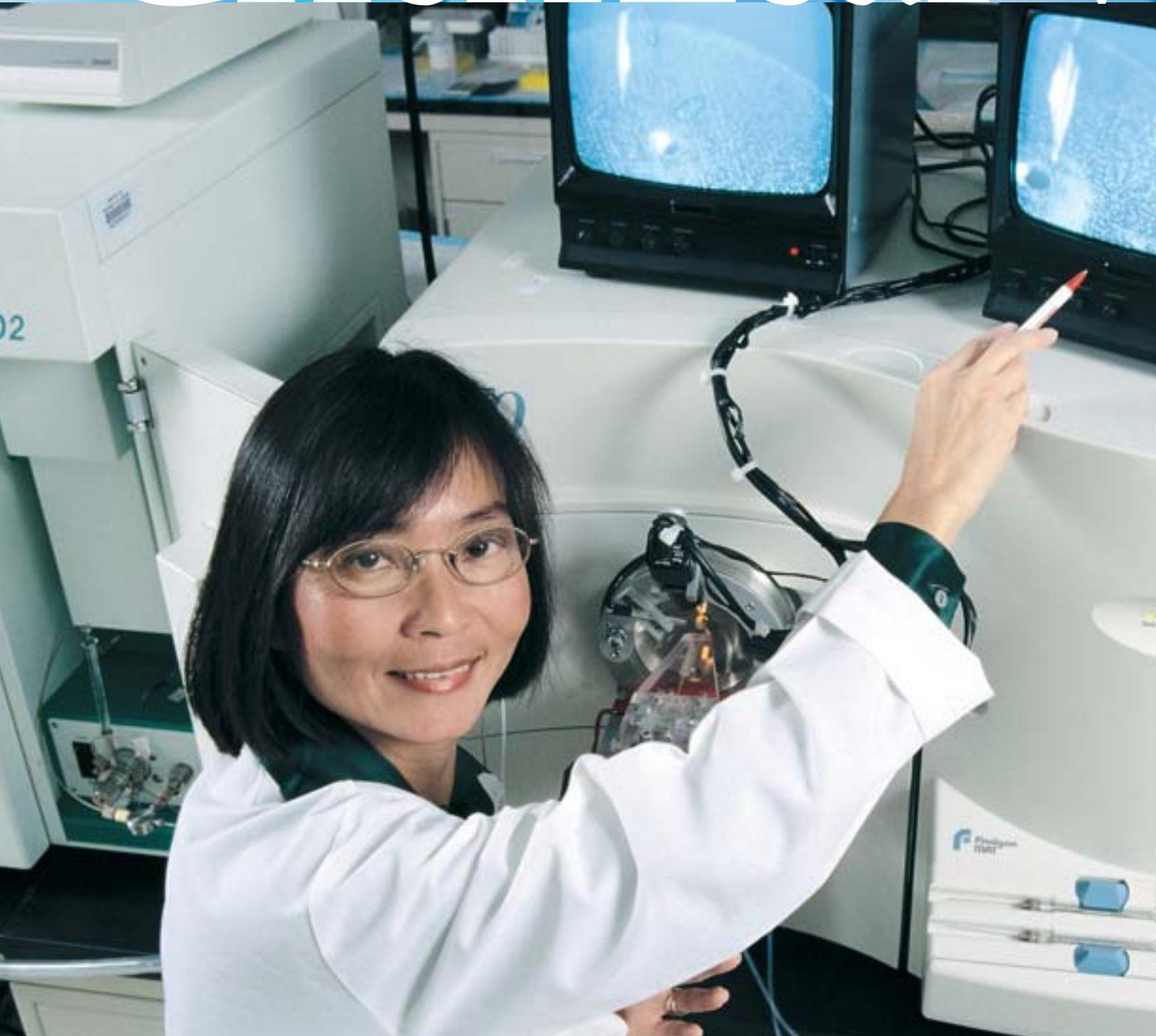


Chemical V



World



***“Don’t just sit
in the dark and
wonder what
comes next.”***

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 helpful 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.

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.

MARGARET HARTSHORN



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.

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



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.

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

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.

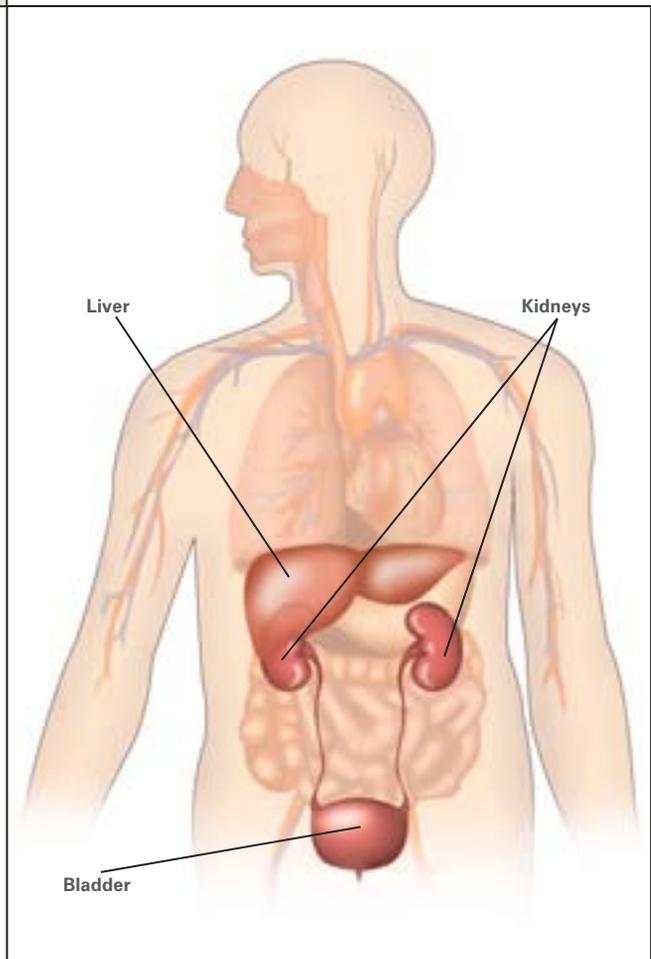
When the body breaks down and excretes toxic chemicals, the byproducts of these chemical reactions can be harmless, or they can be even more toxic than the original substance. Because of their high level of exposure to chemicals, the liver and kidneys are often the most affected by cancer-causing substances. 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.

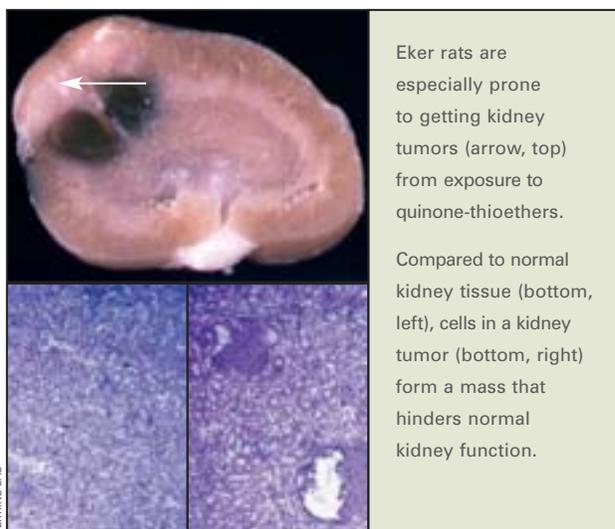
In Eker rats, the kidneys—not the liver—do most of the processing of quinone-thioethers, creating toxic byproducts such as free radicals. These harmful breakdown products cause damage not necessarily by killing



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.



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 tell-tale 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.

