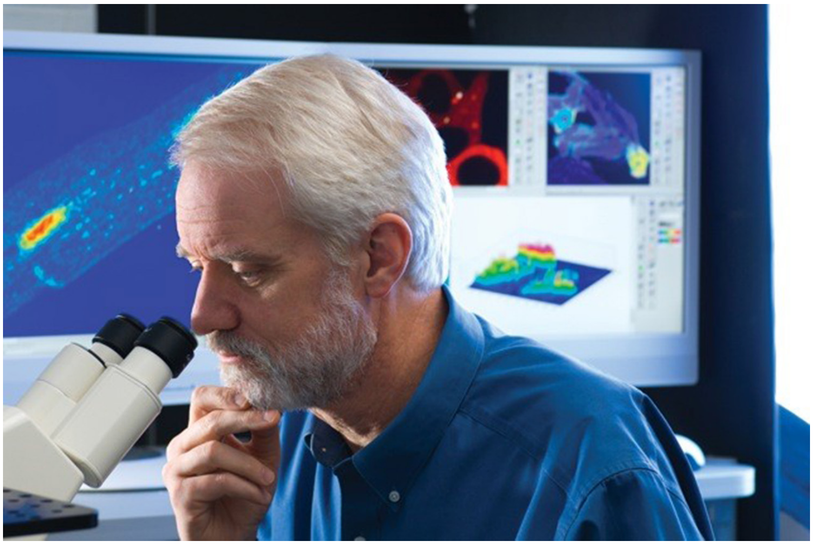
# Donald Bers

## A Heart for Puzzles

Susan Ince

Donald Bers, PhD, grew up loving puzzles. His father, Harold, created well over 100 crosswords for the *New York Times* (71 Sundays), and Don has always liked solving crosswords. He also liked numbers and as a preteen constructed a complex probability-based board game using real baseball statistics.

"I was always interested in numbers and taking things apart to figure out how they work, and it turns out I'm the same way with heart cells," says Bers, distinguished professor and chair of pharmacology at the University of California, Davis medical school.



**Donald Bers**

Bers received his BA in Biology from the University of Colorado and his PhD in physiology from the University of California, Los Angeles (UCLA). At UCLA, his mentor Glenn Langer recognized that Bers was a student who possessed the initiative and logical ability to figure things out independently and follow the path suggested by their experimental results. With that independence, Bers became the sole author on his first published paper, which described a preparation for isolated cardiac sarcolemmal vesicles that could be used to study the roles of the cardiac sarcolemma in excitation-contraction coupling and $Ca^{2+}$ binding.[1]

Throughout his career and documented in nearly 500 publications (cited, on average, more than 100 times each), Bers' research has focused on cellular and molecular factors involved in the control of cardiac muscle contraction in health and disease. The first 15 years were spent developing a detailed quantitative framework of how cardiac cells normally function with respect to calcium handling, electrophysiology, and control of contractile function. Based on numerous studies, his framework of cardiac excitation-contraction coupling has been cited thousands of times and his illustrations are frequently used in presentations of heart cell function.[2] Armed with that understanding and a variety of innovative measurement tools, he began to look at how perturbations in electrophysiology and calcium control contribute to heart failure and arrhythmias, identifying possible strategic pathways for remediation. Using rabbit, rat, and human models, the Bers lab developed a new paradigm in understanding both systolic dysfunction and triggered arrhythmias in heart failure, including the role of upregulated CaMKII (calmodulin-dependent protein kinase II).[3,4] The lab contributed greatly to the recognition of cardiac calmodulin and CaMKII signaling as critical regulators, with chronic CaMKII activation contributing to cardiac and possibly neuronal pathophysiology in diabetes mellitus.[5] For more than three decades, the Bers lab has used computational modeling to test our quantitative mechanistic knowledge of cell functions and to perform in silico experiments to suggest new hypotheses.[6,7]

In the middle of a busy career, Bers took the unusual step of devoting a year to writing a single-author textbook that provided a readable and comprehensive explanation of the generation and control of cardiac contractile force. Often called the Bible of the field, the first[8] and second[9] editions of the book are frequently cited in journal articles and have been used to introduce thousands of students to the study of heart cell function.

Bers has served as department chair at 3 institutions: UC Riverside; Loyola University Chicago; and UC Davis. He has received the Distinguished Achievement Award from the American Heart Association's Basic Science Council (2009), the University of California Davis School of Medicine Research Award (2012), the American Heart Association Distinguished Scientist Award (2012), the Peter Harris Award from the International Society for Heart Research (2016), and the Newton-Abraham Professorship at Oxford (2019). He has published in *Circulation Research* since 1986, joined the editorial board in 1994, and has served as a consulting editor since 2009.

### Tell Me About Your Childhood

I was born in New York City (Manhattan) but grew up mostly in nearby Westchester County. I was active in baseball, basketball, and tennis, but was kind of nerdy even as a kid. Making up my

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own probability-based dice game as a kid, using baseball players' batting statistics was pretty nerdy.

In school, I liked creative writing as well as math and science. My writing skill I might have gotten from my father, who worked creating advertising slogans and was also a creative writer for magazines (not just a crossword wordsmith).

My father died of a first myocardial infarction when I was eight, and I'm sure that at some subliminal level that influenced me towards choosing cardiac research in graduate school. My mother was in the British Women's Royal Navy in the second world war. She came to the US with my father, remained solely a British citizen to the end, and raised my older sister Alison and me mostly on her own from the time I was eight.

## When You Majored in Biology as an Undergraduate, What Was Your Idea of What Your Future Career Might be?

Like many mothers, mine thought I should be a doctor. And that sounded pretty good to me because in college I loved biology. But in Boulder, I accidentally graduated a year early! I went to sign up for my senior year classes and they said "no, you're graduating next month". It was too late to apply to medical school, so I went to graduate school in physiology at UCLA, where I gravitated toward the large heart research lab. There, many of my colleagues were cardiologists, and although they enjoyed seeing patients and the intrinsic rewards of clinical work, they seemed especially excited to come to the lab and work on scientific discovery. That started me rethinking what I really like to do. I liked to solve science puzzles and realized I was enjoying the challenge of combining biology, chemistry, and physics. I did apply to medical school, but when I was invited for interviews I had already decided to stay in the PhD program and be a scientist. I have never looked back.

## Who Were Your Important Mentors at UCLA?

Glenn Langer was a physician-scientist and cardiologist at UCLA, and he taught physiology to our combined group of PhD and MD students. Glenn was polished in terms of natural leadership and in understanding people. He recognized that I had the initiative, logic and drive to figure things out, so gave me a lot of room to grow and I credit him with encouraging my early independence.

Allen Brady was another UCLA mentor. He was the ultimate careful biophysical scientist, and he inspired me to try to learn how things work at a quantitative biophysical and molecular level.

One lesson that I've learned from my many early mentors, and which I use often as a mentor myself, is to be generous. Help other people with their science if you can: We are all in this effort together. Indeed, that international spirit of scientific community and collaboration has shaped my career, and I think that of my trainees.

## Does a Scientist Ever Outgrow the Need For Mentors?

I don't think you ever outgrow it, but it takes different forms. When I was an early independent assistant professor (away from UCLA) and had published a series of what I thought were great papers, the field still viewed me as some kid from Langer's lab. I hadn't established my own name. Alex Fabiato (at the Medical College of Virginia in Richmond), a leader in the field who I had gotten to know through scientific conferences, helped me put that in perspective and have patience about career development and recognition. He told me that what you've published in the last 3 years may take 5 years to actually be recognized. I've given that advice to junior faculty who have the same kind of impatience about career development. There's a time lag.

Later, another colleague-mentor John Solaro (at the University of Illinois Chicago) recommended me for the Physiology Chair job at Loyola University Chicago which I began at 37 as the youngest faculty member in that department. John's experience as a chair and warm personal friendship made him a great mentor for me and helped me learn how to be a good chair.

## Do You See the Responsibilities of a Department Chair as Something That Takes Away From Progress in Your Research, or Do They Also Have the Potential to Enhance It?

There's no denying that it's a challenge and you must work hard to do both jobs well. But as a chair I've had the opportunity to exercise vision and build productive synergistic scientific environments at both Loyola and UC Davis. Just standing back sometimes and watching my colleagues bounce ideas off each other and develop unique new collaborations is rewarding to me. That counterbalances the work of administration, and the environment also helps to make my lab do better science. Indeed, my current department and faculty at UC Davis are really a total joy. I'm not the kid anymore! But I watch with delight how these great young scientists readily spark new collaborations and are so tremendously collegial with each other, and with colleagues outside our department. It feels like a dream team. As I approach the latter stages of my career, mentoring faculty development is even more important. I can imagine that the able crew of this small boat that I've helped to steer will sail on to do great things for science long after I am out of the picture.

## What Do You Advise Trainees to Look For in a Lab?

Don't go for the money, go for the environment where you think you can be successful. In my experience, that means where you'll have colleagues that can help you and where you can help them. That often provides advantages of environmental synergy which includes bringing enriching different perspectives to the science you are doing.

## What Skills Will Science Trainees Need That They May Not Realize Starting Out?

Writing. You must be able to communicate to develop ideas into actionable experimental design, to make illustrations and figures that are intuitively communicative, to present your work at poster sessions and in seminars, and to critically write about it in papers, grants, and progress reports. The criticality of writing skills to overall success in science is often not realized by those starting out.

Increasingly, scientists also need to communicate with nonscientists. In a world where people want answers fast, scientists need to help explain that biomedical science advance is progressive. While it constantly produces new knowledge and understanding, it often takes time to impact health care for the better. But the history of NIH-sponsored research and its international emulators during the last 50 years has transformed biology and medicine.

## Can a Scientist Without a Natural Gift For Writing Learn to Do It?

I think so. I've tried to encourage trainees to write something every week, to write a paragraph or a couple of paragraphs that might contribute later to an introduction, or just describe the experiments they did last week in a way that might also make it easier to pull a paper together later. A few students and post-docs have embraced that and tried to do this. I don't require or review it, but that probably would be worthwhile. But just writing and getting critiques makes people better at it. Too many people keep delaying writing and often do not seek constructive feedback along the way.

You also have to be optimistic and thick skinned, so that when you get critiques on your writing from mentors, collaborators or editorial boards or grant reviewers, you do not let it knock you down for a month (or blame the reviewers for not appreciating the perfect thing you wrote). Use the criticisms to improve your work. Don't be defensive thinking I did it right, but they just didn't get it. If they didn't get it, maybe you can make it clearer. As a mentor, when people get harsh grant critiques, some of them are pretty upset, and they want to talk to me right away, but I enforce a 5-day cooling-off period so they've had time to put it into perspective. At first, many want to rant, which can be cathartic to write down but is almost never useful to send.

## You've Been Studying Calcium Ions for Many Decades. Does It Remain as Fascinating as It Did at the Beginning?

I'm still excited about the science we do and come in every day trying to find out new things. Before she died, my mother asked me what I was doing now. When I said I'm still studying the heart, she said "Well, you've been studying it for a long time. Don't you know how it works yet?" I thought that was cute, but also kind of true. Every time you answer a question, it brings up 5 or 10 new questions. The richness of the understanding we have now is built on thousands of small discoveries. We think about paradigm-shifting science, and all the journals (including *Circulation Research*) would like to publish only those landmark, change-the-way-everybody-thinks papers, but in fact 99.9% of scientific advances are based on research that in critiques we could call incremental. We build on knowledge already there, add new information or bring together pieces of information from different fields, and it creates a new depth and breadth of understanding.

## Which of Your Projects Has Been the Most Rewarding?

What was a challenge but has been particularly rewarding was the single-author book. Not so many people write a comprehensive book instead of a chapter about their own area of knowledge. The first edition took about a year. I worked in a really concentrated way on it, got input from many colleagues with different expertise, and really tried to synthesize the information in a way that was rich in terms of content but also readable for students and cardiologists as well as accomplished researchers who know part of the picture but not the whole thing. It has been rewarding that people have gotten so much use out of it. The fundamentals make it a good tool for scientists in the field, despite the second edition being 17 years old.

## Looking Back Over the Techniques You Used at Different Points in Your Career, What Have Been the Most Dramatic Changes?

Technology has changed a lot. For example, in trying to understand how sodium calcium exchange works, I used radioactive isotopes as a PhD student and then went to Edinburgh as a post doc to learn how to use ion selective microelectrodes, a technique which required some excruciatingly hard experiments with very low yield. Now, with calcium indicators and genetically encoded fluorescent sensors, you can easily get a real-time readout of what's going on inside the cells. Overall, this really is a magical time for biomedical science because almost any experiment you can think of you can do. Some are challenging of course, but the tools are there to do absolutely amazing things.

## Should a Scientist Anticipate Having to Step Back Periodically and Learn New Techniques During Their Career?

Yes. One of the traps that some young scientists fall into is to develop expertise with a specific narrow set of technologies as a student and post doc, and then trying to only ask questions that can be answered by their toolbox. You want to be invested in the scientific questions that you think are important to answer (because if you don't think they're important, you won't work hard enough to solve them or to sell them as grant projects) and you have to develop the appropriate tools to answer those questions and test those hypotheses.

## Do You Still Do Bench Work?

Almost none, but I'm still very engaged and love designing and figuring out experiments to test a hypothesis. A lot of the time I spend with students is at that early point where we have the question and the tools, and it's time to decide how to design the experiment to get the answer. It's like a puzzle: There are 1000 ways to design the experiment, but only 27 are likely to give you useful results, so make sure to select 1 of those—or 2 to 3 so you have complementary ways to test the hypothesis. That kind of analytical approach to problem solving is an area that I still enjoy and in which have something to contribute.

## You Make Your Models of Atrial and Ventricular Myocytes Freely Available to Scientists. Are There Obstacles to That Type of Altruism?

With computer models, I haven't had hurdles. Most of our support is from federal grants paid for by tax dollars so our findings should be freely available to everyone. The same is true when we create new reagents, sensors, or genetically modified animals. In general, scientists are quite good about it, but more of our institutions want to capitalize on patentable opportunities which sometimes raises barriers to the sharing of research tools. It's part of the culture that we live in, but maybe I'm old-fashioned enough about science to think that the products of our scientific research are for all of us to use.

## Where Do You See Your Lab's Research Going in the Next Few Years?

I am excited that some of our mechanistic work with heart failure and arrhythmias has led to some possible opportunities for new therapeutic strategies, and the tools we have developed can now be used for high-throughput screening for new drugs. We can then do the lower-throughput tests in adult and human myocytes to see whether promising new compounds work the way we expect. It might make it to patients, but it might not. Either way I'm excited that we're translating our understanding and might come up with something helpful.

## How Hard Do You Work Now?

I still work too hard, but I like it. When I meet friends my age, the ones who still love their jobs are often researchers and academics. I probably work 65 to 70 hours a week now, instead of 80-plus hours earlier in my career. I'm trying to slow down and try this work-life balance idea with my wife, but I'm still excited about the science and have lots of active grants.

## You Acknowledge Your Wife in the Preface to Your Book. Tell Me About Her

Kathy and I have been married 42 years and she's been an amazing and supportive partner always. She trained and worked part-time as a biostatistician, but she is really a renaissance woman. She is great with math and analytical things but is also a musician, an artist and a voracious reader. She is now retired from biostatistics, but stays very busy with interest groups, playing piano and flute and making things for our 2 granddaughters. She often will travel with me, even to scientific meetings, so many of my science friends also know her.

## What About Your Children? Did They Get the Idea Watching You that a Career in Science Would Be a Good Life?

They both saw how hard I worked, and maybe that more than the joy that it gave me. They both chose different directions but are also both very hard workers in their fields. My daughter veered away from science: Rebecca is now a deputy city attorney for San Francisco. My son has degrees in both physics and music performance/composition. Brian's a super-talented musician now working as audio engineer. He worked in the lab with me one summer but didn't get bitten by the biology bug. My son has two delightful daughters, who are almost 3 and almost 5. That's a really fun age, and my wife and I see them as often as we can.

## When You Aren't Working, What Do You Like to Do?

I play golf, walk, and listen to music. I used to play more active sports like basketball, volleyball, and downhill skiing, but don't do much of that anymore. While competitive by nature, I don't go for extreme sports. I get unplugged when not working and these days don't bring the same intensity to sports that I do to science.

## Should We Look Forward to the 3rd Edition of Your Textbook?

Maybe when I retire.

## Disclosures

None.

## References


1. Bers DM. Isolation and characterization of cardiac sarcolemma. *Biochim Biophys Acta*. 1979;555:131–146.
2. Bers DM. Cardiac excitation-contraction coupling. *Nature*. 2002;415:198–205. doi: 10.1038/415198a
3. Pogwizd SM, Sclotthauer K, Li Li, Yuan W, Bers DM. Arrhythmogenesis and contractile dysfunction in heart failure. *Circ Res*. 2001;88:1159–1167.
4. Yang Y, Guo T, Oda T, Chakraborty A, Chen L, Uchinoumi H, Knowlton AA, Fruen BR, Cornea RL, Meissner G, Bers DM. Cardiac myocyte Z-line calmodulin is mainly RyR2-bound, and reduction is arrhythmogenic and occurs in heart failure. *Circ Res*. 2014;114:295–306. doi: 10.1161/CIRCRESAHA.114.302857
5. Erickson JR, Pereira L, Wang L, Han G, Ferguson A, Dao K, Copeland RJ, Despa F, Hart GW, Ripplinger CM, Bers DM. Diabetic hyperglycaemia activates CaMKII and arrhythmias by O-linked glycosylation. *Nature*. 2013;502:372–376. doi: 10.1038/nature12537
6. Bers DM, Philipson KD, Peskoff A. Calcium at the surface of cardiac plasma membrane vesicles: cation binding, surface charge screening, and Na-Ca exchange. *J Membr Biol*. 1985;85:251–261.
7. Grandi E, Pasqualini FS, Bers DM. A novel computational model of the human ventricular action potential and Ca transient. *J Mol Cell Cardiol*. 2010;48:112–121. doi: 10.1016/j.yjmcc.2009.09.019
8. Bers DM. *Excitation-Contraction Coupling and Cardiac Contractile Force*. Boston, Mass.:Kluwer; 1991.
9. Bers DM. *Excitation-Contraction Coupling and Cardiac Contractile Force (Second Edition).* Boston, Mass.:Kluwer; 2001.