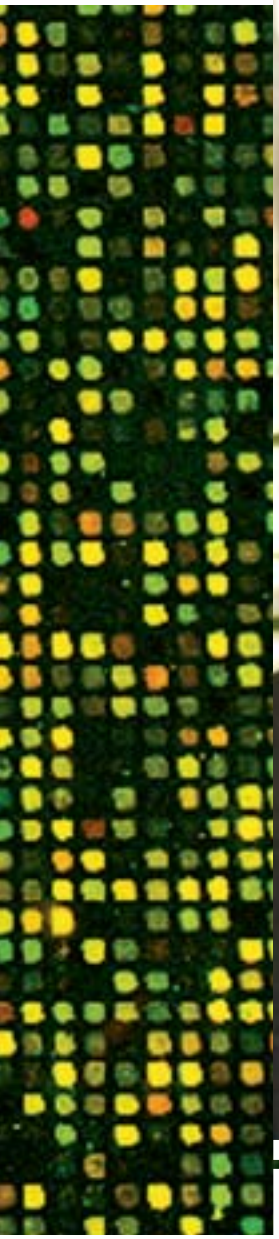
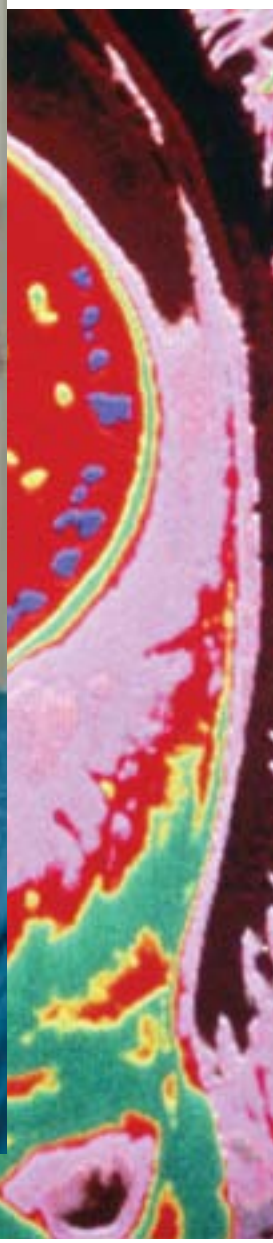
FINDINGS

September 2003





inside

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On the Cover

Photo of Maggie Werner-Washburne: *Tom Brahl*

Photo of Daniel Sessler: *John Lair*

Editor's Note

Do an experiment.

What do scientists mean when they say that?

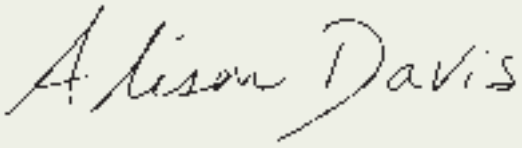
Make measurements? Gather data? Graph your results?

These are all common ingredients of an experiment, but there's one important item missing from this list. The most critical part of a good experiment is the careful thinking that goes on ahead of time. If you ask a good question, your experiment will always give you an answer. It may not be the answer you expected, but it will tell you something.

On page 9, read how anesthesiologist Daniel Sessler's fundamental questions about the way the body controls its temperature have led to major health improvements for surgery patients. Asking a good question is also essential for biologist Maggie Werner-Washburne, who has to plan her experiments carefully to get the information she needs from a flood of data on gene activity (story on page 3).

A hunch is only a hunch until you put your idea to the test. The time it takes to think of a good question is time well spent.

Alison Davis



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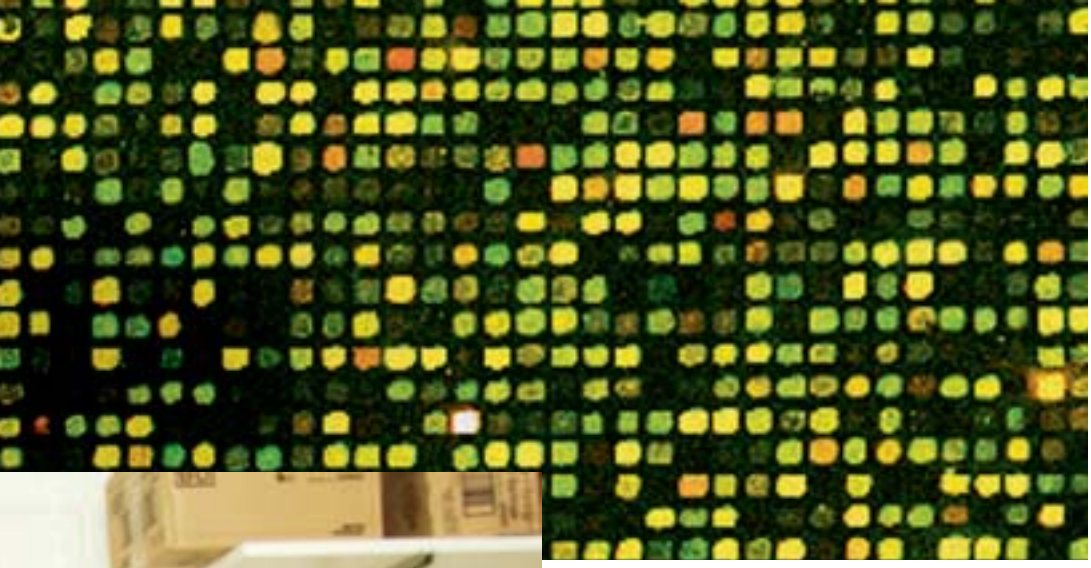
A Perfect Mix



JUANITA MARTINEZ, ANGELINA RODRIGUEZ

TOM BRAHL

"I never expected the joy of science to last so long, and I don't see it ending."

Maggie Werner-Washburne is a biologist at the University of New Mexico in Albuquerque. Werner-Washburne studies quiescent cells.

By Alison Davis

Biologist Maggie Werner-Washburne likes to mix things up.

"I have done this all my life," she says, recalling her childhood on the edge of a Mexican village within a small Iowa town. The daughter of a German father and a Mexican mother, Werner-Washburne grew up in a mixed-ethnic environment, and because of it she learned to be comfortable in two worlds.

Today, Werner-Washburne still thrives on diversity, and her lab at the University of New Mexico in Albuquerque is an ethnic blend.

Many of the graduate students who work in her lab have come from small Hispanic communities, from towns of a few hundred people, and from Native American pueblos and reservations. Werner-Washburne relishes the chance to introduce research to these students, many of whom are the first in their family or community to go to college.

"I get a lot of good students, and I try to help them make it through school without losing themselves or their culture along the way," she says. "It's not impossible."

In a similar vein, she believes that it's not impossible to bridge gaps that separate scientists working in entirely different fields. She thinks someone like herself, who has experience negotiating across cultural divides, can help accomplish this goal.

Bridging Science

In her own lab, Werner-Washburne is bridging the vastly different worlds of biology and mathematics. Her research in a field called genomics is a quest to track the activity of thousands of genes at the same time in living cells.

It's not easy to do.

To tackle this difficult research project, a potpourri of scientific personnel in Werner-Washburne's lab work together. Her coworkers include chemical engineers, computer scientists, biologists, mathematicians, chemical analysts, and statisticians. Lab members congregate in what Werner-Washburne calls a "visualization room" to exchange ideas or simply chat about the day.

It can be very hard to get interactions going in the first place, she says, because computer scientists and biologists speak two different languages.

"Biologists sometimes think computer scientists are simply programmers," says Werner-Washburne, "and mathematicians often think biologists are missing the genes for understanding math."

The key, Werner-Washburne says, is knowing enough about how another person sees the world, and what he or she does, to know what questions to ask. When you have an idea that calls on both camps to come up with their best ideas, it's like magic, she says.

Fast Track

Werner-Washburne monitors gene activity in cells at intervals considered lightning-fast compared to what has been done traditionally (every 5-10 seconds *vs.* a few minutes to several hours). She needed a new kind of tool to sample cell cultures this fast.

The trouble is, you can't just open up a scientific catalog and buy a thing to do that, she says. So her lab constructed a device called a rapid sampler that can grab small volumes of liquid, over and over again, from a culture of growing cells. Werner-Washburne, her lab technician, and an undergraduate student designed and built the contraption, working together with a chemist, a mechanical engineer, a computer scientist, and a chemical engineer.

JASON PADILLA JAETAO, ANGELINA RODRIGUEZ

A mixed group of researchers, including undergraduate student Jason Padilla Jaetao and lab technician Angelina Rodriguez, built this "rapid sampler" for about $600.

Made from scratch, the sampler cost about $600.

The device is simple: At the click of a switch, a waft of pressurized air flows into a sealed glass flask containing cells growing in a culture broth. The sudden change in pressure displaces a small amount of cell-containing liquid into a metal catch tube, which delivers the cell samples to a collecting tube. By setting the test tubes in ice water, the scientists freeze the cells' molecular activity until further processing of the samples can display their gene activity readout.

Werner-Washburne says that because biologists did not expect to need to measure rapid changes in gene activity, no one had developed a tool to do it. She is excited that her research takes her in new directions all the time.

"It's discovery-based; that's what I love about this work."

Cross-Training

Werner-Washburne's joy of discovery began years ago during a 1 1/2-year trekking expedition from Mexico through Central and South America. She had recently completed her bachelor's degree in poetry—yes, poetry—at Stanford University in California.

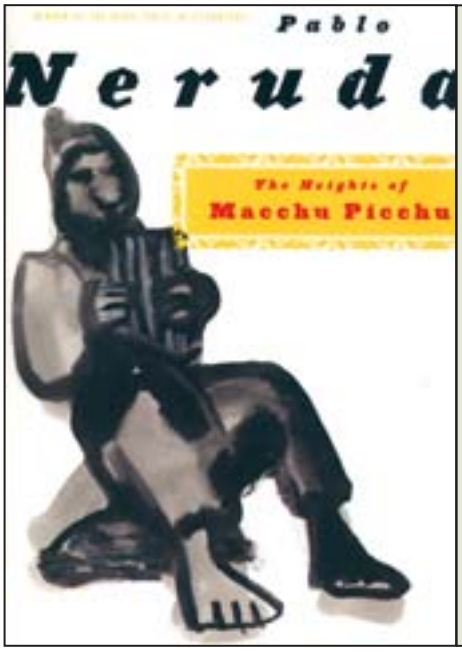
Werner-Washburne did well at Stanford, but she felt out of place and yearned to head southward to find her Latina roots. Her main goal at the time, she says, was to meet the Chilean poet Pablo Neruda, whose Nobel Prize-winning writing had electrified her.

"The minute I crossed the [Mexican] border, I knew I was home," she says.

Werner-Washburne was culturally alive and hungry for knowledge. She took everything in like a sponge. The environment, she remembers, was holistic in the sense that everyday life and science were tightly woven together. She recalls outdoor markets in Oaxaca, Mexico, where merchants sold plants for food and medicinal uses. Werner-Washburne watched locals create brilliantly colored purple cloth by harvesting the natural chemical dyes from mollusks in the nearby sea.

She continued her trek, traveling from Colombia to the Alaskan wilderness, where she worked for a year as a trapper, writer, and teacher for Outward Bound, a nonprofit educational organization. Next, Werner-Washburne worked as a paraprofessional nurse in a Minnesota health clinic serving mostly urban, single-parent Native American families. In addition to providing inspiration for ever better poetry, all of these experiences deepened her understanding of cultural diversity and nursed a growing desire to learn Western science.

Werner-Washburne took her first formal step toward becoming a scientist by signing up for courses at the University of Minnesota in St. Paul. In hopes of earning



Maggie Werner-Washburne was inspired by Pablo Neruda's epic poem, *The Heights of Macchu Picchu*. "After so much John Donne," she says, "the concept that someone could write amazing poetry about an archeological site was fascinating."

a master's degree in botany, she enrolled at the University of Hawaii in Honolulu. Her then-advisor, the late Sandy Siegel, impressed upon her the importance of being scientifically open-minded. Siegel's research interests included studying life in extreme environments, such as space and the Dead Sea.

A few years later, Werner-Washburne completed her scientific training by getting her Ph.D. and doing post-doctoral research at the University of Wisconsin in Madison. Still enamored with plant biology, she focused her attention on studying photosynthesis, the process by which plants convert carbon dioxide into energy using sunlight.

But pretty soon, there was a problem.

Although she enjoyed the topic immensely, Werner-Washburne found great difficulty answering key questions about how cells work with the molecular biology techniques available to study plants.

"There were so many things I couldn't do," she says, and she made a decision to switch to a more versatile model organism for probing basic biological questions: yeast.

Sitting Still

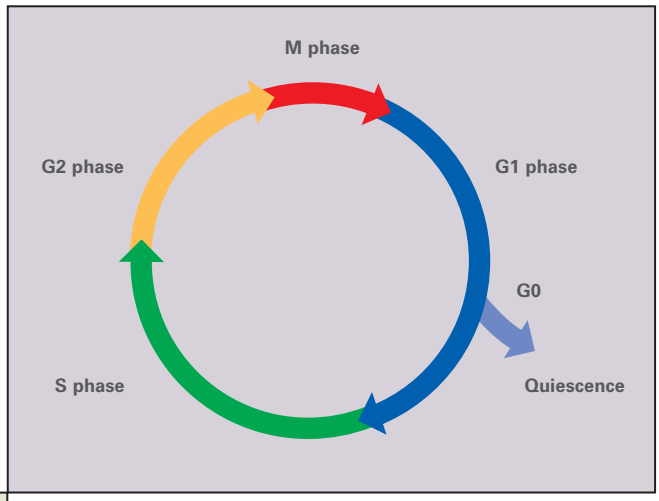
Like the cells that make up animals, plants, and people, yeast cells are eukaryotic. This means that yeast cells have compartments, such as nuclei and mitochondria. Because researchers know a lot about yeast genetics, yeast cells serve as miniature laboratories for thousands of scientists worldwide. They can easily mix and match yeast genes and figure out how the changes affect the cell.

However, the vast majority of yeast researchers focus their questions on cells that are actively growing. Werner-Washburne, on the other hand, is interested in yeast cells that do nothing but sit still. This phase of cellular life is called quiescence.

Quiescent cells are in a stalled stage of growth called stationary phase, a situation that is not unique to yeast. In fact, at any given time, almost all of the cells on the planet are "resting" in stationary phase, a stage scientists call "G-zero" (G0).

Examples of cells in G0 might include yeast cells resting on a grape leaf, the neurons in your brain, or deadly anthrax spores that lie dormant until propelled to grow by some type of signal, which is usually a source of food or energy.

When conditions are favorable, cells that can divide progress through an orderly set of steps called the cell cycle. During the growth part of the cycle, a cell gets larger and makes copies of all its components, including its genetic material, DNA. The division part of the cycle takes place in a step called mitosis, when the cell splits and produces a mother and a daughter cell.

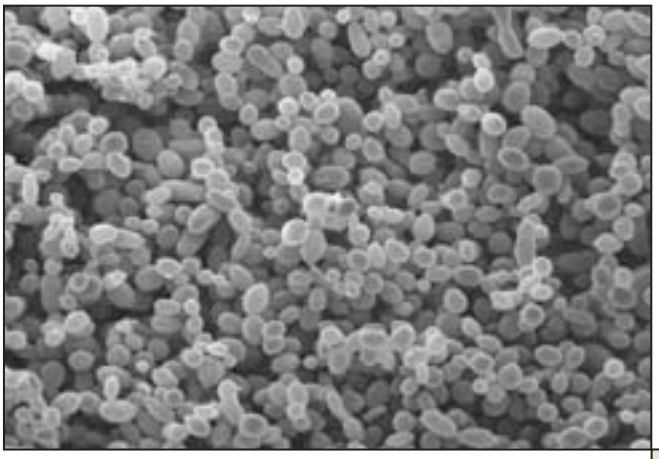


Cells progress through a cycle that consists of phases for growth (G1, S, and G2) and division (M). Cells become quiescent when they exit this cycle (G0).

Cells exit this cycle when they become quiescent. Something in a cell's surroundings sends a signal to stop growing. Researchers like Werner-Washburne suspect that cues in the environment set off genetic switches

inside cells, tuning up or down the activity of specific genes. Deciphering the signals that push cells in and out of quiescence, and finding the genes involved, is keeping Werner-Washburne very busy.

To find quiescence signals, she looks at sequential snapshots of the millions of working parts inside a yeast cell, over thousands of points in time.



LOUIS DE VOS, FREE UNIVERSITY OF BRUSSELS

Brewer's yeast, seen here under a microscope, is a common research tool for biologists who study cells.

All Together Now

Genomics is the study of how all of an organism's genes work together. In this sort of analysis, researchers hope to eventually understand how a functioning unit—like a single organ or even the entire human body—works properly in health or improperly in disease.

Scientists who study genomics use tools called microarrays, which are glass or silicon "chips" that are imprinted with small sections of thousands of genes in a grid-like pattern. The microarrays Werner-Washburne uses for her experiments contain a unique snippet of DNA from each of the 6,000 genes in a yeast cell.

DNA's natural properties make this technology possible. Miniature molecular machines inside your cells (and those in other animals, plants, microbes, and yeast) copy DNA by making an intermediate, complementary, copy of a gene. Scientists gauge the activity of a gene by the amount of the intermediate, called messenger RNA (mRNA), that the gene makes.

Using the rapid sampler device, Werner-Washburne and her coworkers measure the activity of yeast genes by collecting data every few seconds. Inside each collecting tube, the researchers have added special enzymes that automatically make matching copies of any mRNA present. The copies, called complementary DNA (cDNA), are then applied to a gene chip. If there's an exact sequence match and a cDNA corresponds perfectly with a particular gene sequence, that gene's spot on the chip lights up, because it has been tagged with a fluorescent dye.

It doesn't take long to realize that the amount of data from this type of experiment is staggering. Thousands of genes multiplied by thousands of time points adds up to more work than one person—or even several people—can handle.

Werner-Washburne got some help from scientists at nearby Sandia National Laboratories in Albuquerque. The Sandia researchers had computer software that could process such data, and they constructed a specialized microarray scanner that could interpret and distinguish between the output of many different dye colors at once. The end result is a genomics readout (see photo, page 7).

Werner-Washburne has found that when she nudges quiescent yeast cells to wake up by adding the sugar glucose to their culture dishes, a massive change occurs in the level of almost every messenger RNA in the cell. She has identified certain genes that appear to be particularly important for the yeast cells to shift into high gear.

"When needed," she says, "these cells are set to go from 0 to 60 miles an hour in a matter of seconds or minutes."

Similarly, Werner-Washburne can study the reverse process by withdrawing food from the yeast's culture broth. By doing this, then looking for changes in gene activity, she is closing in on several yeast genes that increase their activity when it's time to slow down and enter a resting state.

Understanding quiescence has implications for human health. Many microorganisms that cause infections, such as tuberculosis, are quiescent for weeks to months. What turns them on and off is an unsolved medical mystery.

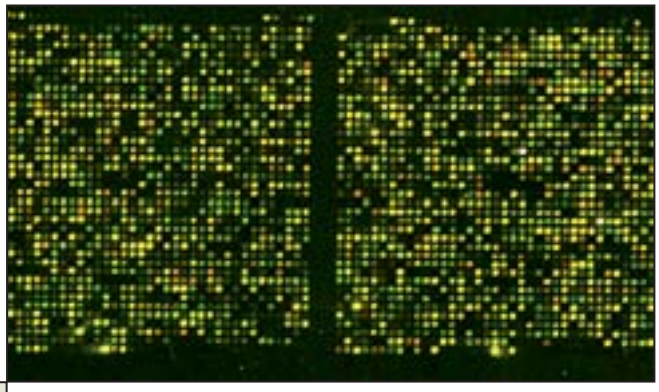
Time for a Change

Genomic research generates an avalanche of data, and computers, statistics, and math are essential for understanding it. Werner-Washburne has learned that math-based approaches are also important for designing

experiments correctly in the first place, and watching her students become increasingly comfortable with statistics and math has been gratifying.

"Biology students don't get enough math," she says. To counteract this deficiency, she holds in-lab tutorials and on-site training whenever possible. In some cases, coworkers at Sandia offer help to her students.

Thinking mathematically and crafting new tools add up to just one part of success in the exciting new research frontier of genomics. Werner-Washburne knows from personal experience that an important part of the mix is blending different cultures of people and keeping an open mind for discovery.



JUANITA MARTINEZ, ANGELINA RODRIGUEZ

Scientists use microarrays (photo) to gauge gene activity.

"I never expected the joy of science to last so long," says Werner-Washburne, "and I don't see it ending." ■

A Pioneering Spirit

TOM BRAHL

In Maggie Werner-Washburne's lab, graduate student Anthony Aragon has to think outside the box.

His Ph.D. thesis research project, cataloging the activity of thousands of genes in quiescent yeast cells, requires him to spend a lot more time planning his experiments than actually doing them.

"It's been really difficult for me to think this way," he says, describing paying constant attention to math and statistics in planning an experiment that will yield data he can trust. For example, Aragon says, most biologists study a process happening over time (often referred to as a time course) by performing each experimental "time point" in chronological order. But then they also process their samples and analyze their data in the same order.

"That's not really a good idea," he says. "You need to randomize each procedure to be able to identify the effect caused by time alone."

While it has been tricky for him to bend his mindset to be more mathematical, his pioneering spirit has certainly helped a lot. Aragon grew up in Manzanola, Colorado, a small, rural town of about 450 people. His close-knit Hispanic family, including grandparents, aunts, uncles, and cousins, all lived next to each other on the same street. Aragon was the first in his family to graduate from high school and the first in his town to go to graduate school.

While Aragon says it was a big deal for him to leave home for his education, he says his family has been very supportive. He also feels at home in Werner-Washburne's lab where he finds the research exciting and the atmosphere nurturing.

"Maggie is always ready to talk," he says.—*A.D.*

Asking Good Qu

uestions

"[Science] is really about asking the right questions and designing the studies properly."

JOHN LAIR

Daniel Sessler is an anesthesiologist at the University of Louisville in Kentucky. Sessler studies how the body reacts to surgery and anesthesia.

By Dan Hogan

Figuring out inventive ways of solving scientific problems is just part of the reason Daniel Sessler can't wait to get to work every day. It's also about figuring out good questions to ask in the first place, then following the unexpected paths those questions can lead to.

"That's why science is so exciting," says Sessler, an anesthesiologist at the University of Louisville School of Medicine in Kentucky.

By asking basic questions about what happens to the human body during surgery and anesthesia, Sessler has challenged conventional medical thinking. And the results of his innovative experiments have already led to big improvements in the health of surgical patients.

All in the Family

Sessler traces his scientific roots back to his childhood days, when his parents instilled in him a life-long love of learning. In the Sessler household, curiosity and creativity were daily staples.

"Every night during dinner, we discussed science," says Sessler, recalling growing up in Berkeley, California. His father, a physicist, would usually get things started by asking Sessler and his siblings a question.

"How would you calculate the circumference of the Earth or the distance to the moon?" Sessler remembers. "[My father] supplied the numbers, and then we did the calculations in our heads."

Sessler's mother, who was also a physicist, provided a different kind of inspiration, urging her children to pursue their educational dreams in the face of all obstacles. The child of immigrant parents from the Ukraine, she overcame prejudice to become the first person from her New Jersey high school to attend college, and she eventually became one of the first scientific computer programmers.

Doctor Scientist

Growing up, Sessler and his brothers did their fair share of homemade chemistry experiments, resulting in what Sessler remembers jokingly as a satisfying number of minor explosions. He enjoyed chemistry and decided to pursue it as

a career, majoring in the subject at the University of California, Berkeley. But even as early as high school, Sessler had been turned on to medicine.

"I enjoyed the idea of working with people, helping them deal with disease, and helping prevent and cure diseases. So I wanted to be a doctor, but I wanted to be a scientist, too."

Sessler completed all the course requirements for medical school even before finishing his undergraduate degree, and he jumped directly into medical school after his third year of college. After that, he was inspired by several scientist mentors. One of those was the late Henry Kaplan, then at Stanford University. Kaplan's pioneering work in radiation therapy helped conquer Hodgkin's disease, a form of cancer that strikes the body's lymphatic system.

"At the time Kaplan started working, Hodgkin's—like other cancers—was uniformly fatal," notes Sessler. "By the time Kaplan was done, Hodgkin's had a cure rate exceeding 90 percent." Hodgkin's disease became the first cancer that was routinely curable and inspired much of the research on other types of cancer.

Ironically, while Sessler was in medical school, his brother developed Hodgkin's disease, and he was treated and cured by Kaplan and his team at Stanford. Sessler's brother is now a National Institutes of Health-supported chemist and biochemist at The University of Texas in Austin.

What appealed especially to Sessler was Kaplan's approach of chipping away at a problem. Sessler recognized that new medical treatments could be developed simply by applying the scientific method: testing hypotheses by doing carefully planned experiments (see sidebar, page 13).

"Even though you think you know the answer, you don't actually know it until you do the test," says Sessler. "And once you do, surprisingly often you find that 'common knowledge' is simply wrong."

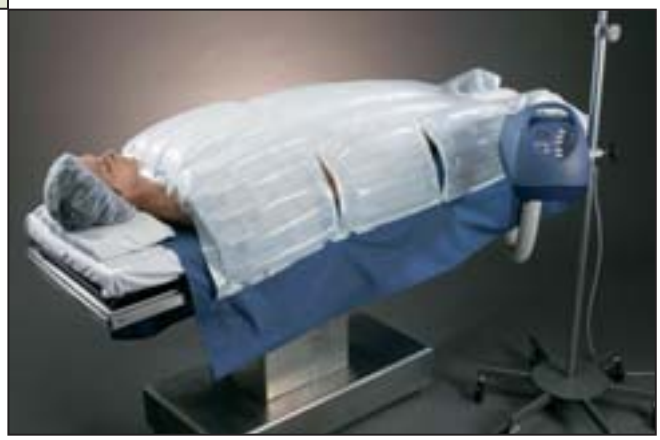
Out in the Cold

As recently as the mid-1990s, doctors thought it was perfectly normal that body temperature decreased during surgery, and they saw no reason to correct for this. Operating rooms were cold, the operations themselves increased heat loss, and the anesthetic medicines that were given interfered with the body's normal ability to control its internal temperature.

"I started studying temperature regulation because I was interested in how the body controls temperature," says Sessler. "I was fascinated by this process: How does the body know what its temperature is? How does it keep internal organs at the correct temperature?"

As an anesthesiologist, Sessler especially wanted to know how and why body temperature changes in anesthetized patients.

"Body temperature is normally very tightly regulated—more tightly regulated even than heart rate or blood pressure," he explains. The temperature of the body's core—the heart, lungs, brain, and other internal organs—is usually within a half degree of where it's supposed to be: 98.6 degrees Fahrenheit.



ARIZANT HEALTHCARE INC.

A disposable blanket and a forced-air heating device can keep patients warm before, during, and after surgery.

Anesthetic medicines, however, "really screw that up," Sessler notes, explaining that these drugs make the body's regulatory system less sensitive. During anesthesia, the body doesn't even try to keep its temperature normal. Moreover, anesthetic medicines act as vasodilators, meaning that they make blood vessels widen. As vessels open, blood flows away from the vital internal organs of the body's core and toward the body's periphery—the arms, legs, and skin. Since blood carries heat, this movement of blood takes heat away from the core, cooling it down in the process.

So, while the body usually clamps down blood flow to the periphery in order to protect the core from cold exposure, the opposite happens during surgery under anesthesia.

The periphery gets warmer at the expense of the core, and the patient suffers from a condition called hypothermia, in which the body becomes too cold.

Turning Up the Heat

Sessler began studying this problem with experiments that tested various potential consequences of hypothermia on the body.

"And to my great surprise," Sessler says, "I found a much larger effect than I ever would have expected." Just a couple of degrees of hypothermia—typical for surgical patients 10 years ago—"turned out to do terrible things to people," according to Sessler.

"For example," he says, "we found that less than 4 degrees [Fahrenheit] of hypothermia triples the risk of surgical wound infection."

Sessler and his coworkers also discovered that hypothermia increases blood loss by interfering with blood clotting, and hypothermia prolongs the amount of time anesthetic medicines remain in the body.

What's more, Sessler adds, the average infected patient stays 1 week longer in the hospital, which can cost more than $20,000. Such patients are twice as likely to require a stay in the intensive care unit, and they're twice as likely to die.

Fortunately, the answer to these problems was obvious: Simply keep surgical patients warm. No new drugs, no fancy technology. Just the minimal additional cost of maintaining normal body temperature during surgery.

"This was my kind of research," Sessler says. "We were evaluating a simple, risk-free, inexpensive intervention that markedly improved outcome. What we're talking about here is a $10 treatment with no risk that enormously improves [patient health]."

According to Sessler, keeping surgical patients warm can be as simple as draping them with a disposable, quilt-like covering (see photo, page 10) through which warm air is blown.

"That's all it takes," he says.

Maintaining normal body temperature is now the standard of care, and surgical infection rates have thus decreased substantially during the last decade. But why would such small changes in body temperature have such a big effect on the body's ability to fight invading microbes?

Daniel Sessler found that giving patients more oxygen reduced the risk of infection after surgery.

Oxygen: The Breath of Life

In their search for clues to shed light on the mystery, Sessler and his coworkers came up with more questions to challenge the standard thinking about anesthesia and surgery.

The researchers demonstrated that preventing hypothermia could reduce infection by increasing oxygen delivery directly to surgical wounds. They wondered if giving patients more oxygen during surgery would further reduce the risk of wound infections.

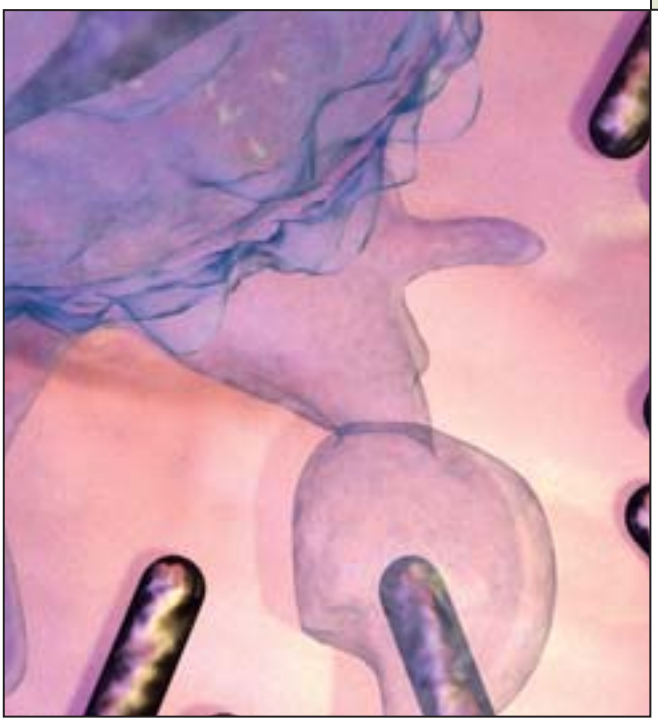
Until recently, conventional medical wisdom said that too much oxygen during surgery would be dangerous to patients.

"The amount of oxygen given to surgical patients has traditionally been relatively low—about 30 percent, which is only slightly more than room air," Sessler notes. "We would give a little bit extra because the lungs don't work as well as normal during anesthesia, but not much more, because oxygen was thought to be toxic."

Sessler and his team decided to put this assumption to the test. They found that supplemental oxygen given during surgery did no harm.

The next step was to see if more oxygen might actually help surgery patients. Sessler and his coworkers increased the oxygen content of the gas surgical patients breathe from 30 percent to 80 percent, and they slashed the risks of surgical infections even further.

"Medical oxygen is the least expensive drug on Earth," Sessler points out. "It costs a thousandth of a cent per liter: It is 40 times less expensive than tap water! And giving it is absolutely trivial—all you do is turn a knob a little further on the anesthesia machine."



THE WALTER AND ELIZA HALL INSTITUTE OF MEDICAL RESEARCH

White blood cells protect the body from infection by 'swallowing' bacteria (rod-shaped in drawing).

A Radical Idea

How does extra oxygen help fight infections? According to Sessler, this part of the mystery is fairly easy to explain.

Earlier laboratory studies had shown that white blood cells called neutrophils use oxygen as ammunition against invading microbes. This "weaponized" oxygen is in the form of free radicals: molecules with unpaired, highly reactive electrons that can damage cells and tissues. Normally, these radicals are hidden in special pouches in neutrophils to keep them from damaging normal tissues.

"In order to fight surgical wound infections, or any bacterial infection for that matter, a neutrophil must eat bacteria and then kill them," Sessler explains. "And it has to do both. If the neutrophils eat bacteria but don't kill them, the bacteria simply pop out after a while and go back to work."

This killing process requires oxygen. According to Sessler, neutrophils convert oxygen into bacteria-killing free radicals.

Sessler and his team are now conducting more studies to examine other factors that may influence the risk of surgical wound infection. These factors include the effect of nitrous oxide, the most widely used anesthetic medicine, as well as the effect of increasing levels of carbon dioxide in the bloodstream.

Keep It Simple

No matter what the study, though, Sessler follows a general principle: Keep it simple. He points out that most of his hypothermia studies were carried out with little more than inexpensive thermometers.

"It's really about asking the right questions and designing the studies properly."

Ultimately, Sessler believes, it's the simple interventions that yield the biggest bang for the buck.

"If you're going to improve [patient] care, the most effective way to do it is to find an intervention that's inexpensive or virtually free, that doesn't have side effects, and that's easy for physicians to implement."

Daniel Sessler founded a multinational anesthesia research program called Outcomes Research. Many of the clinical studies are done at the University of Louisville Hospital.

If you meet those criteria, Sessler explains, doctors will quickly adopt the technology, and this will soon lead to better patient outcomes.

While he was a researcher at the University of California, San Francisco, Sessler created a multinational collaboration of clinical scientists called Outcomes Research. Now based at the University of Louisville School of Medicine, the group numbers 65 members in some 20 different academic medical centers scattered over 10 countries.

Members of his group coordinate about 60 studies at any given time and publish about 25 scientific articles every year. This makes Outcomes Research the world's most productive anesthesia research group.

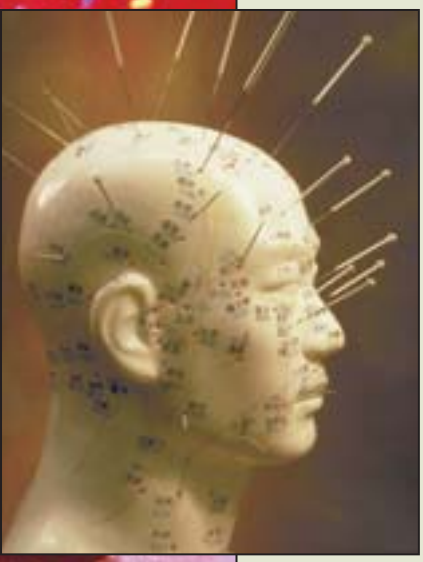
Flexible Thinking

In addition to being committed to science, Sessler has a rich, artistic bent. Encouraged by his mother, he took up modern dance in high school and "did as much dance as a dance major" in college. While attending medical school, he pursued photography as his artistic outlet. He ran a successful freelance photography business while doing his pediatrics and anesthesiology residencies in Los Angeles.

Sessler believes that people who allow their lives to be narrow and focus on only one thing, even if it's science, are missing out on more than they think.

"The best scientists are broad-minded," Sessler observes. "They see connections across many different fields [and have] a flexibility in thinking that allows them to see a step or two beyond the edge of existing knowledge." ■

Bias Be Gone!



Boost Your IQ… Achieve Eternal Youth… Say Goodbye to Baldness…

These and other claims of dubious "miracle cures" flood people's e-mail every day. How can you tell which claims are genuine and which are just plain bogus?

Ask any good researcher, and he or she will tell you that the only reliable way to discern fact from fiction is good science. Put together a testable question, then test your hypothesis by doing experiments: ones that others can repeat to validate your results.

"About half of all clinical studies fail to confirm their hypotheses," Daniel Sessler points out, "even though these hypotheses were not random thoughts, but instead were based on all available scientific literature. And still, only half are confirmed."

Sessler thinks it is critical to test hypotheses in properly designed and conducted clinical trials.

Case in point: acupuncture. Sessler and his coworkers are currently studying this ancient Eastern pain-control technique, which some people believe can be an effective alternative to conventional anesthetic medicines. However, Sessler notes, while some 6,000 research papers have been written on the subject, nearly all fail to meet even the basic standards of modern science. Sessler says such studies are prone to experimenter "bias."

"By bias, I mean the investigator's impression of what the results should be, or [the person's] desire for a particular result," says Sessler. "It's very easy for that bias to influence the results of a study."

To minimize the risk of bias in clinical studies, scientists use two important tools. The first is randomization: assigning patients to one therapy or another by some method that does not involve the researchers. Usually, randomization is done by a computer program that is similar to flipping a coin. Randomization prevents researchers from putting, for example, healthier patients in one particular group and skewing the results.

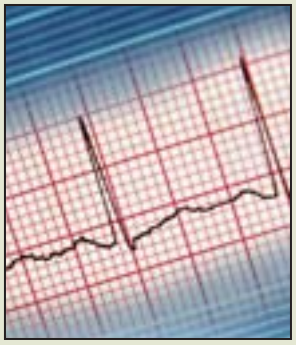
The second tool to prevent bias is blinding: keeping the researchers (and often the patients, too) "in the dark" about what treatment was used in which study subjects. If the scientists don't know which patients get a particular treatment, they are unlikely to influence the results in a way that might confirm their bias.

Sessler's acupuncture research is still in its early stages. He has many hypotheses—but he now needs to do the clinical trials.

"Only then will we know," he says.—*D.H.*

In a Heartbeat

Low-birthweight babies get a difficult start in life, usually spending their first months in a hospital neonatal intensive care unit (NICU). One-quarter of these very tiny infants (those under 3 pounds) develop sepsis within a few days of birth. Sepsis is a bacterial infection that spreads through their blood, leading to organ failure and sometimes death. Currently, diagnostic tests for sepsis in these newborns are imperfect, and often the problem is detected too late. If doctors could better monitor the onset of sepsis, many lives could be saved.



NIGMS grantee **Randall Moorman** of the University of Virginia Health System in Charlottesville is testing the idea that heart rate irregularities may signal the onset of sepsis in these high-risk babies. Along with UVA neonatologist Pam Griffin, Moorman studied two groups of approximately 300 infants who had been admitted to NICUs at two different hospitals for a period of at least 1 week. At the first NICU, the researchers continuously monitored the infants' heart rates while watching for symptoms of sepsis. By correlating these two types of information, the scientists were able to develop a mathematical model of sepsis risk based on abnormal heart rate characteristics.

When the scientists applied their model to similar measurements gathered from babies at the second NICU, they accurately identified which infants were at highest risk for sepsis. The new approach could enable doctors to easily and more accurately predict the onset of sepsis through noninvasive heart rate monitoring.

Natural De-Icer

Sometimes, medical clues come from unexpected places. For example, scientists who are interested in preserving cells and organs for transplantation are learning from fish that can swim in icy polar waters. To survive the frigid conditions, these animals produce a natural antifreeze that keeps their organs supple and functioning rather than frozen solid. If scientists could design similar molecules to preserve the function of chilled human organs, it would be a boon to organ transplantation.

Natural antifreeze works by lowering the freezing point of biological fluids, so that ice crystals will not form until the surrounding temperature dips to sub-zero levels. Years ago, researchers such as Robert Feeney of the University of California, Davis, became fascinated with the antifreeze molecules present in Antarctic fish. However, despite lots of hard work since Feeney's pioneering experiments, chemists have been unsuccessful in making antifreeze in large enough amounts to be medically useful.

Now, NIGMS grantee **Robert Ben**, a chemist at the State University of New York in Binghamton, has gone one step further toward achieving this goal by making customized versions of natural antifreeze. Beginning with specialized proteins that have sugar molecules attached to them, Ben applied a new method to substitute one of the chemical bonds in natural antifreeze with a sturdier chemical bond. With further refinements, synthetic antifreezes will be an important aid to storing human cells and tissues for organ transplants and other medical procedures.

A Breath of Fresh Air

Remember what your parents said about taking off the bandage on your skinned knee to let the cut "breathe?" Turns out they were right. After the bleeding stops, most wounds—even serious, slow-healing ones—heal better when aired out properly.

NIGMS grantee **Chandan Sen** of the Ohio State University Medical Center in Columbus evaluated a simple method to deliver oxygen, a component of air, directly to slow-healing skin wounds. These wounds are an unfortunate but common complication of surgery, burn recovery, and diseases like diabetes. Sen and his coworkers filled specialized plastic bags with pure (100 percent) oxygen and attached the bags directly around the wounds of 32 patients. The researchers applied the oxygen-filled bags for periods ranging from 3 weeks to 7 months, depending on the severity of the wound. Their results showed that three-quarters of the stubborn wounds responded to the treatment and healed.

CHANDAN SEN

Delivering pure oxygen this way holds promise as a cost-effective, safe way to treat serious wounds. Not only does it seem to be as effective as current treatments, but it also has several advantages. The treatment could be easily used at home and it is simple enough to be used by many people at once, such as during a public health emergency or at war.

Stuck on Mom

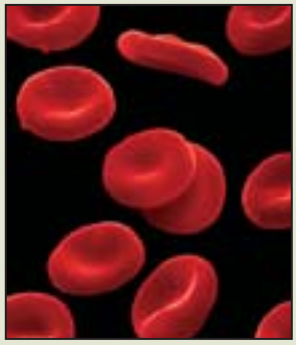
After fertilization, an embryo has just a few days to settle into a woman's uterus, implant, and start growing into a baby. Researchers have learned that during the fertile period in a woman's menstrual cycle, cells in her uterus acquire a sticky sugar coating.

Recently, NIGMS grantee **Steven Rosen** of the University of California, San Francisco, teamed up with fellow UCSF scientist Susan J. Fisher to make an important discovery about implantation, which Fisher had been studying for many years. The researchers found that a molecule on the surface of embryos appears to help them adhere to the sticky uterine lining. Rosen's earlier research had revealed that white blood cells use a sugar-grabbing protein called L-selectin to crawl along the surfaces of blood vessels. Rosen and Fisher reasoned that embryo cells might use a similar method to roll to a stop and implant inside a woman's uterus. They found that trophoblasts, cells that ball up around a developing embryo, were indeed studded with molecules of L-selectin. The scientists performed experiments that mimicked the environment and blood flow conditions inside the uterus. They learned that trophoblasts stuck most tightly to samples of uterine tissue collected from women in a fertile period of their menstrual cycle.

The research holds promise for understanding and treating infertility, since the failure of an embryo to implant properly is a common cause for problems in conceiving a baby and in many types of pregnancy loss.

PC, M.D.?

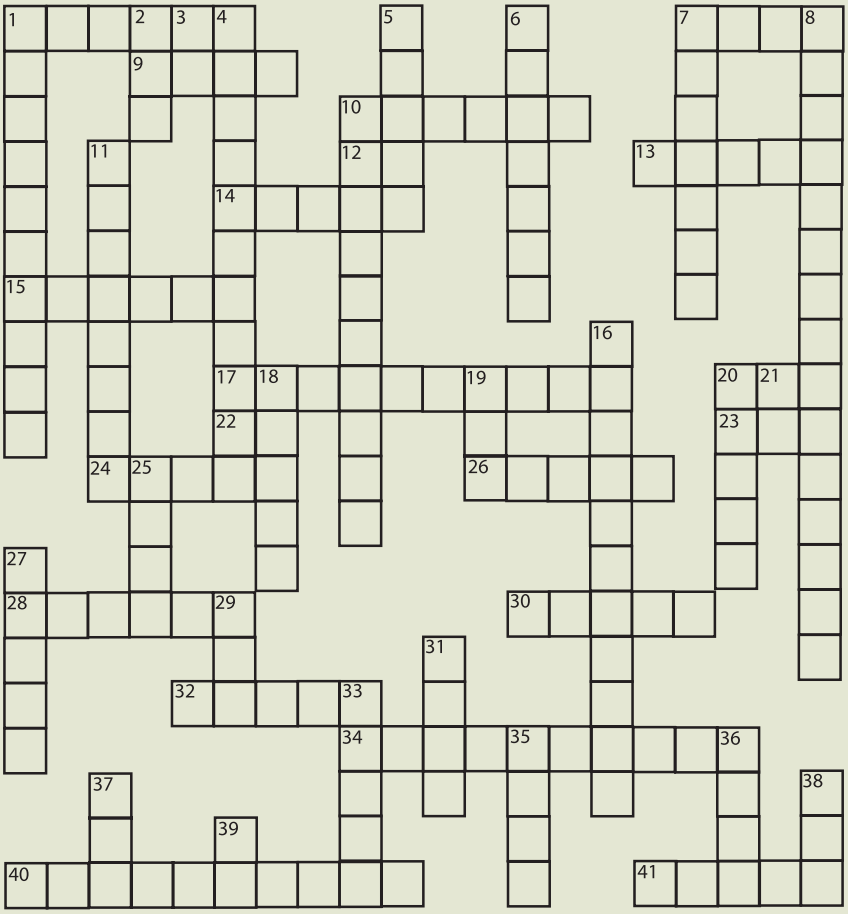
It's unlikely that computers will ever replace doctors. But computer-based methods are doing their part to help researchers understand health and disease. Recently, NIGMS grantee **Bernhard Palsson**, a bioengineer at the University of California, San Diego, created a computer (*in silico*) model of how red blood cells work, based on the results of thousands of previously published experiments on red blood cells. He then used the model to study how genes play a role in a disorder called hemolytic anemia. In this type of anemia, red blood cells self-destruct and bone marrow is unable to replenish the supply. People who have the condition are prone to fatigue, shortness of breath, and a host of other health complications.



Palsson used the *in silico* model to simulate the altered chemical reactions that take place in the cells of people with hemolytic anemia. Scientists know that deficiencies in two critical red blood cell enzymes can cause the disorder. These deficiencies can be inherited, meaning that they are caused by variations in a person's genes. Palsson and his coworkers used their model to look for links between gene sequence variants and clinical measurements from people with hemolytic anemia. The model accurately predicted which gene variants would cause a more severe, chronic form of hemolytic anemia and which variants would cause a less serious form of the disease.

Palsson's model shows that a mathematical approach can help scientists understand how a genetic change can cause a disease. Palsson predicts that in future years, *in silico* models will be commonly used for discovering new drugs as well as for diagnosing and treating disease.

The Last Word



ACROSS

1. Chilean poet Pablo
7. winter white
9. exchanged for money
10. red blood cell disorder
12. negative
13. quaking tree
14. king's wife
15. persons
17. cell resting state
20. yesterday's is
22. world org.
23. baseball bat wood
24. rate of movement
26. vine dweller
28. wound healer
30. single eukaryotic cell
32. classic game of wits
34. gene activity gauge
40. Sessler lab location
41. stove top

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

DOWN

1. fighting white blood cell
2. purpose
3. __ re mi
4. Werner-Washburne lab site
5. inert gas under krypton
6. study in which scientists don't know who got which treatment
7. Anesthesiologist Daniel
8. Biologist Maggie
10. surgery medicine
11. study of how all genes work together
16. 98.6, for the body
18. not over
19. sperm's partner
20. thawed ice
21. similarly
25. table tennis opener
27. injury
29. Nat. Inst. of Health
31. contest
33. little
35. unlocked
36. soft thread
37. large Australian bird
38. hive inhabitant
39. harmful wavelength of light

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