Paul Simpson

With Rigor and Discipline, Researcher Finds a New Way to Protect the Struggling Heart

Jaclyn M. Jansen

In recent years, it's been argued that biomedical research is in the midst of a reproducibility crisis because results from big name labs and even bigger journals publicly fail to withstand scrutiny.[1] But if there is a crisis, one researcher stands out from all the rest for his rigorous, comprehensive, and yet focused approach to science. Paul C. Simpson Jr, MD, Professor of Medicine at the University of California, San Francisco, and Staff Physician at the Veterans Affairs Medical Center in San Francisco, has dedicated his research career to a search for unambiguous truths, developing methods that could be easily reproduced in labs around the world for decades, and making foundational discoveries that have become the basis of a potential treatment for heart failure.

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Paul Simpson

Simpson, a physician-scientist, established his own lab more than 40 years ago. In those early days, he set out to develop the first cell culture system for cardiac myocytes. Drawing on his training as a cardiology fellow, he defined a protocol to isolate and culture neonatal rat cardiomyocytes[2] that is now widely used around the world.[3]

In one of the first uses of that model, Simpson tested the impact of stress hormones on myocytes. At the time, it was thought that adrenaline would kill the cells. In fact, he found the opposite: rather than dying, the cells grew larger. Simpson could hardly believe the data, so he repeated the experiment again and again in different ways. The result was always the same.[4,5]

That seminal and serendipitous discovery became the foundation of Simpson's research. To hear him tell it, Simpson's focus has strayed little from that initial observation. He has only delved deeper, defining the pathways and mechanisms that are responsible for the effect and extending those initial findings from rat to mouse to rabbit to sheep to man.

Simpson and his lab found that adrenaline signals through the α1-AR (adrenergic receptor) family. However, only one subtype, known as α1A-AR, protects the heart in times of stress. Loss of this receptor in mice causes heart problems,[6] but stimulation of α1A-AR strengthens cells, causing an increase in contracting fibers and energy storage. Ultimately, α1A-AR stimulation prevents cardiac cells from dying.[7–11]

In the early 2000s, Roche developed a small molecule agonist for α1A-AR, known as dabuzalgron.[12] The drug, designed to treat urinary incontinence in women, was well tolerated and showed minimal toxicity in phase 1 and 2 trials. However, it failed to effectively treat incontinence, and Roche eventually halted the clinical trials.

Simpson and Brian C. Jensen, MD, a former trainee who is now at the University of North Carolina Chapel Hill, tested dabuzalgron in animal models of heart failure. In every model they tried, the drug improved heart function. At low concentrations, like those used in these studies, dabuzalgron is very beneficial in heart.[9] Now, Simpson and Jensen are working to translate this basic science discovery into a clinical trial to treat patients with heart failure.

While Simpson's singular focus has been on finding a new and better treatment for heart failure, his work has been comprehensive, challenging established ideas in the field. For example, his lab found that a classic fetal gene, *β-myosin heavy chain*, is not a marker of cell hypertrophy as believed.[13] They

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also found that cardiac myocytes have few if any β2-ARs and that α1A-ARs are present at high levels in only 20% of cells.[14]

In a recent conversation with *Circulation Research*, Simpson described his rigorous and diligent research philosophy, how his training contributed both to this philosophy and to his research direction, and the challenges facing young scientists today.

How Did You Become Interested in Science?

I was always good in school, and I had among the higher grades in my class. I was good in science, and I liked it. Science always appealed to me.

It was never a question: I wanted to be a doctor. I knew that from as far back as I can remember. My interest in being both a scientist and doing research developed as I began to learn that you could be a doctor who does research. As I tried these little research things and found that I liked it, I decided I wanted to be an academic doctor and do research.

What Was Your Childhood Like?

I grew up in Nashville, Tennessee, born and raised there. My father was a businessman, and my mother was a homemaker—classic '40s and '50s life back in Tennessee. I have a brother who's a retired dermatologist. He lives back in Nashville. My grandfather was also a physician.

When Did You First Start Doing Research?

When I was in high school, I was an animal care person for Rhesus monkeys at Vanderbilt University.

As an undergraduate at Davidson College in North Carolina, I spent a summer doing psychological research with Down syndrome kids at the University of South Dakota in Vermilion. I wanted to see whether you could make a what's called a Skinner box—something that's normally used to teach animals in a lab—to help kids with Down learn. I made this thing that rewarded correct answers. You haven't heard of it because it didn't work so well. It didn't get published, but it was a fun summer project.

I finished college a little early, and I went to Saint Louis to go to medical school at Washington University. I worked in a couple of different neurochemistry labs there. I learned how to do a lot of biochemistry and things like that.

During my medical residency, I didn't do any research, but just afterward, I went to the NIH. It was in the Vietnam era, and in lieu of other kinds of military service, you could be a research fellow at the NIH, working in the Public Health Service. I was lucky enough to do that.

I worked in a neurobiology laboratory under Marshall Nirenberg (he was awarded the Nobel Prize in Physiology or Medicine in 1968). He was the big influence in my research life. He was an incredible scientist. And he was the one that was always talking about being absolutely sure that everything that you published was as true as you could get and to be sure that the methods were detailed and validated enough that anybody else could read what you did and get the same results.[15]

Nirenberg was simply a super careful, rigorous scientist who also thought that you should study something really important. At the time I was in his lab, he was trying to understand how memory worked.

You Had a Significant Amount of Experience in Neuroscience. How Did You End Up in Cardiology?

I had my own psychiatric issues when I was in college. As a result, I thought I wanted to be a psychiatrist and do neuroscience research. I wanted to learn how the brain works. But then I went to Massachusetts General Hospital to do my residency, and I was impressed with the cardiologists there. They were a group of outstanding physicians and people. I was so impressed that I switched and decided to be a cardiologist.

It was a big switch. But I also thought it was going to be too hard to figure out how the brain works. Forty years later, they are finally starting to make progress, so I was right on that!

Where Did You Get Your Start in Cardiology?

I became a cardiology fellow at Massachusetts General Hospital. Towards the end, I went to Glenn Langer's lab at UCLA. He was a really fine scientist and he helped me learn how to culture neonatal rat cardiac myocytes. I was also able to watch some of the operation of his lab.

A few years later, in 1977, there was an opening at the San Francisco VA Hospital and UCSF for a cardiologist who was interested in basic research. In those days, there weren't many cardiologists interested in basic research, so I got the job. They gave me this brand new, empty space and told me to set up a lab. That's what I did. It was a fantastic opportunity. It took a while to get going, but eventually it worked out. Since then, it's been the usual career of trying to get papers published and grants funded. I just try to keep it going.

How Do You Spend Your Time at Work Now?

I have a lab, and I'm also a clinician, so I am quite busy. I have a cardiology clinic one day a week, and I share clinical duties in the Cardiology Division with my colleagues. I work in the Coronary Care Unit and see patients that are in the hospital with heart problems.

I spend about 50% of my time in the clinic and the other 50% on research. It does vary—when I'm doing a clinical rotation, I'm seeing patients 100% of my time. At other times, I am able to focus 100% on research. But if you average it out, I'd say it's an even split.

What's Your Lab Like Now?

It's a small lab with about half a dozen people. I really like to be close to the data and to pay attention to what's going on in the lab. I just don't have the time to properly oversee a large number of trainees.

Over the years, it's been about a 50/50 mix of physician-scientists and PhD scientists. Since my lab began, I've trained about 100 people, including high-school students, a few grad students, plenty of post docs, and a couple of people on sabbatical. About half of my former trainees are now in academics, and the rest are in either industry or somewhere in private practice.

I do have two staff research associates who have been working in the lab for 20 and 30 years. It gives me a really stable base and continuity in protocols and knowledge. The trainees come in and out, but never more than a couple of new trainees and my staff researchers are always there.

I also have a really close collaborator that deserves mention: Anthony J. Baker, PhD. We've been working together for 20 years. His skill set is working with contraction and calcium and electrophysiology, which are all areas where I don't really have expertise. He's an expert on the right ventricle. We've been really fortunate to be able to work together and publish papers together using our combined expertise.

Are There Qualities That You Think That Are Important to Be Successful in Science?

I think the things I learned from Marshall Nirenberg are still important today: try to study something that's important and new.

That means you've got to know the literature, so I am insistent on doing a lot of reading.

I think you also have to be really careful, paying attention to everything you do to be sure that you can reproduce it. And when you have the data, you need to be as sure as you can be that you've got it all right before you publish it. That means doing controls over and over again, as many different controls as you can. Try to see if there's a different way to look at your experiments and results. Test your hypothesis in a different way, and see if you get the same answer. You can't just do a couple of experiments. You need to try to be sure that you've got it right.

You've Emphasized the Importance of Rigor in Research, but There Is a Lot of Public Talk About a Reproducibility Crisis in Science. Can You Comment on That?

Our system requires you to publish at a certain rate to keep your funding going, which means there is a rush to try to get papers out. It causes people to cut controls and skip validations. We aren't following Marshall Nirenberg's principles.

I've suffered by having periods in my career where I'm not putting out many papers. In fact, I recently had a grant review that said I hadn't been very productive. They said, "Well, he hasn't published anything in the last couple of years, so he's not very productive." Good science takes time, but time between papers can be a problem.

The same was true for Marshall Nirenberg. There was talk of booting him out of NIH, and he published the papers that got him a Nobel Prize. You should have seen him. He got down to details that you would not even think about, like the shelf you had your things on. He drove a lot of people in his lab crazy with how much detail he wanted in a protocol.

It takes time to do really good science, I think. And the system is not really set up to accommodate that.

What Are Some of the Other Steps Young Scientists Can Take to Ensure That Their Research Is Rigorous and Reproducible?

There have been lots of papers published about reproducibility and blinding experiments and how to best control your work. We need to be sure that young scientists are trained in these principles of rigorous research.

I also try to have things reproduced by more than one person. If a result is really right, then people ought to be able to get the same answer even if they have their own little quirks when doing protocols. If findings don't hold up, they don't serve as a building block for the next step.

It feels really good that I've been doing this research since the early 80s, and it's all been right. We are almost ready to try a drug in people, because things have been correct all along.

Aside From Your Attention to Detail and Rigor, Can You Talk About Other Qualities That Are Important to Be a Successful Scientist?

You must have a good eye for what's important. If you really know the literature, you can spot things that are contrary to what people think. And you can understand what experiments will be important. For me, it started with putting adrenaline on heart cells and seeing that they get bigger. At the time, nobody knew that. I could have just moved on to the next experiment since this one didn't work the way I thought it would. But instead I realized it was interesting and novel.

You also need to be fairly good at writing, because it's the key ingredient to being successful. Writing is the fruit of our labors. Sitting down in front of the computer to write is my favorite part of the research process. I like to look at the data, make figures, and put our science into context.

You also need to get used to rejection. It is a big part of the business. I've counted up how many grants and trainee awards I've written and how many I was awarded. Turns out, I have written about 100 and only received about 50. That's a 50% rejection rate! I'm not sure if it's average, but you have to believe in your work, certainly.

You Seem Incredibly Dedicated to Your Work. How Hard Would You Say You Work?

This career is a lot of work. I don't think there's any getting around that, so you have to like what you do. I like doing the science and it's enjoyable to me. I probably do some work every day, unless I'm on vacation. It's hard to say a number of hours, but it's a lot. I try to take time to exercise. I don't work late at night anymore, like I used to. I try to spend evenings with my wife and take vacations.

How Do You Balance Your Work and Home Life?

I would say that balancing hasn't been my strong suit. I've been through ups and downs in marriages and relationships. For the past 13 years, I've been quite stable in a great marriage. My wife has twin boys, and we've got a great relationship. We live in the Bay area and have a really pleasant life.

I have a couple hobbies at home. I like to go to the gym—I'm sort of a workout nut. I also like to take walks and go on hikes with my wife. I like gardening. I get a lot of pleasure out of working in the yard. We have a home where there's a lot of gardening that needs to be done.

And, I guess I have to admit, I like stupid TV. My wife and I sit down at night and watch whatever program happens to be on at the time: *Game of Thrones*, *Better Call Saul*, or *Breaking Bad* are all relaxing for me.

When I'm on vacation, I like to take a bunch of books and do a lot of reading. I don't do much reading for fun when I'm in my daily life, because I try to do a lot of scientific reading. But vacation gives me a chance to catch up.

Is There Anything Over Time That You'd Say You Wish You Had Done Differently?

It is hard to think of anything that I would have done differently. Maybe I wish I had spent a little bit less time working at some points, and paid a little bit more attention to life outside the work arena. But I'm doing better at that now. I guess that would be the one thing that I would do differently: I'd be a little bit more mindful about what I do when I'm not working. I didn't pay as much attention to that part of my life during the first 15 or 20 years of my career.

Over the past 13 years, my wife deserves credit for all her support and encouragement. My work was more of a point of conflict in past lives!

Are There Common Mistakes Young Scientists Should Avoid?

Reproducibility is the most common thing I have to counsel people about. I tell them to be more careful. You should be able to tell me how you did something, and it should be written down exactly. Marshall Nirenberg would say "Don't tell me the data, tell me how you did the experiment."[15] Young scientists tend to want to see results, but sometimes, they don't pay enough attention to how they got there. And the how is really the key.

When young scientists are starting out on their first grant, by far the biggest mistake I see is not being focused enough. My rule of thumb is you should always be thinking about your next grant. Even after you have funding, you should be thinking about how the experiments you are currently doing are going to lay the foundation for your next grant proposal. That means you have to stay focused on what you are doing and make progress towards what you want to do next. It is continually developing a focused story. It's easy to get distracted and lose your way, but then you don't have good data to support your next round of funding.

Even though I haven't been incredibly productive in terms of number of papers, I think if you have good data and something interesting, you can stay funded. Just focus on good data, something interesting, and a developing biological story.

How Do You Feel That Science Has Changed Over the Last 40 or so Years of Your Career?

Obviously, we can do a ton of things that we used to not be able to do. Science has advanced tremendously, and we are way more sophisticated at ferreting out basic mechanisms.

At the same time, the reproducibility issue has also been one of the biggest changes that I've seen. I don't remember worrying about that so much early on. Every time you read a paper, you have to wonder whether or not you can believe it. That's a problem.

Some of the so-called high-impact journals like *Science* and *Nature* and *Cell* seem to be the worst offenders. I find that I hardly read them anymore. I'm not confident that the research has been carefully validated.

Science is a lot harder now, I think. The funding is tighter, which makes it a tougher business. That makes the need to publish more urgent. I went a couple of years at least before I published my first paper when I started my lab. I didn't get fired. I don't think you'd last if you did that now.

Are There Other Unique Challenges That Young Scientists Face Today?

I've had a lot of brand new scientists in the lab, and I've been counseling a couple who left the lab recently. The biggest challenge is getting that first R01, and then the next challenge is staying focused on what you said you would do so that you can get your second R01.

To get the first R01, you need good data. You have to be a good writer with a good story and keep plugging away. You've also got to believe in yourself, and believe that what you found is interesting, true, and important. Once you've convinced yourself of all of those things, then you just have to keep plugging away until you can convince others that you're onto something, too.

Disclosures

None.

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