Karlin Bornfeldt is stubborn. Once she gets curious about something, she does not let it go—turning questions around in her head, examining the issue from varying perspectives, thinking about alternative solutions, and applying a variety of tools to the problem.

The question that sparked Bornfeldt’s curiosity during her PhD research at the University of Linköping was how diabetes mellitus accelerates atherosclerosis. She has never lost interest, and in 3 decades of research, she has worked to uncomplicate the most deadly of diabetic complications.

Bornfeldt, joint professor of medicine and pathology at the University of Washington in Seattle, arrived at the university in 1991 as a postdoc to work with Russell Ross, PhD, and Edwin Krebs, MD. She joined the faculty in 1995 and is now associate director of the Diabetes and Obesity Center of Excellence, deputy director of the Diabetes Research Center, and director of the Viral Vector and Transgenic Mouse Core at the university.

When Bornfeldt established her independent laboratory in 1997, she recognized the need for a mouse model of diabetes mellitus—accelerated atherosclerosis that could separate the effects of diabetes mellitus per se from the effects of diabetes mellitus—induced hyperlipidemia. The laboratory created a transgenic mouse that develops type 1 diabetes mellitus in a process similar to that of type 1 in humans, with viral infection inducing T-cell–mediated destruction of beta cells, and also develops atherosclerosis. Using that model, the team showed that, even with no lipid abnormalities or cholesterol in the diet, diabetes mellitus accelerates the initiation of atherosclerotic lesions by stimulating macrophage accumulation within the vascular wall. In contrast, when the mice are fed a cholesterol-rich diet and then given diabetes mellitus, they develop severe hypertriglyceridemia and advanced atherosclerotic plaques. Later, when the team induced type 1 diabetes mellitus in mice after they had already developed advanced atherosclerotic lesions on a high-fat diet, the disease increased intraplaque hemorrhage—an effect that requires triglyceride-rich lipoproteins.

With these studies as a foundation, the laboratory set about investigating in vivo the molecular mechanisms that promote an inflammatory environment and accelerate atherosclerosis in diabetes mellitus. The team discovered a key role for long-chain acyl-CoA synthetase 1, an enzyme that catalyzes the thioesterification of fatty acids. Monocyte preparations from humans and mice with type 1 diabetes mellitus exhibit increased acyl-CoA synthetase 1, whereas myeloid-selective deletion of acyl-CoA synthetase 1 protected monocytes and macrophages from the inflammatory effects of diabetes mellitus and prevented accelerated atherosclerosis in diabetic mice—while having no impact on lesions in nondiabetic mice. To see whether increased glucose metabolism is sufficient for inflammatory myeloid cell activation, as in vitro studies had indicated, they overexpressed the glucose transporter GLUT1 in myeloid cells but found it did not induce cytokines, and in their mouse model of type 1 diabetes mellitus, it did not promote atherogenesis.

Currently, a major focus of the Bornfeldt laboratory is examining how diabetes mellitus affects high-density lipoprotein (HDL). Using human samples collected over time from people with diabetes mellitus, they are looking at changes in blood samples that predict the development of cardiovascular events, then studying these molecular targets in the current mouse models. Bornfeldt is excited about this approach, which flips the usual sequence of first identifying possible mechanisms in mouse models and then seeing whether they apply to humans.

Since 2001, Bornfeldt has served as a fellow of the Council of Basic Cardiovascular Sciences of the American Heart Association. She is an associate editor of Circulation Research. Among other honors, Bornfeldt was awarded the American Diabetes Association’s Edwin Bierman Award in 2014 for her mouse models of diabetes mellitus–accelerated atherosclerosis. In 2013, she was chosen as the Russell Ross memorial lecturer in vascular biology. “Obviously, that was very meaningful because he was my mentor,” says Bornfeldt.

Where Did You Grow Up?
I was born in Stockholm, but when I was in 2nd grade we moved to Strängnäs, a small, very old town that was an early seat of education in Sweden.

When Did You First Become Interested in Science?
I was always drawn to the natural sciences. My dad taught biology and geography, and he would often take my sister and me into the woods to look at things. That was exciting, and I was always curious about how things work, bringing back dead animals to dissect in my room. My friends were more interested in typical girl things, so I did a lot of that on my own.
How About Your Mom?
My mom was a librarian. She always had a very curious mind and was interested in nature and literature. After I got my PhD, she went back and did a PhD of her own in Swedish literature. She lives in Uppsala and continues to take classes at the university. I think it’s great that she still maintains her curiosity.

Did She Instill a Love of Literature in You?
Yes, I read a lot as a kid. Now I don’t get much of a chance, but I’m rereading a book that fascinated me as a teenager. It’s about a woman explorer in the Victorian era, Mary Kingsley, who travelled alone to West Africa before women did that kind of thing. The writing is very old-fashioned, but I can see why I was attracted to it.

What Did You Imagine Your Scientific Work Might Be Like?
I always knew I wanted to be a scientist, and biology was my favorite topic by far. Before starting college, I really admired people like Jane Goodall who went out to study wild animal species and save them from destruction. When I started studying at the university level, I realized that many exciting questions could be asked in the laboratory without going to some remote place, and that those field jobs were pretty rare. I also became more and more interested in cell biology.

Did You Ever Consider Getting an MD Instead of a PhD?
I didn’t consider it because I really wanted to do research and pursue an academic career, but that was mainly based on the Swedish system. I think that if I had been educated in the United States, I probably would have pursued an MD or MD/PhD.

Do You Think Your Career Would Have Been Different?
Not very different. My research is now turning more toward human translational research. It probably would have happened sooner if I had an MD, but I’m getting to the point where I can use all the methods and models in the lab to study human samples.

How Did You Get Interested in Cardiovascular Disease?
When I decided to get a PhD, a laboratory looking for a graduate student was studying diabetes, and the principal investigator was Hans Armqvist, a physician scientist and diabetologist. It was a small laboratory but I liked that he would come down directly from the clinic. You had a real sense that what you were doing was relevant to people with diabetes mellitus.

Some People Take on Postdoc Projects and Training That Are Intentionally Very Different From Their PhD Work. Can You Describe How That Was for You, How Much Was Different and How Much Continued a Pathway You Were Already on?
My PhD project had studied the artery wall but not really atherosclerosis, so I wanted to get more understanding of the atherosclerotic process. Russell Ross, at the University of Washington in Seattle, was one of most prominent scientists in the field of atherosclerosis, so I applied and was lucky enough to be accepted.

It was a logical continuation of my PhD work but also involved a lot of new things. I learned about models to study atherosclerosis and the processes that occur. The Ross laboratory wasn’t studying diabetes, but when I had a chance to set up my own laboratory I took my interest in diabetes and combined that with all the knowledge I had gotten from the Ross laboratory on atherosclerosis.

Is It Unusual to Stay at the Same Institution Where You Did Your Postdoc?
It’s actually pretty common at the University of Washington because it’s a great place to be.

How Has Work in Your Lab Changed the Common Understanding of the Role of Hyperglycemia in Diabetes-Accelerated Atherosclerosis?
We have asked questions about how elevated glucose might affect the artery wall in animals. A lot of the previous research had been done on isolated cultured cells, but it’s hard to know from cultured cells whether the same things happen in mice—and also uncertain whether mice are a good reflection of what happens in humans.

Using our transgenic mouse model, we showed that even in the absence of diabetes-induced lipid abnormalities, type 1 diabetes could stimulate the atherosclerotic process. But we’re still not sure whether that is a direct effect of glucose on vascular cells, and the effect of glucose might be pretty small in relation to other risk factors, such as lipids.

In type 2 diabetes, other risk factors such as dyslipidemia and high blood pressure are much more common and may overcome the effects of hyperglycemia and diabetes itself. So glucose doesn’t seem to be sufficient to explain cardiovascular disease, but good glucose control is certainly very important in controlling complications of diabetes, especially microvascular complications in the kidney and retina.

How Many Transgenic Mouse Models of Diabetes Do You Study in Your Lab?
It depends how you count. We have two models of type 1 diabetes, and our virally induced model mimics some of the autoimmune changes that occur in the pancreas. We also study a model of insulin resistance and obesity in mice fed a high-fat, high-sucrose diet. A fourth model develops the renal complications of diabetes, and we’re working on ways to induce cardiovascular complications in those mice.

So we have several different models of diabetes, plus several different transgenic mouse models where we can either knock out or overexpress certain proteins.

That Must Take a Lot of Effort to Keep Going.
Yes. Keeping mice takes a lot of work, but the time commitment grows after they are diabetic. Just like humans with diabetes, they need daily blood glucose checks and insulin injections. So it’s time-consuming but the laboratory is good at it by now; they are diabetologists for mice.

Are There People With Diabetes Who Don’t Develop Complications?
Cardiovascular complications are the main cause of mortality in type 1 diabetes, but there are certainly people who never develop any complications. We’re initiating studies now where we’re collecting plasma samples to look at immune responses and HDL changes in people who have had type 1 diabetes for many years without complications, comparing them with subjects who have had diabetes the same length of time but have developed several micro- and macro-vascular complications. Understanding why complications do not develop in some people might be as important as understanding why complications develop in others.

We’re starting to think about translation a little differently now. Instead of using mouse models to try to come up with a mechanism that might apply to humans (and there is always uncertainty about
whether or not that is true), we are looking from the other side and trying to find things in humans that predict the cardiovascular events associated with diabetes. Then, once we have molecular targets that look like they’re predictive, we can use mouse models to study how those things work. I’m excited about that approach.

**How Did You Get Interested in HDL and Diabetes?**

Through a collaboration with Jay Heinecke, MD, whose laboratory is right next to mine. He is very interested in the HDL proteome in relation to HDL function—what proteins are attached to HDL and how that can change the cardioprotective function of HDL. In talking with him I realized that there is a lot that is unknown about how diabetes affects HDL. So that was something I was very curious about.

**Any Advice or Reflections for Young Scientists on What It Takes to Succeed?**

Before you start doing research, it’s hard to really understand how much time and effort it takes. Someone might have unrealistic expectations when they first start and think everything is going to work and yield amazing results. But it usually isn’t like that. You work on a problem for a long period of time. Sometimes you have success, and that is incredibly exciting and what holds you up, but a lot of the time things don’t work out like you expect and you have to rethink, to go back to the drawing board. You have to be stubborn and keep turning your questions around in your head and thinking about alternative possibilities and solutions. That’s rewarding, too. And, personally, I think it’s important to challenge yourself, to not get set in your ways. I often force myself to do things that I’m uncomfortable with.

**What Were Some of Those For You?**

I guess I’m a bit introverted, like many scientists, so speaking in public has been one of those things. I make a point of asking questions at seminars to get a constructive discussion going. Younger scientists might not realize that these things don’t always come naturally to senior people.

**Is Public Speaking an Important Skill for Scientists?**

Yes, definitely. Selecting your mentor is also very important, not just selecting the big shot in the field but anticipating what you think your interaction will be and whether you will have a fruitful experience. And collaboration is very important, more so these days than in the past. There are lots of opportunities for interdisciplinary research, so people have to develop a wider network of people and collaborate.

**Were Any of the Skills and Realities of Being a Scientist Surprises to You?**

It evolves as your career goes on and you need to learn new skills. For example, I’m spending more time on administration now, which is something I hadn’t really thought I would do much of, but I find I enjoy it and find it rewarding.

**Can You Give Me a Sense of Your Current Time Commitments?**

I no longer spend any time at the laboratory bench, unfortunately. I have an open door policy and I go into the laboratory to see what people are doing. So I still get the data as they are collected and that excites me now.

Overall, I would say almost half of my time is spent writing grant applications and thinking about grant applications. The other time is divided between teaching and supervising students in the laboratory, writing manuscripts and reports, and completing administrative duties. On top of that, mostly at night I do a lot of editorial work for different journals, *Circulation Research* in particular.

**Do You Have Any Particular Advice for Young Female Scientists?**

I think that women scientists should not see themselves as being different from male scientists, and everybody should be viewed according to their contributions and not their gender. However, I know and realize that women have some challenges that men don’t have. It’s much better now but, to a large extent, family responsibilities have fallen on the woman. Many women I know decide not to have their own laboratory but become a laboratory manager instead. This is often driven by a wish for more time with the family, which is perfectly understandable.

**How Have You Combined Work and Family?**

I married a mathematician just at the end of my postdoc and had my first child as a junior faculty member. I usually work full days in my office and laboratory, and then again in the evenings when my two sons are in bed. And if you’re a scientist you’re almost always thinking about it at the back of your mind—thinking about it not because you have to but because you love it.

**What Do You Like To Do When Not Working?**

I like being out in nature. We have really nice places to go around Seattle and I love hiking when I get time.

While hiking in the mountains in Sweden as a kid, I learned something that has served me well during my career and I try to pass it on to junior scientists: Don’t get overwhelmed by your goals. In Sweden, there are little stone cairns marking the trail. You have a goal in mind—somewhere is the summit that you’re trying to reach—but you just focus on reaching the next cairn. As you do research, take pleasure in your little achievements and finding tiny pieces of the puzzle along the way. Once you’re at the summit, you can see all the little parts that led to a research success and that’s very rewarding.

**References**


Karin Bornfeldt: Sticking With a Complicated Problem
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Circ Res. 2016;119:508-510
doi: 10.1161/CIRCRESAHA.116.309518

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