Garrett Gross: Probing the Processes of Protection

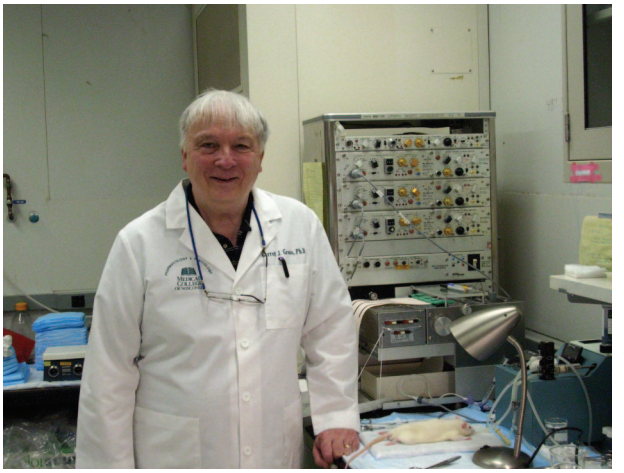
Ruth Williams

In keeping with the idea that a little bit of bad can sometimes be good, transient ischemic episodes in the heart can be protective against more serious future attacks.

This protective process, called preconditioning, was identified in 1986.[1] Just a few years later, Garrett Gross and his colleagues discovered that drugs that opened cardiac ATP-sensitive potassium channels mimicked the preconditioning process.[2–4] The gateway to the molecular understanding of preconditioning was opened, and the field grew and grew.

Gross was, and still is, a preeminent leader in that field. In the late 1990s, work by his team showed that opioids, just like potassium channel openers, could mimic preconditioning.[5,6] This discovery spawned yet more excitement and research activity, partly because of the ready availability of opioid drugs, such as morphine.

Today, Gross, who is Professor of Cardiovascular Pharmacology at the Medical College of Wisconsin, Milwaukee, is still hunting for cardioprotective compounds and deciphering how they work. He talked to *Circulation Research* recently about his persistent passion for preconditioning and cardioprotective drugs.



Where Did You Grow Up?

Why did I grow up? That's a good question. Oh, where? [Laughs] I grew up in South Dakota. It was in a small town with only about 1500 people, so everybody knew everybody else's business. It was a farming and dairy community. I used to go out and work on the farms in the summer and bale hay and things like that. It was good exercise.

My father was the local pharmacist, so I also worked in the drug store during my younger years, on and off throughout high school and college. It was the family business. My mother helped out too, as well as being a housewife.

Did the Family Business Stimulate Your Interest in Science?

I definitely would agree with that statement, that and the fact that at school, I enjoyed the chemistry and biology classes the best.

My father bought me a chemistry set when I was young, and I was always attempting to build a bomb or a rocket in my garage. I think my love of rockets also had something to do with me being born on the 4th of July.

Where Did You Go to College?

I went to school at South Dakota State University. That's where my father had gone to school, 30 years before me, to obtain his pharmacy degree.

I studied pharmacy, too, expecting that I would take over the family business at some point—I was an only child, so the business was mine if I wanted it.

The Bachelors degree in pharmacy was a 5-year program, and after that, I took the state boards, but in my last year of school, I studied pharmacology, and I started to become interested in research. I began a Master's degree program right after I graduated, and I had just started work in the laboratory when my father suddenly passed away. He had a heart attack and dropped dead mowing the lawn. It was a hard time. He was only 55. I actually think that's one of the main reasons I became interested in heart disease research.

I had to put the Master's program on hold and go back and run the drug store for the summer after he died, but after 3 months of working there, I knew that it wasn't what I wanted to do. I decided I'd rather venture out into the research world, so I returned to finish the Masters at South Dakota State.

You Moved to the University of Utah for Your PhD. Why There?

It was the first school that accepted me. I'd heard that they had a very good pharmacology department. The chairman was Dr Lewis Goodman who was coauthor of the book *Goodman and Gilman*—probably the most famous pharmacology book in the world—so I thought it must be a good place. And it was. The training program was very good.

What Were You Studying?

Membrane transport of ions in isolated toad bladders. The toads were shipped up from the Amazon River Basin, and they were really big! You could remove their bladders

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and look at membrane potential and ion transport very nicely, and you could study the transport of various ions across these membranes by using radioactive tracers. This was probably my first attempt at studying potassium channels.

At the end of the PhD program, I didn't know what I was going to do for sure, but I knew I was interested in cardiovascular science. Utah wasn't a strong place in that area, so I started looking elsewhere.

I ended up joining a pharmaceutical company, the Warner Lambert Research Institute, in New Jersey under the guidance of Dr Martin Winbury, a world-famous investigator with his main interest in the physiology and pharmacology of the coronary circulation and drug actions. In spite of my lack of training in cardiovascular pharmacology, there must have been something Dr Winbury saw in me, and he offered me a postdoctoral position in his laboratory.

I was studying the effects of beta-blockers on myocardial blood flow in the heart, under ischemic and normal conditions. I was there for a year and a half or so and really enjoyed learning many new techniques and information about the heart and how its blood flow was regulated. Unfortunately, the position was terminated after 18 months for lack of funds, so I had to move on.

Luckily, I met Dr Eric Feigl, an internationally renowned physiologist from Seattle at a meeting in the spring of 1971 or 1972, and he decided to give me a position in physiology at the University of Washington in Seattle. Again, I was studying coronary blood flow and its regulation by beta receptors in the heart. Eric was an outstanding mentor and a key person in my development as a scientist. I was with him until the fall of 1973 when I got the job offer to come to the Medical College of Wisconsin. Eric is still active in science, and we remain in touch, even now—40 years later.

How Did Your Work on Preconditioning Come About?

It started as a serendipitous finding by the PhD student, John Auchampach, I had in my lab at the time (around 1986 or 1987). We were studying ATP-regulated potassium channels in the heart, and we were looking at drugs that open these channels and their cardioprotective properties. The drugs seemed to reduce infarct size, and we were trying to figure out potential mechanisms.

In 1986, a paper came out from Bob Jennings and Keith Reimer's lab at Duke, reporting that preconditioning in dogs produced a marked reduction in infarct size. This paper contained a graph that looked just like our potassium channel graph, so we thought maybe these channels are involved in preconditioning. We blocked them with a KATP antagonist, glibenclamide, and sure enough, preconditioning was abolished.

Later, we found that opioids also protected the heart, similar to preconditioning, and that's interesting because opioids are used so much—almost every patient who comes into the hospital with a heart attack is given morphine for the pain. And here, we had identified a potential second beneficial effect of morphine that could possibly reduce ischemic damage and infarct size.

Have There Been Any Trials?

No, there haven't been any specific trials that I know of yet. We are currently looking at a drug that is being developed by a company in Sweden, Eribis Pharmaceuticals. The compound is an opioid derivative of the enkephalin class called EP94, and it has been shown to reduce infarct size in the pig heart at a very potent dose. Eribis would like to use it in patients with a myocardial infarction in the operating room, so that they might develop a clinical trial if it works out. There is a lot of interest in that currently.

There is also some clinical evidence for opioid–induced cardioprotection.This is based on a collaboration with Dr Robert Maslansky, at Bellevue Hospital in New York City. He ran a methadone-maintenance clinic for heroin addicts, and he read our papers and proposed that maybe his patients on chronic methadone might be cardioprotected. He looked at the information on his patients over the years and found that indeed the patients on methadone had less coronary disease than nontreated patients. These findings were published in the *American Journal of Cardiology* several years ago, and this work continues to keep us moving forward in this field.

What Are You Currently Interested In?

I'm interested in eicosanoid metabolism and protection of the ischemic myocardium. Eicosanoids are metabolites of arachidonic acid. They are converted by the cytochrome P450 enzyme system into compounds that are very cardioprotective. We know they are produced in the body, but the problem is that they are very short lived—their half life is a matter of seconds to minutes. So, we have a chemist from Texas Southwestern Medical School, Dr Camille Falck, who is attempting to make some longer-acting novel analogs. We're going to test these agents and see whether they have a greater effect on infarct size than the endogenous compounds.

What Is the Best Thing About Your Job?

The students I've had have been delightful to teach and mentor. I love to do that: discussing experiments, results, and papers with them. They are sometimes very raw when they come in, and their first seminar is not very good, and they are quite nervous. But when they leave the lab, they are polished, and very competitive for outstanding jobs, and that's rewarding to see. Being a mentor is the most important thing to me, I think. I'm probably more proud of that than anything. I don't have my own children, but I do have a cadre of postdocs and graduate students that are like children to me. They still come and visit or call me on the phone frequently.

What Is the Key to Good Mentoring?

Spend time in the lab with the students. Don't stay in your office and ignore them. Encourage them.

I tell the students to go to meetings and meet people who are well known in the field, as one of the keys to success is whom you know and the circle of friends you have. So, when I'm at meetings, I try to introduce my students to the people I think they should meet, and this certainly helps them compete for the best jobs.

Besides Encouraging Your Students to Meet People, What Other Advice Do You Give?

Work hard. But then it's not really work if you enjoy it. I really enjoy this career. It's great. You make lots of friends and do lots of traveling. There's always something new happening, and that is what is nice about science. It can be tedious at times, but when you make a breakthrough, then it's really worth it.

How Hard Do You Work?

I love to come to work. I like to get up as early as possible and get to work. I'm an early riser. I'm normally in the lab by 7:00 to 7:30, and there's nobody else here at that time, so I get quite a bit of work done for a couple of hours. I work on weekends too. Last weekend I was here both days from about 8:00 to about 2:00 to 2:30.

Oh, So You Have a Lie-In on Weekends?

Yes, I sleep an extra hour!

Do You Expect Hard Work and Long Hours From Your Staff, Too?

I currently don't have any students and postdocs. I'm winding down a bit and thinking about retiring in a year or two. But I used to expect it, because we would be here working together. But they enjoyed it . . . I think.

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