HOW I FINALLY FOUND A HOME IN THE NEUROPHYSIOLOGY OF VISION. OR, SERENDIPITY ON THE WAY FROM MATHEMATICS TO VISION

Nigel W. Daw

I have to say that I am very honored that Kai Erikson invited me to give one of these Intellectual Trajectories. Mine has two things in common with a lot of the others presented. First, I came from Europe, which seems to be true of quite a lot of the people here. Second, my career was really a lot of serendipity, a lot of chance, and a lot of luck. My career didn't actually start until I'd reached the age of thirty. But like a lot of other people, I'm going to go back much earlier than that to London in 1933 when I was born, six years before the Second World War. Shortly before that war, we moved to a wonderful old house in Kent called Westbere, which had previously been Joseph Conrad's house. When the war came, this house that had our family of four people was taken over by the army and occupied by at least a platoon and I think maybe even a company of troops. We went to live with my grandmother in Seaford in Sussex, and from there we went to a farm in Berkshire where my father had a friend with an empty farmhouse—very nice. Two things I remember about that farm. One was that it had this wonderful octagonal cow shed where the cows would all face into the center to be milked. We learned how to get into this cow shed and inside we discovered dozens of small planes, like Piper Cubs—no use for military purposes. We were able to get in, climb into the cockpits, and play with the controls until somebody found out and nailed our entrance shut. The other thing I remember was a school next door, St. Andrews, with enormous windows that had a very hard time keeping up the blackout regulations. We were on the route from Germany to Coventry, so if there were any planes that hadn't found any targets in the automobile factories and the plane factories in Coventry, they'd come over on the way back and they would drop their bombs on these lights in the middle of nowhere. It was great, they just went harmlessly into the woods. But afterwards they left big craters, and we could go and play there and pick up the shrapnel and stuff like that.

After a couple years of the war, at the age of eight, I entered what in England is called a prep school, named Tormore, which, like our family, had also moved from

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Kent; the school was evacuated to a house called the Vyne near Basingstoke. I don't know if anybody has been there. It's now a National Trust property. It's a really magnificent old Elizabethan house. On one end it had a couple of wings. Upstairs on one wing there was a gallery with carved oak all the way down all the walls, and the downstairs was a gallery full of statues. The upstairs gallery was called the Oak Gallery, and it was occupied by sixty or eighty beds with boys in them. That was our dormitory. The downstairs, called the Stone Gallery, was occupied by three classes that would go on simultaneously, hoping that the one in the middle didn't interfere too much with the ones at the ends. I was definitely a nerd at Tormore. I was no good at sports, which was demonstrated one day when the forward line of my team went way past the defense. We had the ball, the only thing between us and the goal was the goalkeeper, and they passed the ball along from the right forward to the right wing to the center forward to the left wing. I was left wing and they expected me to score a very, very easy goal. Well, of course, I missed. The one time I did successfully do some kind of physical thing was during the annual pudding contest. The cook would climb to the top of a big ladder. She would have cooked the most enormous pudding, a pancake actually, a most enormous pancake, and she would throw it out and the boys would all scramble to try and get as large a bit of pancake as they could. Well, she threw it just in front of me and I landed on top of it, and after about fifteen minutes with about twenty or thirty boys on top of me all trying to get this pancake away, I emerged; and after I'd stood up and taken all these little bits of pancake off my sweater, there I was, I had the most pancake. So I won the pancake prize.

The other thing I had at Tormore was a wonderful math master who would put up problems on the board every week, and I really delighted in going in and solving these problems. Very simple mathematics but I really enjoyed it. So, the headmaster said, "Why don't you try for a scholarship to Winchester?" This was a year early. He said, "Try it out and see how you do." So I went to Winchester and sat through the exam with all the usual subjects—Latin, Greek, divinity, English, history, and math—and they offered me a scholarship. They said, "Most of your subjects aren't quite up to your mathematics, but we'll let you in and let you have a go." Then the question arose as to whether I should actually go to Winchester a year early as a scholar. It was decided that I should, so I entered Winchester, which you may or may not know is the oldest school in England not attached to a monastery. It was founded in 1389 (I think the first class arrived in 1393) by William of Wykeham, who was Bishop of Winchester and Chancellor of England, along with New College at Oxford where Werner Wolf went. Werner is now in Hawaii, I guess.

I went to Winchester and did the usual stuff, nothing spectacular. I remember in particular going to chapel eight times a week, once a day and twice on Sundays. That gave me a lifelong love of Bach and Handel and music in general, old music. The other thing I remember was living in a fourteenth-century unheated building. In the winter one of the things one would have to do would be to break the ice off one's bowl of water in order to wash one's face. I suppose my one big achievement at Winchester was when I sat for the math prize and the last question on the math exam was Bertrand Russell's paradox. I'm sure a lot of you know it—consider the class of all classes that are members of themselves—is this class a member of itself or not? And when you work it through, the answer comes out that it can't be a member of itself and it can't not be a member of itself. So there's something wrong with the whole system of logic. I had never heard of Bertrand Russell's paradox, but sitting there in front of this piece of paper I managed to work it out and get the right answer and express it well enough to win the prize. So then the question came, where should I go to college? Again, I was still pretty good at math so I applied to Trinity College in Cambridge, which was probably the best college in either Oxford or Cambridge if you were in mathematics.

In those days, one had to do one's national service in the British army and I thought it would be less of an interruption if I did it before I went into Trinity College Cambridge. That turned out not to be true as I'll tell you in a minute. So I went to sign up for my national service with the King's Royal Rifle Corps, which had its basic training in Winchester. The King's Royal Rifle Corps was founded in the eighteenth century because the British were fighting these pesky colonials, as you know, and they wouldn't stand up and fight like men. They hid in the bushes and took potshots at the British army. So the British came to the conclusion they had to have a regiment that didn't march in formation in red, and they formed the King's Royal Rifle Corps, known as the Green Jackets because they didn't wear red coats, they wore green coats. I was in the Green Jackets for two years, and I totally lost my mathematical ability. Before going into the army I could go to sleep at night with a math problem in my brain, and wake up in the morning with the solution. After two years in the British army, I just simply couldn't do it. So I went to Trinity and took Part 2 of the math tripos, which is what scholars were supposed to do—miss Part 1, and go straight on to Part 2. I got a second, and my tutor called me in and he said, "Daw, we don't expect our scholars to get seconds. We expect them to get firsts." Well, I hadn't gotten a first, and a career in mathematics, at least a distinguished career in mathematics, promptly went out the window. In those days, if you wanted to become a professor in mathematics at a respected university, Manchester, Liverpool, Birmingham, London, any of those as well as Oxford and Cambridge, you didn't just have to be the best mathematician in your year at Trinity College Cambridge, you had to be the best mathematician in the past five years from Trinity College Cambridge, and I clearly wasn't going to make it. Accompanied with which was my father's opinion of academics. He was a businessman and he used to say, "Don't go into academia, the politics is the worst of any politics in any walk of life, absolutely the worst," which in England in the 1950s was probably true. It was a static situation. There were a limited number of professorships and the pickings were slim. I don't know if it was true in this country at that stage but it's certainly not true in this country since then, where if you don't like what you have at one university you go to another.

Trinity was a wonderful experience, and it also had an interesting history. It was founded by Henry VIII as an amalgamation of two colleges: King's Hall, which was a college for the sons of courtiers, and Michaelhouse, which was a college for poor scholars. Even today, almost five hundred years later, there are those two elements in the college. The two groups of people hardly talk to each other, but it's a large college, eight hundred undergraduates, so there were still plenty of people to talk to even if you didn't want to talk to the toffs. I had a good time there. For my third year, my father—who, as I said, was a businessman—said, "Well you are still good at mathematics, why don't you become an accountant?" So I took a year of law. At the end of the year of law I decided that I didn't really want to become an accountant, and I went into Her Majesty's civil service, sort of a compromise between academia and business. I did that for two years and at the end of two years I discovered that Her Majesty's civil service isn't business and isn't academia, it's just boring.

My father saw that I was bored and that I really didn't know what to do with myself. Fortunately he had a friend who was both a scientist and a businessman. This friend was Edwin (Din) Land, who was president of the Polaroid Corporation. My father talked to Land, who invited me to join Polaroid in his group working on the psychology of color vision. Din Land was a fascinating character, and at the end I can tell you a little bit more about him. He had a small group doing research on the psychology of color vision, and he had two reasons for forming this group. One was that he really wanted to make color film (at that stage they just had black-and-white) and the second was that he really wanted to be known as a scientist rather than as an inventor. He actually had made some inventions that involved extraordinary science. The chemical reactions in the Polaroid film involved transferring the image from the negative to the positive. For color film, there are three images that have to be transferred, a red image, a green image, and a blue image, involving not only chemical reactions but also an extraordinary understanding of the kinetics of all the reactions to get them from one layer to the other at the right time and the right place. But Land said that he didn't want to be known for that, partly because he didn't want Kodak to find out exactly how it worked. He was worried that they might steal it and of course they tried to. So there were these two reasons for his group in color vision, and I remember part of my job was to help him advertise his theories of color vision, which on one occasion involved taking Torbjörn Caspersson to the Parker House in Boston for a brunch. Caspersson, as you may or may not know, was secretary of the Nobel Prize Committee at that stage. So Land was really promoting himself as a scientist rather than an inventor. With Land I actually made my first visit to Yale. Land was friends with Kingman Brewster—they both went to the same Friday evening supper club in Boston. So Kingman Brewster invited Land to give a talk here. I don't know if anybody here attended that talk. It wasn't given in an auditorium, it was given in some hotel somewhere and the equipment had to be set up on the dance floor in the middle of the dining room. It was a nightmare and it didn't go all that well.

Anyway, after three years at Polaroid, it became clear to me that I had to move on. Color vision has always been a very controversial subject. There was the controversy between Newton and Goethe in the seventeenth century. There was another big controversy between Hering and Helmholtz in the nineteenth century, and in the twentieth century it was Land versus everybody else, partly because of Land's personality. He wouldn't acknowledge any of the other people in the field, and as a result none of them wanted to acknowledge him. I remember after I left Polaroid I wrote a review article for *Trends in Neurosciences* on color vision.[1] I sent him a draft of the article, and he called me up and invited me to go to Boston to visit him and discuss the article. It became clear that the main purpose of this visit was to persuade me to take out a sentence where I had said that Land's theory of color vision was really in some senses very like Helmholtz's concept of discounting the illuminant. I said, "Why do you want me to take out any reference to Helmholtz?" and he hemmed and hawed—he didn't like that sentence at all. He didn't like any thought of the idea that his theories might be similar to something that Helmholtz had expressed a hundred years before.

It also became clear to me that one wasn't going to solve all the controversial arguments by arguing about the psychology of color vision. One really had to go into physiology and record nerve cells and find out what was actually going on. So the question was where? I went to see David Hubel and Torsten Wiesel at Harvard, who were the preeminent vision physiologists at that time, and they said, "We don't take graduate students, sorry." Then I went to MIT to see Jerome Lettvin, whom Gary Haller here has met, and Jerry said, "Yeah, come and do a Ph.D. with me," and he got on the phone to Pat Wall who was executive officer of the Biology department. Jerry said, "I have got Nigel Daw here, he wants to come and do a Ph.D. I think that's a terrific idea, because if he comes and does a Ph.D. with me, I can go to Polaroid and use all the apparatus there." I went over to Pat Wall and I said, "Well, I really want to get a Ph.D., but I'm really not at all sure that a deal like this is the right way to do it."

Then William Rushton, who was a physiologist from Trinity College Cambridge and an authority on color vision, came to visit. I said, "What do you think I should do?" He said, "Well, you can come to Cambridge, but in Cambridge we only accept one Ph.D. student a year and that Ph.D. student is somebody who has got a first in the physiology tripos. I can talk to Matthews [the chairman] if you want, but I don't think there is any great hope." He said, "Why don't you go and try Ted MacNichol at Johns Hopkins?" Edward MacNichol was working on the color vision of the goldfish retina. So I wrote to MacNichol and it was arranged that I would have an interview. This interview actually took place on the July 4 weekend while Leila and I were on our way back from our honeymoon. The other part of the story that I should also mention is that this very energetic woman came to work for me at Polaroid Corporation. We fell in love with each other and when we announced our engagement, the head of the lab called her in and said, "I think you should leave this job and go home and shop for your trousseau now you're engaged to Nigel." Well, this didn't go over very well with a feminist Wellesley graduate. All the other women at Polaroid had been hired through the Kennedys at Smith. It may have gone over okay with a Smith graduate, but it certainly didn't go over well with Leila. So that was the other reason why it was clear that I had to leave the Polaroid Corporation. If she had to go, I was going to go.

I didn't have any college-level courses in biology. I didn't have any college-level courses in chemistry. All I had under the English system was mathematics, then four years of work on the psychology of color vision in the United States. Nevertheless MacNichol interviewed me. Leila and I went back to Boston. I then went down to the Marine Biological Laboratory, where the chairman of the Hopkins department, Spike Carlson, was working for the summer, and interviewed with him. I applied, with no GREs, none of the required courses, and just three letters, one from my tutor at Cambridge, one from Land, and I regret to say I've forgotten who the third one was from. It turned out that they had an open position on their training grant and they admitted me. That never would have happened nowadays.

I knew that the color-coded cells that were being investigated at that stage in the monkey lateral geniculate and in the goldfish retina were all what are called opponent color cells. They were excited by red in the center of the cell's receptive field and inhibited by green in the surround or the periphery. For the phenomenon of simultaneous color contrast, where a gray spot in a green surround looks reddish, which was essentially what we'd been investigating at Polaroid, this clearly was the wrong way around. What one wanted was a cell that was excited by red in the center and excited, not inhibited, by green in the surround. So I went to look at this question in the goldfish retina and discovered that actually these opponent color cells in the goldfish retina were double-opponent cells, excited by red in the center, inhibited by red in the surround, inhibited by green in the center, excited by green in the surround. David Hubel named them double-opponent cells when he concurrently found similar cells in the macaque cortex. The only reason MacNichol hadn't found this out was that he was using spots of light in the surround rather than an annulus of light, and intensity and area are not reciprocal, so he didn't get the full response. That gave me a thesis.

Then the question came up, where should I go for a postdoc? I applied to Gian Poggio in Vernon Mountcastle's Physiology department at Hopkins and was accepted there. I also went to see Hubel and Wiesel and they said, "We do take postdocs even if we don't take graduate students and maybe now we'll accept you." The first thing I did at Harvard was to look for double-opponent cells in the macaque lateral geniculate nucleus. I thought maybe Hubel and Wiesel had made the same mistake that Ted McNichol made—they hadn't used the right stimulus. However, working with Alan Pearlman, we searched and didn't find any. Thus, it was a huge stroke of luck that Hubel and Wiesel did not accept me as a graduate student at Harvard and Ted MacNichol did at Hopkins.

Alan and I then went on to the cat lateral geniculate nucleus and started looking at what the cat geniculate might show in the way of color. At that stage cats were the prime affordable model for the neurophysiology of vision in humans. The first thing we did was to train cats to discriminate color against a bright background that knocked out all the contributions from the rods and only left the contributions in bright light from the cones. After a thousand trials, we found that cats do see color with bright lights above saturation of the rod system, so that the rods are inactive (one hypothesis was that cats see color by using rods in conjunction with a single class of cone). It took a long time. They can do a light/darkness discrimination in fifty trials, but a color discrimination takes twenty times as long. Not only did it take them a long time, it took us a long time.

While I was there, the Nobel Prize was awarded for vision to George Wald at Harvard, who discovered that there are separate red, green, and blue pigments in the photoreceptors of the macaque. It was shared with Keffer Hartline at Hopkins, who had worked on various retinas, particularly the Limulus retina, and Ragnar Granit, who was professor of physiology in Oslo. They gave it to him for what he called the dominator-modulator theory. He claimed that in cat retina there are dominators which are brightness detectors, and if you measured the response of some of the ganglion cells in the retina and subtracted out the dominator response, you got different curves. The subtraction gave him a red response, a green response, or a blue response, but it wasn't a response—it was just a mathematical subtraction of the spectral sensitivity of the receptors from the overall spectral sensitivity. Alan Pearlman and I went into the cat geniculate and discovered that there weren't any modulators there, really. All the cells in the upper two layers of the cat geniculate gave the dominator response. If you go down through the first two layers and get to the third, you find some double-opponent cells: green-blue double-opponent cells just like the ones in the goldfish retina except that they are blue-green instead of red-green. David Hubel was absolutely delighted with our result. Hubel had a rather unique instinct for what he called turkeys. These were people whose scientific results he just simply didn't believe, and as far as he was concerned, Granit was a turkey and should never have gotten the Nobel Prize. At the party that Hubel and Wiesel gave for the awarding of the Nobel Prize in vision, I raised my glass and I said, "Here's to the next Nobel Prize in vision, Hubel and Wiesel and Mountcastle." And David said, "Why Mountcastle?" You may not know, but Mountcastle essentially discovered columns in the cerebral cortex. He discovered them within the somatosensory system. This was a rare occasion on which I thought that Hubel was wrong. Mountcastle was not a turkey—he was a very good scientist. Hubel and Wiesel did get the Nobel Prize several years later, along with Roger Sperry.

Then I got offered a job at Washington University. Washington University had just built a new building and they'd hired Carlton (Cuy) Hunt, who was chairman of physiology here at Yale. They also hired Max Cowan as chairman of anatomy. After a few years, with recruitment by these two chairmen, Washington University rapidly became the best place in the country, I think, for neurobiology.

After that, my intellectual trajectory, which had really started when I left Polaroid at the age of thirty, became logical. I was no longer depending on serendipity. I worked on the rabbit retina looking at the effect of various neurotransmitters. I tried out depriving the rabbit retina for directional sensitivity, rearing rabbits in a drum that went around them continuously in one direction, because rabbits have a lot of directionally selective cells in the retina, and I wanted to see if properties of cells in the retina can be changed by visual exposure, just as cells in the cat visual cortex can (another result from Hubel and Wiesel, who showed that the ocular dominance of cells there can be changed by closing one eye). It was a negative result. So I went on to do the same experiment in the cat cortex to prove that the apparatus worked. It did work, fortunately, in the cat. I was scooped by Wolf Singer in Germany and Max Cynader in Canada. They found the same result, so I didn't have anything to publish. I decided to go on and investigate what is the critical period of directional mechanisms as compared to the critical period for closing off one eye (exposure to a particular stimulus is effective in young animals during the critical period, but not in adults). It turned out that the two critical periods are different. This started a whole line of research done by myself and others on how the critical periods for different visual properties are different. That went on to mechanisms of plasticity in the visual cortex, involvement of NMDA receptors, cyclic AMP, protein kinase A, nitric oxide, and the Nogo mutant, which involves myelin. Now, we have a pretty good understanding of critical periods for development of the various properties of vision, and the biochemical mechanisms that control them in the visual cortex, and possibly some clues to treatments that might ameliorate human conditions where the development of the visual system is affected by problems such as strabismus, anisometropia, myopia, and cataract, which lead to amblyopia (poor vision).

About half of this work was done at Washington University and about half at Yale. After I had been in St. Louis for a year, Leila said to me, "When are we going back to the East Coast?" I said, "When you find a job. Find a job on the East Coast and then we'll think about it." So, after twenty years of raising children, getting her M.F.A. at Washington University, and teaching at Southern Illinois University and various other places, Leila got an offer from Massachusetts College of Art and Design in Boston and I said, "Take it. If you like it after a year, I'll start looking." After a year she liked it and so I started looking, and I had a choice of a soft-money job at Harvard with Gerry Fischbach or a hard-money job at Yale with Marvin Sears and Pasko Rakic. Later on when I got onto the tenure allotment committee at the medical school, I discovered that I was really lucky that they were able to push that through, but they did and I decided to take the hard-money job at Yale. This turned out to be a very, very wise decision. First of all, I had some wonderful colleagues in neurobiology and ophthalmology. Second, I had all the facilities of Yale, music and theater and art museums and everything else, as well as proximity to New York. Third, we were able to get a house on the shoreline for about $300,000, which would have cost a million in Boston; and fourth, I was able to get to work in fifteen or twenty minutes when it would have taken an hour or an hour and a half in Boston. We could never have afforded the same kind of life in Boston. Last, we both loved sailing, and I could go home, run a hundred yards down the road to the shore, and jump on my boat. So we had a commuter marriage for ten years but it really worked out well. We had a townhouse (Leila's loft) in Boston and a country house in Branford. I was able to write two books as well as spend full-time in the lab.

I might make one final comment over my career. Some of you guys seem to relish being chairman. I studiously avoided as many administrative duties as I could. For a while I was running the Division of Biology and Biomedical Sciences at Washington University in St. Louis, which was responsible for the recruitment of all graduate students in the Biology department and at the medical school. William Rushton had told me about how few people they educated in Cambridge. My view was that everybody should educate three graduate students in their lifetime, one to replace themselves, one to go to a lesser institution, and one to drop out of the system. Well, after a few years Max Cowan was replaced by Louis Glaser, chairman of biochemistry, as head of the division, and Glaser didn't like my ideas at all. He wanted lots of graduate students and he said, "There are always biotech companies and biochemical companies around to hire them. There's plenty of place for hundreds of biochemistry students to go and work after we graduate them. We should admit more." Thus I resigned. I studiously avoided becoming chairman, and for that reason I was twice persuaded to become acting chairman, first in physiology and biophysics and second in anatomy and neurobiology. I managed to avoid any real responsibility.

Notes

1 Nigel W. Daw, "The Psychology and Physiology of Colour Vision," *Trends in Neurosciences* 7 (1984): 330–35.