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ESSAY

Mentors: Doing science with Alan Hodgkin

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My purpose in writing this essay is to recall my experience as a trainee in Alan Hodgkin's laboratory in Cambridge, England in the early 1970s. Alan is widely known for a brilliant analysis of the nerve impulse with Andrew Huxley, but less is probably known about his day-to-day approach to science and his mentoring style. It is these aspects that I will concentrate on.

I went to Alan's laboratory on the recommendation of Mike Fuortes, my boss in the Laboratory of Neurophysiology at the National Institutes of Health. Mike had collaborated previously with Alan in work on photoreceptors of the horseshoe crab. At the time, virtually nothing was known about how absorption of light in visual pigment molecules was coupled to conductance changes in the photoreceptor membrane. They suggested that light acted in a series of steps to form a "substance," presumably diffusible, that opens a membrane conductance (1). Mike and I subsequently obtained evidence in turtle cone cells that an intermediary substance might have a different role: to close a membrane conductance (2).

When I went to his laboratory, Alan encouraged me to work on vision but he was busy with his new job as President of the Royal Society as well as with winding up an analysis of experiments on calcium effects in squid axons. I thus saw rather little of him for nearly a year. Our weekly lunches together at the University Centre were strained, and I found the tea room conversations in the Physiological Laboratory obscure and tiresome. I was trying to incorporate rhodopsin into artificial membranes, but it wasn't working. Furthermore, England lacked the conveniences of America. When something at home was urgently needed, the stores were typically closed ("Bank holiday, dear"). I made a decision to cut my losses and return to America. When I told him this, Alan became agitated and said, "No, no! We're going to work on photoreception! What papers and books should I read? Order animals and equipment for intracellular recording! Set up the optical bench!" He became totally engaged in the new line of work and even drove down to Heathrow Airport with me to pick up our first batch of turtles, which were chosen for their large and hardy photoreceptor cells.

We began to record from turtle photoreceptors with intracellular electrodes and things started to work pretty well, but Alan became worried about whether the optical bench I had made was really state of the art. He asked Andrew Huxley to come up from London for a look: "Andrew knows optics; he built the first interference microscope." Andrew found much wrong with my version of the optical bench, but he made helpful suggestions for improvements and indeed brought us several lenses and prisms from an optical shop in London a week or so later. With our new optical bench, we set out to obtain a quantitative description of cone transduction and to infer something about the coupling between visual pigment and membrane conductance.

Alan Hodgkin and Denis Baylor, 1991. Photo courtesy of the author.

Alan loved experiments. Typically, we did experiments two or three days a week, usually beginning in the late afternoon and continuing into the wee hours of the morning. Sustenance consisted of chunks of some wonderfully British stuff called "Sporting and Military Chocolate." We sat in near darkness while I fished for a good cell to record from. He sat at a table with a dim lamp writing equations and waiting patiently until I got a good cell, at which point he sprang to life and suggested what to do next. I liked to record large responses to bright flashes but he insisted on first getting many small linear responses to dim flashes, the idea being that one had to understand the simple,

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linear behavior first. Alan was obsessed with knowing the absolute stimulus intensities and insisted on calibrating the light after every night's recording session. This involved measuring light intensities at multiple wavelengths using a finicky radiometer. It was a tedious and time-consuming task. Nevertheless, he always insisted on repeating the first several measurements to make sure that nothing had changed in the source or the radiometer during the course of the calibrations. By the time we had finished experimenting, the gates outside the laboratory were locked and, to get out, I scaled an iron fence with spikes on top. I always wondered what would happen if I got impaled up there in the middle of the night.

In those days, we had no analog-to-digital converter, so the procedure was to photograph each oscilloscope sweep on a long roll of film. The next day I projected the film in a photographic enlarger and traced each sweep on graph paper to make measurements to a fraction of a millimeter. Hans Meeves, a previous collaborator of Alan's, had warned me about tracing sweeps on the top sheet of a pack of graph paper. Alan once saw him doing this and insisted that the tracings be redone because the effective magnification would change as sheets were removed.

Alan was totally devoted to a quantitative approach and getting the quantitative things right. The drafts for each paper in preparation were kept in a manila folder, but by the time the paper was nearing submission, a companion folder appeared. This bore the title of the paper with the subheading, "equations and quantitative statements in text." In this folder, each significant equation was justified or rederived. Each quantitative statement in the text was justified by a pointer such as "See analysis of cell 4 of April 2 and cell 2 of May 10."

On weekends, Alan would often work on a quantitative theory. He would come in on Monday morning and present it, saying, "I wanted to work this out and at first I got into a terrible muddle, but it finally worked out and looks like this." On Saturdays, when he wasn't working on a theory, he came into the laboratory and sat at his desk in an unusually relaxed, expansive mood. We discussed science, and I asked questions. His replies were priceless: stunningly simple and clear. What came across, in addition to his complete intellectual command, was his deep affection for the ideas. Alan had two generalizations about science, which he called "Hodgkin's laws": (1) An experiment will always turn out in the most ambiguous way possible, and (2) The simplest and most boring explanation is always correct. Upon hearing about someone's claim about the latest "breakthrough," he often said, "Interesting if true." And on seeing something that was obviously crazy, he simply looked up and wrinkled his nose.

Alan's technician, "Cook," was a small, rosy-faced, eccentric man who was totally devoted to the boss. Once, when I was preparing a figure with many experimental points lying close to a theoretical curve, I pointed out to Cook how beautiful the fit was. Cook replied, "Well, the Professor wrote the equation, didn't he?" Cook also told me that, on the morning Alan was notified of his Nobel Prize, he went into his workroom and found on his desk an envelope containing a generous check and a note saying simply, "Here, Cook, here's yours."

Alan was fundamentally shy and modest. As a lecturer, he was very lucid but not a showman, and I was surprised to see how nervous he was in presenting the Nobel work on the nerve impulse to the undergraduates in an advanced physiology course. His nervousness may have arisen partly from his shyness and partly from his desire to make the lectures as elegant as the work itself.

Together, Alan and I described the laws that govern phototransduction in turtle cones (3–5). We showed that, for small responses evoked by dim lights, the transduction behaves linearly, obeying superposition and time invariance. That is, when the number of photons being absorbed is small, each photon evokes an elementary response that adds perfectly with the responses evoked by other photons. Background light of appreciable intensity changes the state of the transduction so that each photon now evokes a smaller, briefer response. By preventing the cone response from reaching the maximal amplitude, this change allows a cone to signal light intensity over a very wide range. We also obtained curves that described the sensitivity of turtle cones to light of different wavelengths. We developed a quantitative model for cone transduction that incorporated several features of the Fuortes-Hodgkin model (1, 6). The s-shaped delay in the rise of the response suggested that in vertebrate cones, as in Limulus photoreceptors, a series of intermediate steps intervened between light absorption and the membrane conductance change. Knowing that light hyperpolarizes cones by reducing a conductance, we assumed that the steps produced particles of a blocking substance that bound to and closed channels in the surface membrane. The model accurately reproduced experimental responses to light over a wide range. In computing the behavior of the model, we were fortunate to have the assistance of Trevor Lamb. Nice as the cone model was, it was based upon the assumption of a blocking substance, and eventually this proved wrong. We know today that light acts by the opposite mechanism: destroying a substance (cyclic GMP) that in darkness holds channels open.

My time with Alan Hodgkin was my Camelot. I charged my scientific batteries, learned how to approach science and how to conduct myself as a scientist. Alan mentored by one-on-one interaction. In spite of his seniority and fame, he made me feel that we were colleagues, not mentor and trainee. He immersed himself in all aspects of the work—from theory to instrumentation to the taper and resistance of the microelectrodes. It went without saying that we would demand the best of ourselves. He could be impatient with stupidity but was gentle and patient in introducing new ideas. I tried to pass on Alan's approach to my students and postdocs, and I hope that they will pass it on to theirs.

Lesley C. Anson served as editor.

References

1. Fuortes, M.G.F., and A.L. Hodgkin. 1964. *J. Physiol.* 172:239–263.
2. Baylor, D.A., and M.G.F. Fuortes. 1970. *J. Physiol.* 207:77–92.
3. Baylor, D.A., and A.L. Hodgkin. 1973. *J. Physiol.* 234:163–198.
4. Baylor, D.A., et al. 1974. *J. Physiol.* 242:685–727.
5. Baylor, D.A., and A.L. Hodgkin. 1974. *J. Physiol.* 242:729–758.
6. Baylor, D.A., et al. 1974. *J. Physiol.* 242:759–791.