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Influences: Growing up in Yale Physiology

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I arrived in New Haven in January 1980 in the middle of a sleet storm after a leisurely cross-country trip from California. I had just completed my PhD at Stanford University's Hopkins Marine Station in Monterey—surely one of the most beautiful places in the country to do basic biological research, with seals and sea otters cavorting less than 50 yards from the laboratory. Whatever its intrinsic merits, New Haven was a considerable shock to someone who had spent less than two weeks of his life east of the Mississippi River. I had come to begin a postdoctoral position at Yale Physiology, a department that had a defining influence on my scientific outlook and career.

My doctoral research, with Stuart Thompson and Petter Getting, had been on potassium channel inactivation in molluscan neurons and left me with the desire to delve deeper into channel biophysics. I greatly admired Chuck Stevens's work and was thrilled that he accepted me for a postdoctoral position in his laboratory, but I had to find an interim position for a couple of years until space in his laboratory became available. Figuring that it would be nice to move only once, I applied to other laboratories at Yale; Dick Tsien turned me down, but Knox Chandler accepted me, and I was eager to begin working in his laboratory. Upon my arrival, Knox helped me to settle into the laboratory, the department, and the city, making the transition essentially problem free.

I soon began to meet the people that would influence my scientific development, both during my time at Yale and, in most cases, for the rest of my career. The department was roughly split between scientists working on excitable membranes, ion channels, and transporters and those doing renal physiology. The core group of laboratories that I would interact with were Chandler's, Stevens's, Dick Tsien's, Stephen Smith's, Larry Cohen's, Joe Hoffman's, Steve Baylor's (until he moved to the University of Pennsylvania), and later Bill Agnew's. Among the renal physiologists, I developed a great admiration for, and friendship with, Gerhard Giebisch. In addition, Roger Thomas was on sabbatical in the department during my first year there, along with his postdoc Bill Moody, who had been a friend and fellow graduate student at Stanford.

Equally important to me were my fellow postdocs and graduate students in the department. Bruce Bean, Peter Hess, Charlie Cohen, Martha Nowyky, Aaron Fox, and Eduardo Marban worked in the Tsien lab. Dick Horn, Joe Patlak, Gary Yellen, Judy Strong, and David Corey were in the Stevens laboratory. I worked alongside Malcolm Irving, Jim Maylie, and Steve Baylor in Knox's laboratory. Toshi Hoshi (who would later become my first postdoc) was a graduate student with Stephen Smith. As a group, we bonded strongly and spent a lot of time together outside of work. I attribute some of this to the sorry winter weather that was not particularly compatible with social activity other than hanging out together near a fireplace or at one of the superb Italian restaurants in town (Connecticut's version of Mexican food was intolerable). Our similar life and career stages were conducive to social interactions, and we had a lot of fun together. It is difficult to overestimate the lasting influences that all of these talented people have continued to have on me, and I am thankful for the friendships that started then and have lasted since.

Another key part of the department was its outstanding electronics shop, staffed by excellent analogue and digital designers and fabricators who worked with researchers to develop superb instruments (such as the Yale patch clamp developed with David Corey). I also enjoyed the Medical School's Historical Library, where I would often sneak off to wander the stacks, finding such treasures as a collection of A.V. Hill's reprints with his handwritten marginal notes on such things as the difficulty of certain experiments and the cold weather on particular days.

Informal gatherings, such as afternoon tea times, also characterized the departmental culture. They provided daily opportunities to exchange results, tell stories and jokes, and exchange (mostly) mild insults. These sessions often turned into joke and insult contests between Knox and Larry Cohen. Lunches, especially with Knox, were both educational and fun, as he was able to weave together science, personality profiles, stories, jokes, and teasing of lunch companions into meandering monologues. Like most who knew him, I found Knox's stories to be highly entertaining. I was there long enough to hear some of the stories repeatedly, but his delivery made then fresh every time.

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With this collection of characters and a strong departmental culture, I began to realize that I was in the right place at the right time. There were certainly other comparable places, but Yale Physiology was a world-leading center of ion channel research at a time just after the discovery of gigohm seals by Neher, Sackmann, and collaborators. It was, however, a challenging environment. Despite the friendliness of its members, the department was a tough place where incomplete, half-baked, or erroneous arguments were instantly identified and not tolerated.

The demanding culture of the department was especially evident in its seminar series. The audience was well informed, always critical, and sometimes rather aggressive. Speaking to this group was a challenge, and not all speakers could handle it. Shortly after arriving, I witnessed a speaker rendered speechless by a request about 20 minutes into his talk to "go back to the beginning and give another introduction because the motivation behind the work didn't make any sense." I promised myself right then to never talk in front of that audience. As I gained more confidence, I eventually overcame this fear. But later, while rehearsing a Gordon Conference talk that I had worked very hard on, I was told by my heroes in the audience (Knox and Dick) that they didn't understand what I was talking about! This triggered three days of panic as I reworked the presentation, but the criticism was essential in helping me to organize ideas and communicate effectively. The "tough crowd" reputation of the Physiology department was widespread. I remember several of us triggering grumbles along the lines of "oh no, Physiology is here to wreck our seminar" as we arrived at a Pharmacology department seminar.

My experience in the Chandler laboratory was initially rather frustrating, as I was unprepared for the slow, careful, and thorough pace of the research, to which I initially reacted with impatience. I later realized the value of such an approach, and my laboratory has developed the same tendency to take its time on projects and publish long, thorough "Chandlerian" papers, sometimes in sequence. I doubt, however, that I will ever challenge Knox's achievement of taking up an entire issue of *JGP* with back-to-back papers!

I learned an incredible amount of science from Knox about muscle physiology, excitable membranes, computational and quantitative approaches, simulations, and other aspects of physiology and biophysics. But my main focus in the laboratory was on optics, particularly polarization microscopy. Knox took laboratory members to the MBL Quantitative Light Microscopy course, taught by Shiya Innoue and colleagues, where we learned about the fundamentals of, and contemporary developments in, polarization, interference, and fluorescence microscopy. Back in the laboratory, I built a microscope and we worked through topics like birefringence, the Poincare sphere, and Jones calculus—an elegant matrix-based method for understanding changes in polarization as light travels through combinations of objects with different optical activity. Years later, I told Knox how impressed I was with Jones's method, but that I was sorry I couldn't remember it anymore. He surprised me by admitting that he couldn't remember it either. I collaborated with Steve Baylor and later Steve Hollingworth on experiments to determine the interactions between calcium ions and the indicator dye antipyrylazo III. I learned a tremendous amount of material while in Knox's laboratory, most of which has been and remains important to my subsequent research.

Knox also generously allowed me to spend six weeks in Woods Hole working on squid axons with Mike Cahalan. I enjoyed learning this classic technique, and Mike became a lasting friend and colleague. While there, I met Clay and Clara Amstrong, Pancho Bezanilla, Paul DeWeer, Brian Salzberg, Isabel Llano, Eduardo Perozo, and others.

I moved to the Stevens laboratory about the time that Horn and Patlak left for faculty jobs at UCLA and Vermont. It turned out that Chuck, along with Gary Yellen, left around the same time for a relatively short sabbatical with Harald Reuter in Bern, Switzerland. Their absence gave me the opportunity to thoroughly learn the new gigohm patch-clamp methods. During his travels, Chuck encouraged anyone who was interested to bring their preparation to me to see if I could get good seals. This ended up being fun and instructive, as I met many people with many types of cells. I found mammalian red blood cells to be the greatest challenge, as they tended to slither up into the pipette instead of sealing to it. This was a period of early and rapid growth in patch-clamp methods as the field fiddled with, and argued about, electrode insulation (i.e., Sylgard vs. spar varnish), glass (i.e., Corning 8161 vs. 7052), polishing techniques (bare wire vs. glass bead), and just about everything else. This prompted Chuck to offer the "Stevens prize" of a decent bottle of wine for anyone who could develop a method that substantially increased the probability of achieving high-resistance seals. I don't recall anyone ever receiving it.

Chuck convinced Cold Spring Harbor Laboratory to offer a three-week course in patch clamping and put David Corey in charge of it, with Gary Yellen and I, along with experts from other institutions, acting as instructors. We taught it for two summers before handing it over to others. The course was another terrific opportunity to meet and work with other excellent scientists, including Peter Stanfield, Fran Ashcroft, Haru Ohmori, Hugh Matthews (who lost a frog in a darkroom to everyone's amusement), Craig Jahr, Rich Hume (who could play a pipette washer like a trumpet), Vince Dionne (who, along with Chuck's daughter

Meg and some students, got radiation poisoning from an undiscovered ultraviolet light), Rich Lewis, Diane O'Dowd (who would later become my second postdoc), and Dave Dawson.

The Stevens laboratory was developing a lot of hardware and software for patch clamping, so a small company called Cheshire Data was formed to sell the computer interface and programming environment, Basic 23, that David Corey and Gary Yellen developed along with Henrik Abeldgard from the electronics shop. My wife Mary became the business manager, and the company was run out of a closet in our house. I remember David spending several days choosing the perfect company stationary.

David and I shared a rig where we installed two toys of Bert and Ernie from Sesame Street after realizing that they had a certain resemblance to Bert Sakmann and Erwin Neher. We called them the patch-clamp gods. This led to an awkward situation for Chuck when Neher visited the laboratory. Noticing them, he asked what they were. Chuck explained that some people believed they helped to make better seals, and then quickly changed the subject and ushered him out of the room.

The work I did with Chuck on single sodium channel gating resulted in three publications that I remain very proud of. We had a true collaboration, with important contributions from each of us. But perhaps more consequential was the great deal of science I learned from Chuck's patient teaching, innovative approach, mathematical abilities, and unique way of doing research. I can't imagine how different my work would have been without his tremendous influence.

Although I didn't work in his laboratory, Dick Tsien's generosity and support had a great influence on me. But our story is from a different and later time, when we were at Stanford together in the Department of Molecular and Cellular Physiology. He was my chairman and then later I was his chairman. We collaborated and shared postdocs. That department, where six of the original nine faculty members had previous affiliations with Yale, also became a terrific scientific environment with wonderful colleagues who inspired me a great deal.

Knox, Chuck, and Dick had three quite different styles, but all became successful and influential biophysicists. Each was an essential influence in my development. I paid close attention to their individual ways of doing research–their particular and distinct strengths, all of which seemed to be beyond my capabilities. I began to appreciate how diversity in approaches and personalities was essential for a first-rate research program and something to cultivate in a department. I realized that I wouldn't be successful in trying to emulate any of them, but that if I worked hard and learned from each of them, I could find and develop my own approach. I hope and believe that I have taken fragments of each of their characteristics and amalgamated them with my own to become a better scientist.

After considering various positions at other institutions, Chuck eventually accepted the directorship of a new Section of Molecular Neurobiology at Yale, and we moved across the street. This diminished my contact with the Physiology department but brought new colleagues to Yale such as Mu-Ming Poo and Susan Amara. Chuck kindly offered me a position as an assistant professor, with an understanding that I would leave if I got an attractive offer somewhere else. The position allowed me to get an NIH grant, buy equipment, and recruit postdocs and students. I left to join the Stanford Neurobiology department a year and half later in 1985.

I arrived at Yale as an eager but inexperienced and naive beginning postdoctoral scholar. I left as a confident scientist, ready for a career as an independent investigator, with experience and insight that prepared me for the next 35 years of managing my own laboratory. I am profoundly indebted to my teachers and colleagues and to the culture they engendered: a collegial and often playful attitude toward people and research, an unyielding expectation of excellence, and a belief that the strongest criticism should come from within. I have had other important influences, including Denis Baylor, Clay Armstrong, and Chris Miller, but I grew up as a scientist at Yale.

As I look at the current roster, the only faculty from back then that are still active in the department are Larry Cohen, Biff Forbish, and Clifford Slayman, although Fred Sigworth arrived at about the time I left. My friend Vic Pantani and Henrik Abeldgard are still in the electronics shop. The rest have moved on, have taken emeritus positions, or have passed away. Last year, we lost Knox Chandler, a generous, gentle, and funny man; an outstanding, brilliant, and innovative physiologist and biophysicist; and a tremendous influence on those fields, on me, and on others. I would not be the same without having worked with him. I am not alone in missing him greatly.

Lesley C. Anson served as editor.