cases originated from one bacterial source and thus might indicate a disease that is spreading from the original source. The new findings mean that public health officials could potentially stop an outbreak after the first few identified cases by staying on the lookout for listeriosis clusters.

Blasting Cancer

To help diagnose cancer, doctors often use a microscope to examine small tumor samples obtained through procedures called biopsies. Although it is routine, this process isn't foolproof. Some of the subtle molecular changes that predict a tumor's behavior, such as how likely it is to spread or whether it will respond to certain anticancer medicines, are too tiny to be seen with a microscope. NIGMS grantee **Richard Caprioli** of Vanderbilt University in Nashville, Tennessee, has developed an experimental technique called imaging mass spectrometry that may allow more precise diagnosis of cancer and other disorders.

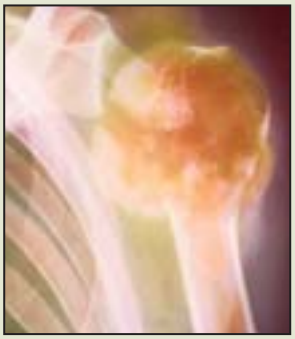
The method takes "molecular photographs" of individual proteins in cells and tissues. Caprioli and his team froze chunks of lung tumors and samples of healthy lung tissue and then cut them into very thin slices. The scientists coated the tissue slices with a chemical solution and slotted the specimens into a lab instrument called a mass spectrometer. A laser beam inside this machine blasted a series of sites on the specimens, shaking loose molecules at each site. These molecules were captured by a detector, analyzed, and displayed as "pixels" in a final, computer-drawn image. Each pixel contained a record of the molecules located in a specific site in the tissue sample.

Caprioli developed a specialized computer program to compare the samples and identified a protein pattern for one particular type of lung cancer that is very difficult to classify by looks alone. Caprioli's mass spectrometry method also successfully predicted whether individual patients would have a good or poor prognosis for surviving the cancer. This information could help doctors decide how aggressively to treat each case of cancer.

Basic Studies Yield Myeloma Drug

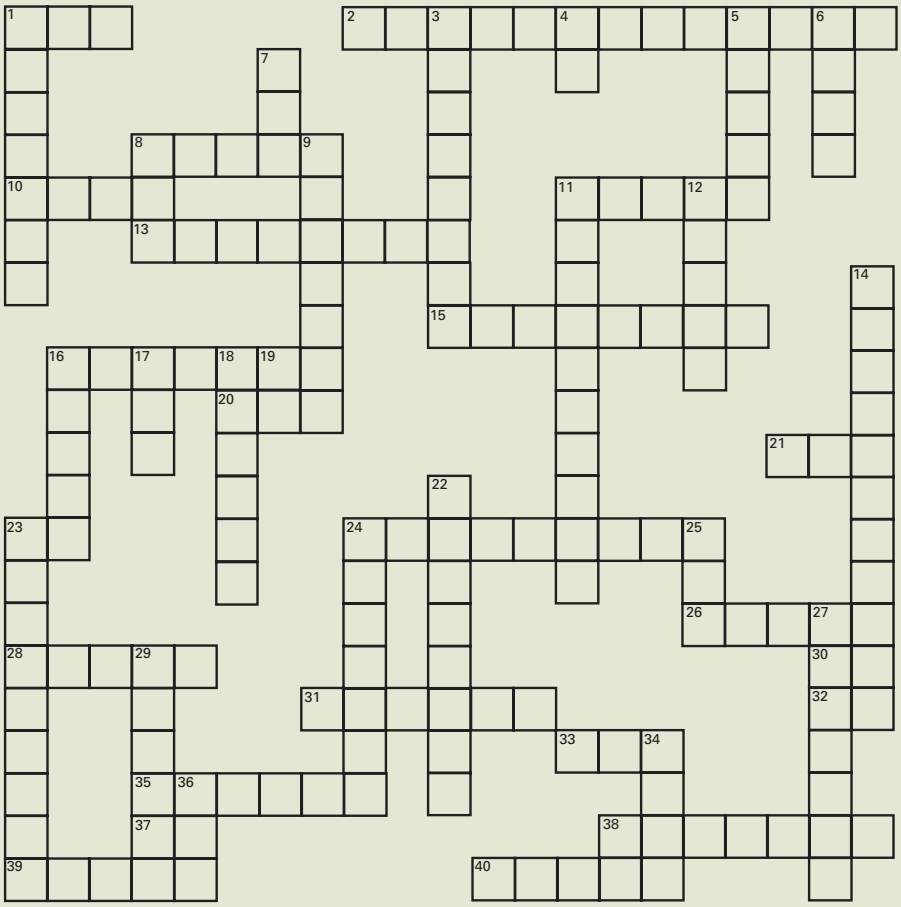
A series of lab studies begun in the 1970s by NIGMS grantee **Alfred L. Goldberg** of Harvard Medical School in Boston, Massachusetts, has led to a promising new cancer drug now on pharmacy shelves. The medicine, named Velcade™, was approved by the U.S. Food and Drug Administration in May 2003 to treat a deadly type of bone marrow cancer called multiple myeloma. Velcade is now being tested in more than 30 different clinical trials to determine if it can be helpful in treating many other types of cancer.

Velcade is a brand-new kind of cancer drug that targets a molecular machine found in virtually all cells. Goldberg was a pioneer in the discovery that our cells use this machine, called the proteasome, to continually break down their own protein components in order to remove improperly made or damaged proteins and to control cell growth and other vital processes. He reasoned that small molecules that block proteasome function might be useful in treating different diseases.



Goldberg and other researchers founded a small biotechnology company that went on to design and make Velcade based on detailed chemical knowledge of how the proteasome cuts up proteins. The discovery and development of this drug differs from the traditional approach, which relies on the screening of large numbers of chemicals to find those that that can slow the growth of cancer cells. The findings also show how advances in understanding basic biology can help scientists find new and better ways to treat diseases.

The Last Word



ACROSS

1. hears with an antenna
2. social influence on genes
8. eye-shutter
10. scientist Robinson
11. these make up the whole
13. producing electricity
15. deadly bacterium
16. myeloma drug
20. isn't
21. rats have it
23. comp. sci.
24. hormone detected by smell
26. similar
28. the body's principal one is in the SCN
30. not out
31. gene involved in circadian rhythms
32. bot. toxin
33. sped
35. grape in the sun
37. tubercul.
38. get rid of, as in chemicals
39. bee babysitter
40. pumping organ

DOWN

1. hunting bee
3. substance in a reaction
4. not stop
5. happens before greets
6. basic unit of life
7. our star
8. buzzing research subject
9. place for the cook
11. cuts up proteins
12. poison
14. "nurture" in the debate
16. between us and Mercury
17. scientist Serrine
18. model for experiments
19. carry out
22. action
23. 24-hour physiological activity
24. proteasome victim
25. many years
27. Israeli communal settlement
29. maps
34. after this
36. Pres. Lincoln
38. emerg. hospital locale

Puzzle answers can be found at
http://www.nigms.nih.gov/findings/

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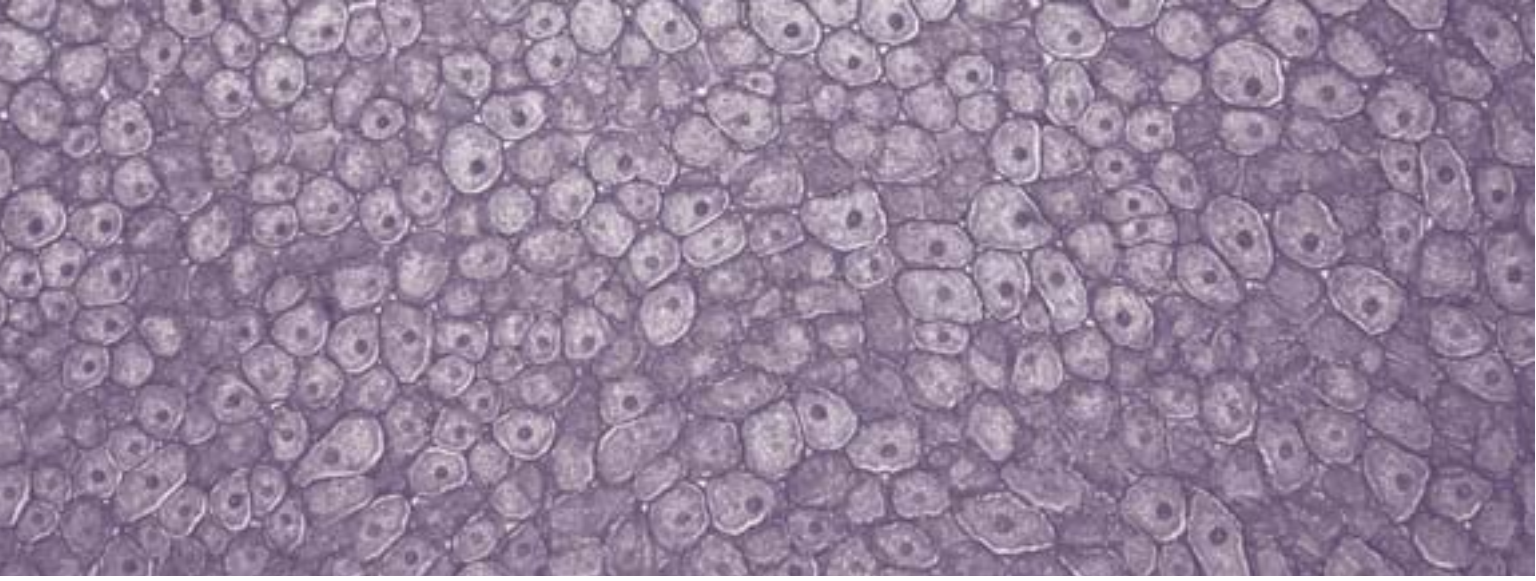

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