Asking Good Qu

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JOHN LAIR

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

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.

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

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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."

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

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."

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."

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.

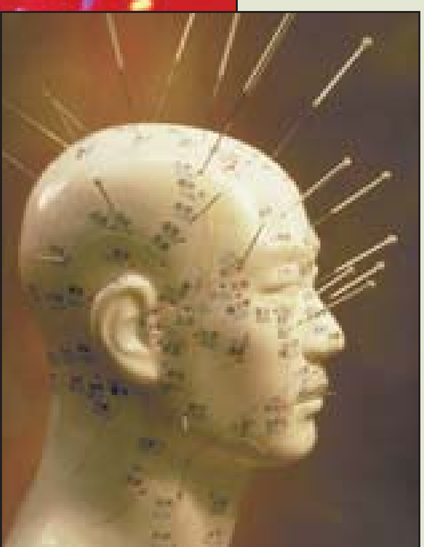
Flexible Thinking

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.*