

ESSAY

JGP 100th Anniversary

Influences: Find a friend

Frances M. Ashcroft

I never imagined that I would become a scientist. I spent my childhood in a tiny village in the depths of the English countryside where women got married when they grew up and never went out to work. Except, that is, for my mother, who was the head of the village school. She absolutely loved her job and she was very good at it, so it was obvious that I should also have a career. She was the earliest, and probably one of the greatest, influences on my life.

Rambling around the beautiful Dorset countryside as a child instilled in me a passion for nature and led me to study Natural Science at Cambridge University. I specialized in Zoology in my final year, focusing on animal physiology. I then did a PhD with John Treherne on ion fluxes in insect muscle. In those days, unlike today's PhD students, we were given a room and left to beg, steal, or build the equipment we needed. There were no postdocs to help, and if you were lucky, you might have discussed your project with your supervisor once a month. It was very much sink or swim. John's specialty was insect nerve, and I was working on muscle. When I asked for help, he was wont to reply, "I don't know, Fran; you'll figure it out." Eventually, painfully, I did.

Although John did not help me much with my project, he was a truly wonderful human being and taught me an enormous amount about how to live. He was wise, kind, and infinitely caring, and he supported me and many others through difficult times. He was interested in everything, ran various enterprises to support his impecunious graduate students, and wrote both novels and nonfiction as well as scientific papers. I doubt I would ever have written popular science books without his influence.

I then did a PhD in Leicester with Peter Stanfield. I was his first postdoc, and it must have been a shock for him to find out that I knew very little about biophysics, nothing about physics or electronics, and was quite incapable of building and servicing my own voltage clamp rig. I was very stressed by my ignorance and once even dreamt that I was doing experiments with Peter and Richard Adrian... and that my job was to polish the equipment! Peter dealt with all this with equanimity. He taught me everything I know of biophysics, he did experiments together with me, and he was prepared to listen to my ideas and even



Patrik Rorsman and Frances Ashcroft still hard at work together after 33 years. Photo courtesy of Jim Johnson.

try them out. It was a very productive time. His meticulous approach and care in the execution and analysis of experiments was invaluable training.

After a year in Los Angeles (with Hagiwara), I arrived in Oxford as an inexperienced young researcher with the wonderful prospect of six years of salary and the chance to establish an independent laboratory. Soon, I was also the proud possessor of

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a three-year project grant from the Medical Research Council. It was on how the permeating ion influences the kinetics of the acetylcholine receptor channel; in the event, I never did a single experiment on the topic! I was eager to use the newly invented patch clamp technique, but there was no one in Oxford who did this and only three people who did in the whole of the UK. Happily, David Colquhoun and his team in London were willing to show me what to do. Given that I was (justifiably) insecure about my experimental abilities, I am now amazed at my determination to take on something completely new.

What transformed my approach, however, was a Cold Spring Harbor course on single-channel recording that I attended in 1983. It was run by Chuck Stevens and David Corey and featured many pioneers of patch clamping as course instructors, among them Gary Yellen and Rich Lewis. I was lucky enough to be taught by Rick Aldrich, an inspiring and wonderfully patient teacher. Rick also had another skill: he was very good at playing the bongo drums. Late one night, the whole course had a party in which Rick played the drums, Rich Hume improvised a trumpet on the pipette washer, someone rattled sheets of metal, and I was the go-go dancer in a dress of aluminum foil! But probably the most important thing I took from the course was a comment by Julio Fernandez to the effect that the whole-cell patch clamp configuration opened up the study of small cells. It was a revelation to me as I was far more interested in the physiology of mammalian cells than single-channel kinetics. All I had to do when I got back to Oxford was pick my cell.

At that point, Steve Ashcroft serendipitously came to my laboratory to pick up a colleague. Steve was an Oxford biochemist studying insulin secretion from pancreatic β -cells who had discovered that glucose must be metabolized to stimulate release. I'd been contemplating studying β -cells as they have glucose-stimulated electrical activity, and their impaired function results in diabetes. So, we decided to team up. I confess I was also intrigued that Steve had the same surname as me (I didn't foresee the complications that would later ensue as a consequence of people thinking that we were married!). We became great friends, and our collaboration led to the discovery that glucose stimulates insulin secretion by closing a potassium channel (the K_{ATP} channel) in the β -cell; it's something I have worked on ever since. Steve taught me a great deal about the β -cell, metabolism, insulin secretion, diabetes, and jazz; and although he's long retired, I still phone him if I have a thorny metabolic question.

I first came across Patrik Rorsman when I was asked to review his paper showing that the glucose-sensitive channel was the same as the ATP-sensitive channel discovered by Nick Hales and Dan Cook. Patrik's paper almost exactly resembled the one

I was preparing. It was a devastating blow, but what could I do? I accepted his paper and consigned mine to the bin. Some months later, at a β -cell conference in Alicante, I met a tall, lanky, young Swede in the swimming pool. He had a quick mind, an infectious enthusiasm, a wonderful sense of humor—and his name was Patrik. We quickly realized it would be far more fun to collaborate than compete, and soon I was visiting him in Gottingen to do experiments and he was visiting Oxford. Eventually, Patrik moved with his family from Sweden to Oxford to take up a Chair in Diabetes. Our collaboration has been one of the most important things in my life, and after 33 years, we are still publishing papers together.

Another wonderful colleague who has had an enormous influence on my scientific life is Andrew Hattersley. I shall never forget the phone call in which he told me that he and Anna Gloyn had found the first mutation in the K_{ATP} channel associated with neonatal diabetes and asked me see if it had a functional effect. It was the beginning of another wonderful collaboration. Together, we showed that gain-of-function mutations in either the Kir6.2 or SUR1 subunit of the channel impair the ability of ATP to shut it, so preventing electrical activity and insulin secretion and accounting for the patients' diabetes. We also found that most mutant channels respond to sulphonylurea drugs, which has enabled thousands of patients to switch from insulin injections to tablet therapy, with substantial improvement in their clinical condition and quality of life. Working with Andrew and meeting the patients has given me an entirely different perspective. When my papers and grants are rejected, I no longer wallow in despair. I think of the small child who ran up to me at a patients' meeting and cried, "Dr. Ashcroft, I love you," and threw his arms around my legs. I have been extraordinarily fortunate to see my science actually benefit people, and I have Andrew to thank for choosing me to work with.

It will be apparent from this essay that apart from my mentors, Treherne and Stanfield, and the brilliant young people—too many to mention individually—who have worked in my laboratory, the most important influences on my career have been my long-term collaborators: Steve, Patrik, and Andrew. They have been wonderfully stimulating and generous colleagues. We've had fiery arguments about science and everything else under the sun, laughed and cried, and drunk a lot of wine together. They have been there for me through triumph and disaster, and it has transformed not only my science but also my life. I thank all three of them. My advice to everyone is to find a friend. It makes science much more fun and you can do so much more.

Lesley C. Anson served as editor.