David Gutterman

Focusing on the Little Things Leads to Big Discoveries

Jaclyn M. Jansen

In research, as in life, we often focus our attention on the big things. For example, the large arteries in the heart are probably some of the most well-studied parts of the human body, but the majority of our circulatory system is made up of much smaller blood vessels, including arterioles that are only a little thicker than a human hair. For David Gutterman, MD, it is that attention to the little things that has led to unexpected discoveries and major insights into cardiovascular function in humans.

Gutterman, who is Professor and Senior Associate Director of the Medical College of Wisconsin Cardiovascular Center, has focused his research on understanding the microcirculatory system and how it dynamically regulates blood flow to feed our organs. He takes the unusual approach of using primarily human tissue in his research.

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The microcirculatory system is controlled by the delicate balance of chemicals released from the endothelium, the innermost lining of all vessels. Two of these chemicals play a major role, namely, NO and hydrogen peroxide. In healthy adults, blood flow or chemical agonists stimulate NO release, which causes vasodilation. NO also modulates oxygen consumption and prevents inflammation and atherosclerosis. In contrast, blood flow in patients with heart disease releases hydrogen peroxide instead of NO. Like NO, hydrogen peroxide is a dilator substance, but it can also be proinflammatory and promote atherosclerosis. Discovery of this switch from NO to hydrogen peroxide set off a flurry of studies to understand why the shift occurs and how to prevent it as a possible means of treating cardiovascular disease.

Gutterman identified 2 unexpected compounds, TERT (the catalytic subunit of telomerase) and ceramide, that play opposing roles in the switch between NO and hydrogen peroxide.[1–3] In its primary role, TERT acts in the nucleus to maintain telomere length, stabilizing DNA. Gutterman and his colleague, Dr Andreas Beyer, found that TERT unexpectedly plays an additional role outside the nucleus. The protein can enter the mitochondria to promote NO formation, inhibiting oxidative stress and halting the production of hydrogen peroxide.[3] The results suggest that upregulation of TERT may be one way to help protect blood vessels in patients with heart disease.[4,5]

In contrast, ceramide, a proinflammatory lipid, is required for the often damaging switch from NO to hydrogen peroxide. Gutterman and his colleague, Dr Julie Freed, found that blocking ceramide in blood vessels from patients with heart disease could force them to shift from producing hydrogen peroxide back to NO.[2] With these discoveries, Gutterman has provided insight into how the microcirculatory system is controlled, offering potential methods for treating cardiovascular disease.

Gutterman's work also extends to the role of exercise in vascular function. In many ways, cardiovascular disease is a form of chronic stress. But certain types of exercise, like weight lifting, also act as a stressor. For example, researchers have known for decades that weight lifting leads to a dramatic, acute spike in blood pressure.[6] In animal studies, such a spike is sufficient to impair vascular endothelial function. Gutterman and his colleagues tested whether the same phenomenon occurs in humans. They found that in seasoned athletes a brief spike in blood pressure had little effect on vascular endothelial function.[7] But for couch potatoes, a smaller jump in blood pressure during weight lifting impaired endothelial function, reducing NO-mediated dilation.[8] The results were similar in cell culture: microvessels from nonathletes switch from NO to hydrogen peroxide release when pressure increases, mimicking the results for patients with cardiovascular disease.[9] Now, Gutterman and others are working to understand how routine exercise in athletes protects blood vessel function from the deleterious effects of stress.

In a recent conversation with *Circulation Research*, Gutterman discussed how he became a successful scientist. His career has been marked by a notable attention to detail and an open mind, which together have enabled his major discoveries about vascular function.

Where Did You Grow Up?

I was born in Pennsylvania, but I spent most of my childhood in Piedmont, North Carolina. Over the years, I've kept moving north (first to Iowa then Milwaukee). From the perspective of the weather, it has been the wrong direction. I miss the warm humid southern summers and mild winters. But here in the Midwest, I have found an impressive work ethic, wonderfully collaborative scientists, and

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fantastic job opportunities. I don't enjoy the winters, but they do keep me indoors and productive a good part of the year.

What Was Your Family Like?

I have twin sisters who are 2 years younger than me. That was tough when we were young from all the taunting and practical jokes, but fortunately, we outgrew that, and we are very close now.

Both of my parents had undergraduate degrees, and my father went on to get a PhD in engineering. He was the first in his family to get an advanced degree. He was in business and manufacturing, not research. Education was always a priority in my family. Being a nerd, I enjoyed school and rarely got into trouble.

When I was very young, my father's brother invited him to move from Pennsylvania to North Carolina. My uncle was in the furniture business, and he thought my dad should use his engineering degree to build metal furniture frames. So my family moved, and my dad and uncle started a company that did exactly that.

How Did You Become Interested in Research?

I always liked science and math. I never thought about going to medical school until I was in college. I always thought I'd go to graduate school in math or chemistry.

As I thought about it more, I realized that if pursued a graduate degree in math, then I would do very little chemistry in the future. Conversely, if I went to graduate school in chemistry, my math work would be limited. But by attending medical school, I could apply both chemistry and math in my research. I decided to apply and see what happened.

How Did Your Parents Feel About Your Decision?

My parents were certainly an influence in my going to medical school. I don't think they were excited about my interest in math and chemistry. My plan was to apply to medical school, and if I did not get in or if I didn't like it after the first year, I'd leave and do something else. I was accepted to University of North Carolina, Chapel Hill, and never looked back.

Did You Ever Consider Only Practicing Medicine Rather Than Doing Both Clinical Work and Research?

I've always been interested in research. I can't remember a time when I haven't been motivated by curiosity. I want to understand why we practice medicine a particular way rather than just learning what to do.

My first formal experience with research was as an undergraduate in a chemistry lab. It never led to a publication, but the work was exciting discovery science. When I got to medical school, I found a research lab right away. I spent my first summer collecting human samples of gonococci from patients at the county health clinic. Our goal was to make antibodies against proteins on the surface of gonococci so that we could ultimately make a vaccine for the disease. That project was also a complete flop, but it was still a pivotal point in my career. I became fascinated with the approach of addressing interesting scientific questions, no matter how the experiments turned out. Although I have always enjoyed caring for patients, I knew then I would not be happy unless research was a component of my career.

What Made You Move From the South to the Midwest?

During medical school, there was one teacher, a private practice gastroenterology physician, who I really liked. He had an excellent approach to medicine, and I enjoyed his teaching. I decided that no matter where it was, I would at least apply to the residency program where he had trained. That caused me to interview at the University of Iowa. At that point, I didn't even know where Iowa was on a map. But after a short visit, I was hooked. Iowa City is a wonderful college town, very similar to Chapel Hill, and the University was a very strong place for cardiology.

My first rotation was in cardiology. On my first day of internship, I asked my attending how I could do research. He put me in touch with a very prominent cardiac physiologist and cardiologist, Melvin Marcus, MD, who became my mentor. He didn't ask me any questions during that first meeting. He just took me down to the lab and that was it.

Those years at Iowa were really what refined my interest in cardiovascular research. I stayed there for 18 years, starting with my internship and ending a few days after I was promoted to full professor.

What Made You Leave Iowa?

I'm a bit of a sedentary guy, and only moved once in my career. But that move was professionally very good. Many of the coronary vascular researchers had left Iowa by 1998, and I really missed being part of a big team.

It was the people at the Medical College of Wisconsin (including one formerly from Iowa) who reached out to me. MCW was a haven for microcirculatory research at the time. The opportunity was a great one. MCW is a very collaborative place, and I've been able to take advantage of the broad expertise here, as a PI and a collaborator.

Your Career Life Is Very Full. What's Your Life Like at Home?

My wife and I have been married for 36 years, and we have 3 daughters and recently a granddaughter. Our youngest child left our home a year and half ago. I miss having them around. Otherwise, home for me is largely a time without distractions to complete work that I don't have time to do during the day. I also try to relax for a little while—it helps to bring a fresh face to existing projects.

How Did You Balance Your Work and Your Home Life When Your Daughters Were Growing Up?

My kids all turned out great, and my wife is responsible for that. She was a pharmacist, but when our first daughter was born, she decided to stay home.

I incorporated my daughters into my life, bringing them to the lab, riding bikes together, and watching videos together. My youngest and I almost completed all of the Star Trek episodes before she went off to college.

I tried to make my family a priority, like we all try to do. I set aside time specifically for them, and I tried to avoid additional responsibilities on weekends and evenings. I was able to attend almost all their events and performances. I attribute this to my wife who ensured that I blocked off time on my calendar.

In retrospect, I was more of an intermittent and sometimes indirect influence on my kids while they were growing up. It's tough to maintain a good balance when you are young and trying to build your career. There is no magic formula; it requires a lot of give and take.

Did You Do Much Science at Home With Your Kids When They Were Young?

Of course, though much of it was more biological. We had a microscope, and we would take samples from dirt under rocks or

water from a creek. We also played with a chemistry set at home. I would bring them into the lab, and they did some manipulations under the microscope there. None of them got the research bug though. I didn't want to push them toward science. They have diverse careers, and I could not be prouder.

What Do You Do When You Aren't in the Lab?

I do a lot of bike riding. I get a lot of ideas for science on a long bike ride when the usual distractions are not present. I also volunteer at my synagogue.

I really like my work and often end up spending my weekends and evenings working, especially now that the kids are out of the house.

How Hard Do You Work?

If I'm not doing 60 to 70 hours of work a week, it feels like I'm on vacation. But research doesn't feel like work. I'm learning new things all the time, and that's exciting. When I take more than a couple of days off, I start feeling antsy about getting back to work—though maybe that's not a good thing.

There were certainly times when I felt tension between work and my home life—especially around grant deadlines which test work-life balances. In the aggregate, it felt like I was able to balance appropriately, but my wife might have a different opinion on that!

What Advice Would You Give Young Investigators?

One of the more unexpected pearls that I have discovered is that it is really important to surround yourself with early-stage trainees, like undergraduates and graduate students. Even though they don't have formal training, they have the right thought processes. They bring unbiased input to conversations in the lab, and their unique, out-of-the-box ideas have often had a profound impact on the lab. Trainees and technicians have raised provocative ideas that I wouldn't have considered.

I also think it is important not to be isolated from your community of scientists. I'm an introvert, but I love attending national scientific meetings—they feel like a family reunion. I find that maintaining connections and interactions is not only important for advancing your research—research is largely a team sport—but also for developing friendships. In fact, I go fishing periodically with a group of coronary physiologists from around the country.

Are There Any Common Mistakes Young Scientists Should Avoid?

Let every experiment be a hypothesis and don't go into the experiment with an expected outcome. This advice can be hard to follow, but if you don't, it is easy to miss unexpected but important observations.

I also suggest that young researchers keep a balanced portfolio of projects. Pick 2 or 3 ideas to study at a time—not 10. One should be a core, bread-and-butter project. You also need a high-risk, high-yield project to diversify your portfolio. Finally, I think it is important to have a collaborative project.

An ancillary practical piece of advice—which is not always possible—is to try to ask questions that are interesting no matter how they turn out (in support of or refuting your hypothesis). Those types of experiments are reportable either way, which means that you'll always have material for papers.

You've Been Doing Intense Research for Quite Some Time. Do You Ever Consider Retirement?

I do but not in the traditional sense. Rather than fully retire, I would love to take a position where I could be a mentor to younger faculty. I've found that I really enjoy helping new scientists become successful in winning grants—even more so than getting my own.

When people join my lab, they pick a project that isn't assigned to anyone else. If it gains momentum, then they can take it with them wherever they go. My goal is to get them to a point where they can successfully apply for an R01. Watching trainees take off on their own, securing extramural funding and establishing their independent academic careers, has been the most rewarding experience I have had in science.

Disclosures

None.

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