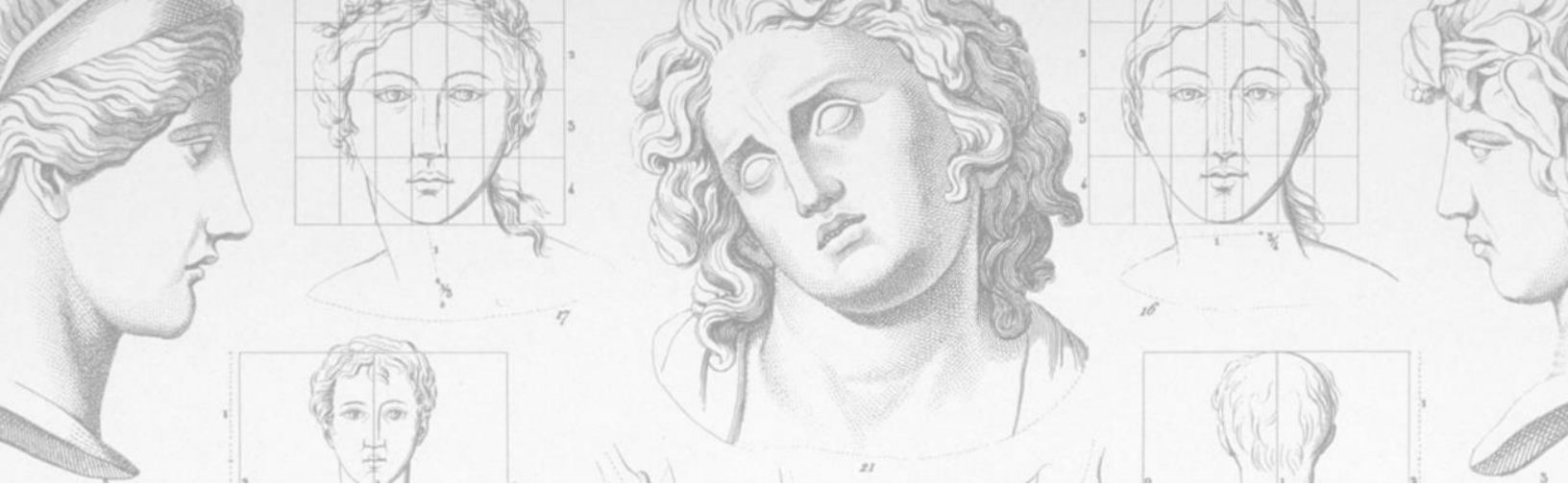

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National Institutes of Health, Office of Mathematical Research: Surgeon, U.S. Public Health Service (Biophysics) (1962)
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Retina Foundation, Boston: Research Associate (1966)
Massachusetts Institute of Technology, Biology Department: Research Associate (1967)
Yale University School of Medicine, Physiology Department (1967–1978): Assistant Professor, Associate Professor
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Association for Chemoreception Sciences (AChemS). Chairperson (1981)
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Honorary degrees, University of Copenhagen (1999); University of Pavia (2006)
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Gordon M. Shepherd has carried out fundamental studies of the integrative properties of dendrites, dendritic spines, and synaptic microcircuits, using the olfactory bulb as a model system. His contributions include the first physiologically based circuit diagram of a brain region; electrophysiological analysis and computational prediction with Wilfrid Rall of dendrodendritic synaptic interactions for feedback and lateral inhibition; discovery of the representation of odors by spatial activity patterns in the olfactory glomerular layer; and databases and neuroinformatics tools for dendritic properties, computational neuronal models, and brain microcircuits. Among his books are The Synaptic Organization of the Brain (5th ed.), Neurobiology (3rd ed.), Foundations of the Neuron Doctrine, Creating Modern Neuroscience, and Handbook of Brain Microcircuits.

Gordon M. Shepherd

I was born "at the bottom of the Depression," as we used to say with a certain amount of pride. My generation was the last to have childhood memories of those years, so harsh for so many, though muted for a child growing up in a middle-class academic family in a small midwestern college town. The economic recovery followed by World War II in the early 1940s instilled in us a belief that we could overcome adversity, together with a belief in progress.

My father, Geoffrey Shepherd, had immigrated in 1908 as a boy to Canada with his family, settling on a ranch, West Plains, in southwestern Saskatchewan just over the border from Montana. His father and brother survived their first winter in a sod hut, so in that real sense I come from pioneer stock. He raised us on stories of the "pioneer spirit," of their survival in the hardscrabble landscape and harsh climate of the northwest plains, where hot summers brought their plague of drought and grasshoppers, and bitter winters required feeding the cattle at forty degrees below zero. There was a quiet heroism about it, a grandeur of the vast and open plains, that exerted its pull on me from his stories and our visits there. Wrenching himself from his family and the ranch, he earned a college education and followed a friend to Ames, Iowa, to become a graduate student at Iowa State College in agricultural economics, one of the premier programs in the country.

My mother was Eleanor Murray, a third-generation Scot in the United States, who grew up in Cedar Rapids, Iowa, went to Coe College, and worked for several years as an editor in the U.S. State Department in Washington. She was a sister of Bill Murray, one of father's graduate school roommates at Iowa State. She and father married in 1931. I thus had both an immigrant's and a native born citizen's view of life in these United States.

Despite the Depression, in 1935, as a young faculty member at Iowa State, father took us on a study tour to Europe for several months. I was later entertained as a child by stories of the adventures of a 2-year-old in Paris, Copenhagen, Norway, and the United Kingdom. It must have planted some internationalist engrams in my young brain.

In 1938 my parents built a new house on Oakland Street near the college. This wooded street was a remarkable neighborhood, with a mixture of academics and townsfolk. For me it was the best possible place to grow up, giving one a sense of the value of learning, together with a sense of common human values. Iowa State at midcentury was an extraordinary institution.

Despite having a "cow-college" image, its academic standards were high and its faculty was world class. Our neighbors and friends included Henry Gilman in chemistry (NAS, FRS), Jay Lush in animal genetics (NAS), Frank Spedding in atomic physics (NAS), and George Snedecor, whose textbook on statistics was a best-seller worldwide. A few blocks away was Paul Errington, one of the country's leading naturalists. The chair of father's department was Ted Schultz, later a Nobel Prize winner in Economics. Rainer Schickele, the future PDQ Bach's father, was also in economics; Ken Boulding, future president of AAAS, was in sociology. Uncle Bill later twice ran for governor and founded Living History Farms. Christian Petersen was the sculptor-in-residence at the college. My parents gave me art lessons from Velma Rayness, a regional painter.

Perhaps most intriguingly (though we didn't know it at the time), the digital computer was invented by one of our neighbors. In a court case in the 1970s, it was determined that around 1940, John Atanasoff, then a member of the Iowa State physics faculty, had invented the first digital computer, whose working principles were used, though without acknowledgement at the time, for the subsequent building of the ENIAC. Although only 7 at the time, I remember seeing him and his family outside their house during my roamings about the neighborhood.

In 1941–1942 we lived in Washington, D.C., while father was recruited into the planning for agricultural price controls for the inevitable war. On December 7, 1941, we were a witness to history. Out for an afternoon drive, we went by the old State Department Building (now the Executive Office Annex) where mother had worked. In addition to roses blooming in December, we saw a knot of people by a side door with several black limousines parked nearby. People there said that Japanese ambassadors were meeting inside with Secretary of State Cordell Hull; something bad had happened at Pearl Harbor in Hawaii. Soon the ambassadors hustled out to their cars; I snapped a photo with my box camera; World War II was about to start.

Because of the Depression and the war, our life in Ames centered very much on the neighborhood. I was lucky to have good buddies to play with. In this connection I was intrigued to read David Hubel's memoir about his own childhood, in which he related how children of modest means of that era were left to their own devices for play and projects. That was certainly true for us: days were filled with backyard sports, card games, reading the comics, listening to the radio, palling around. We played our part in the war effort by engaging in pitched battles with mud balls as grenades in the back ravine. During the winter we would gather at my cousins' house down the street to have sandwiches by the fire, play canasta, and listen to the Sunday night lineup of radio comedies. Caroling at Christmas was a neighborhood tradition.

During the war we daily followed the battlefronts in the newspapers. The maps gave graphic testimony to the grinding progress of the Allies. I think my interest in maps as representations of knowledge began at

that time. The tide of success in the war of course was more evidence of our belief in human progress.

After the war, as a teenager, I began to read. Mother directed me to Thomas Hardy, whom I liked, both for the aphorisms about human nature embedded in his narratives, and the way he described the entire environment within which the individual characters worked out their fates. At 16, I made $15 on the offer of my Grandfather Murray for memorizing Gray's *Elegy*. Having spent the first 12 years of my life under FDR, I got interested in the presidents and memorized them all. On frequent visits to my Murray grandparents, I absorbed U.S. history from books in their library and wrote my own history of the presidents, complete with text, pictures from magazines, and electoral maps for each campaign, created with a home mimeograph—author and publisher at age 15! On one occasion I accompanied my grandparents to a meeting of veterans of the 1898 Spanish-American War, in which grandfather had served as a medical officer just out of medical school. In the show was a hypnotist, the only time I've seen people stretched out like boards between two chairs. I doubted then, and since then, that I could let go of my consciousness to have that done to me (if it really happened!).

The exploding of the atomic bombs in Japan in August of 1945 gave rise to a lot of news and information about the physics behind the bomb. Father was much interested in this, stimulated by Spedding's role, and we absorbed numerous magazine articles and several books explaining the periodic table, uranium and plutonium (Iowa State was important in its production), nuclear fission, and so on. I was impressed with how the bomb was a product of both experiment and theory, and began to think of this as the natural way to carry out any kind of science.

Although my main aim in life at that stage was sports, I was too scrawny to get on the varsity, so I began to be interested in science in a small way: listened to my crystal radio, learned Morse code, built a radio, feasted on the Hallicrafters catalogs with their enticements to build your own TV (strange how 2" screens in big clumsy boxes quickly became obsolete, but now those little screens seem to be the future, housed in thin slivers of plastic).

A curious side event was Grandmother Murray being named American Mother of the Year in 1947. She had been an early feminist, chair of the city School Board in the 1920s, and had written extensively on family matters and then international affairs. It also reflected of course her five children and their spouses, who were successful in various ways in academia, medicine, and the military. They became increasingly important role models.

In the early 1940s father began publishing a textbook in agricultural economics, which eventually went into seven editions over the next 40 years, followed by two other textbooks. So there were often index cards spread over the living room floor as mother prepared the indexes, a condition that seemed a normal part of home life.

Summers were a time to find a job. Fortunately, through my friend Bob Brayton's dad, we got on a crew of buddies detasselling corn during the teenage years. Although the Iowa summer temperature often was in the high 90s, we all felt lucky to have a job and a steady income (50 cents an hour). Later I spent the summers of 1951 and 1952 on the home ranch in Canada working for my rancher cousin Jack. It was an exhilarating experience, actually to be living the life father had lived, among the broad sweeps of the prairie and under the enormous sky, working with Jack and neighbors, handling animals, branding, building fences, putting up hay. For a while I tried to imagine a career for myself as a rancher. But reality set in, and after the second summer I hungered for the life of the mind. However, that experience reinforced my feelings of closeness with good people battling adversity to scratch out a living in the real world.

My high school academic record was relatively indifferent. I was lucky to have fast-friends: Dick Day who every week it seemed had a new theory to challenge me, and Bob Brayton who stimulated my interest in math and science. Among my high school teachers, Ronald Easter taught physics and chemistry with discipline, and Mary McNally especially opened my eyes to world literature. My biology teacher Richard Trump in a recent memoir recalls that I could be a bit flippant. When we graduated we were asked what we thought we would become in life; I answered "I don't know what I *will* be, but I know I *won't* be a doctor."

Iowa State

With my lackluster record I was not going to compete for any scholarships to go to eastern colleges. And I couldn't very well argue that I needed to go to a college with a better faculty than Iowa State where my father taught! Anyway, my buddies were going there. Furthermore, with four siblings we had to save money, and tuition at Iowa State was just $54 a quarter. Even at that, mother found the Laverne Noyes full-tuition fellowship for children of World War I veterans, which father had been in Canada.

An interesting sidelight along the way was that television was just starting in the Midwest in the late 1940s, and Iowa State's radio station, WOI, got one of the first licenses. I had taken part in a radio program of 'Penrod and Sam' (playing Penrod) in 1948, so was on the spot as the station shifted over to television, occasionally serving as floor director for a WOI-TV-produced talk show. When I started out in college in 1951, they employed student announcers, so I sat in the broadcast booth and did the announcing at the breaks. I can still remember my lines: 'This is WOI-TV, Channel 4 [sic], in Ames. WOI-TV, the first educationally owned television station in the nation, is dedicated to bringing the best the College has to offer, in programs of education, entertainment, and public service. The time is eight o'clock, and Wonder Bread is good bread . . .' the last indicating how the

station was functioning at the border between public and commercial. One of the programs I announced was "Through the Magic Window," created and produced for children by my cousin Joy Ringham, which was popular all over the Midwest. We realized at the time that we were extremely lucky to be in on the ground floor of the television era; there were people all over the country begging to have my simple job of announcing program breaks. Much later I had occasion to meet John Chancellor, the NBC TV commentator. He was telling others about his early experiences in television news around 1950, so for fun I challenged him that I had been in television before he had. It was close! TV beckoned as a career, but I was more interested in exploring academic careers.

At Iowa State I started out in economics but couldn't work up much interest. It seemed to be all about money—how dull. Later I read a quote from George Bernard Shaw: "I started out in economics, but cheerfulness kept breaking in." My sentiments exactly. Fortunately, at Christmas of my sophomore year my cousin David Murray, then a student at Washington University Medical School, got married. At the gathering of the clan I hung out with Dave, Grandfather Murray in general practice, and Uncle Ed in epidemiology at Harvard, eager to understand their knowledgeable exchanges about medical matters. I immediately decided this was the guild I wanted to join.

From then on courses in the premed curriculum were interesting and challenging, and my academic record improved significantly. My two most inspiring teachers were Howard Hamilton, who had revised Lillie's *Embryology of the Chick*, and taught an outstanding course in experimental embryology, and Keith Huntress, who gave a marvelous course in modern poetry, which gave me a deep sense of how to use words carefully to convey meaning. These influences have lasted a lifetime. I also was a student assistant to Norman Graebner, a leading American historian, helping him add to his thousands of index cards. It made me toy with the idea of becoming a historian, which father rapidly squelched; my aim should be a career of practical value!

For the summers of 1953 and 1954 I traveled east to bunk in with Uncle Ed Murray in Cambridge, Massachusetts, working as an operating room technician at Mount Auburn Hospital in Cambridge. The job and the Harvard ambience were quite a change from the ranch, but having the family connection made me feel equally at home. The second summer I interviewed for a job with George Wislocki, chair of Anatomy at Harvard, who had contributed to identifying the hypothalamo-pituitary portal system. His interview technique was straightforward; after a brief welcome, he said: "How good are you?" "Very good," I replied. By all rights I should have signed on, with a chance to work with members of the Harvard faculty, but the job consisted entirely of looking after rats in the animal room and I was afraid of allergies, with which my brother was plagued.

I applied to three medical schools: Iowa, Cornell, and Harvard. Iowa accepted me; Cornell to my astonishment offered me a full scholarship; and Harvard accepted me with partial support. It was hard to turn down the Cornell offer, but with a Harvard Ph.D. father, one uncle at the public health school, and another a Harvard graduate from an old Boston family, the die was cast.

Shortly before graduating from college, I heard from a physicist neighbor, Joe Keller, about Norbert Wiener's "cybernetics," read his book, and decided that I wanted to study how brain circuits control human behavior. Over a half century later I'm still working at it.

Harvard

Starting medical school, I wanted to plunge into brain research. I tried to get into the medical sciences group, but it was full. I talked to J. C .R. Licklider at MIT, known for his involvement in information technology and cybernetics, but no position. So medical school began to be a bit frustrating. In our histology class Pat Wall came over from MIT to teach the neuroanatomy part. I asked him for the best introduction to neuroanatomy, and after a moment's hesitation he said with his characteristic twinkle: Herrick's *Brain of the Tiger Salamander*. I went out and bought a used copy for a dollar. Herrick showed how one could construct a complete wiring diagram of a "simple" vertebrate brain. I guess this planted the seed of later microcircuit wiring diagrams in my own brain.

Through Pat I was able to land a summer job at MIT with Walter Rosenblith (later Provost), in Norbert Wiener's old RLE barracks laboratory. My job was to take part in experiments on auditory evoked potentials in cats and run an early analog computer to do auto and cross correlations of the responses. It was an exciting time, with a large group of young people who became leaders in auditory physiology, including Moise Goldstein, Larry Frishkopf, Dan Geisler, and Nelson Kiang. Fourier transforms were the method of the day. I realized that this kind of linear mathematical approach was not going to give me the kinds of insights I wanted into neural function at the cell level. I also interacted quite a bit with Karl Pribram, visiting there for the summer, and also got to know Jerry Lettvin, whose laboratory was in the same building. Although our study didn't lead to a publication, a subsequent study applying the computer to auto and cross correlations of cardiac arrhythmias with classmate Van Angelakos was my first paper, in 1957. This was an early example of the application of computers to electrophysiology. With this start, I've worked with experiment and computation my entire career.

In the next summer, of 1957, I fulfilled a need I had long felt to engage in foreign service. Several Murray ancestors had been missionaries, and Uncle Ed had had a storied career, teaching at Robert College in Turkey,

exploring the interior of Asia (reported in two *National Geographic* articles), studying Brill-Zinsser disease in Yugoslavia, and now working on trachoma in the Middle East. I got help from the chair of neurology, Derek Denny-Brown, to arrange an externship in neurology at the American University Hospital in Beirut, with added support from Ed to study inclusion blenorrhea, an eye disease like trachoma, in the Palestinian refugee camps in Lebanon. It was a fascinating time, the summer after Suez. My new Arab friends at the University were alive with strong feelings about Suez and Palestine. Many had lost their homes in 1948. To learn some background I audited a course on modern Middle East history taught by Albert Hourani, an Oxford don and a world expert in this subject. I took detailed notes, which I still study, of his wise observations on how politics works in the Middle East. In the hospital, I attended a young British woman in an iron lung who had contracted polio in Iran, surely one of the last persons stricken with that disease. Through the neurologist Fuad Sabra, my host, I also met his brother-in-law, Charles Malik, the Lebanese philosopher and politician, who was soon to be president of the UN general assembly. It was a memorable evening observing him receiving the local politicians in his home. At one point he shook his head and confided to me, "I only wish to return to my books and my refractions." Accessing one's memories through refraction rather than reflection I found intriguing.

Although I enjoyed my medical classes I knew my heart was in research, so began looking for a laboratory after medical school. Spring of 1958 took me to the Federation Meetings in Philadelphia, where I heard an inspiring talk by Charles Phillips of Oxford University reporting the first intracellular recordings in the brain above the spinal cord, from Betz cells in monkey motor cortex. Vernon Mountcastle reported on his discovery of cortical columns at the same meeting, so those were exciting times. I decided I wanted to work with Phillips on the local circuits that mediate the cortical re-excitation and recurrent inhibition that he had discovered. Fortunately a fellow medical student from Iowa, Rex Jameson, had returned from his Rhodes Scholarship at Oxford, and put me in touch with a former Oxford student, Elmer Pfefferkorn, who knew Phillips. After meeting and talking about my plans with Elmer, I wrote to Phillips. He wrote back with the words: "Any friend of Elmer Pfefferkorn needs no further introduction to me." It was the way science worked in those days. I was lucky to receive a USPHS postdoctoral fellowship in 1959 and have been supported by the USPHS and/or NIH ever since (50 years and counting).

Also during my last year in medical school I visited my friend Dick Day in Washington, D.C., where he fixed me up on a blind date for New Year's Eve with someone he had just met. Her name was Karen Margrethe Gadegaard, a Danish exchange student at Vassar, a young woman full of *joie de vivre* who he said would be more than a match for me. Indeed she was, and has been ever since. That summer Grethe applied to St Hugh's College

in Oxford and was accepted. We were married in her village church in Humlum, Denmark, and began our studies at Oxford in September 1959.

Oxford

Europe was still recovering from the war, and life in both Denmark and Britain was frugal. Television was not a part of our lives in either place. Buildings in Oxford were covered in soot; renovations were just beginning. Students at Oxford wore black gowns ("sub-fusc") and got around on bicycles. Phillips had arranged a wonderful flat for us, at the top of the ancient Priory in Iffley village, from which one could see the spires of Oxford floating in the distant haze. We cycled into Oxford every morning down the Iffley Road and across Magdalen Bridge. I was attached to Trinity, where Phillips was a tutor. Grethe and I spent many pleasant lunches on the Trinity lawn admiring the herbal border or at the White Horse among the patrons playing push ha'p'ny.

I started out as a postdoctoral fellow and shifted to work for a D.Phil. (as it's called in Oxford), both firsts for Phillips. When I arrived he was stimulating the motor cortex and recording from the spinal cord to carry out his pioneering studies of the control of the hand. However, my mind was set on cortical circuits. He remembered that his colleague Tom Powell had suggested the olfactory bulb as an ideal model for functional analysis of a cortical system, and after a joint meeting we launched this as a new project. Nothing at the time was known about the cellular physiology of the olfactory bulb. So I went off to Blackwell's to buy the two volumes of Cajal's *Histologie du Systeme Nerveux* and burned into my brain those black-etched images of the neurons in the olfactory bulb and throughout the brain.

The fact that this was a project on the olfactory bulb in a motor systems laboratory indicates the degree of freedom there was in research in those days. In fact, I still have a letter from Phillips before I arrived, emphasizing that in thinking about a project I must not feel restricted to what he was doing.

Phillips led the way in setting up the preparation for working on the olfactory bulb in the rabbit. He and Tom worked with me through the fall, during which we ascertained that stimulating the lateral olfactory tract with single shocks elicited antidromic action potentials in presumed mitral cells, that this was followed by long-lasting inhibition, and that the shocks elicited a succession of field potentials which could be used to identify the layer of mitral cell body recordings. He then turned the project over to me to pursue for a doctoral thesis.

It was just at the end of the era when one was expected to build one's own amplifier. Fortunately the Tektronix 502A oscilloscope was just arriving in England. To control vibrations, Phillips had the shop build a massive animal holder out of steel pipe (while wheeling it down the corridor it slipped

and made a small gash in the linoleum; the mechanic George Johnson quipped: "You've made your mark at Oxford." Fifty years later the mark is still there!). For micropipettes, we used the microforge built by the machinist Edgar Schuster. Pulling micropipettes on that pioneering setup required extremely steady nerves! Schuster also custom-built us a head-holder for the rabbit. The laboratory technical assistant was Charles Carr, a meticulous and amiable gentleman, who as a young man in the 1930s had been the last technician hired by Sherrington, a rather nice connection to my scientific lineage (Phillips a student of Eccles a student of Sherrington).

As I took over the project, and began to compare the physiological results with those images of Cajal, I realized in an "aha" moment that my project from then on would not be about the olfactory bulb, but about dendrites and axon collaterals. That has been my use of the olfactory bulb, as a model, ever since.

The first priority was to correlate the field potentials with the bulbar layers. As it happened, Tom Powell had just returned from collaborating with Vernon Mountcastle on their classic papers correlating the functional columns with the anatomy of the cortex. We therefore applied Tom's methods directly to the olfactory bulb, a correlation between layers and field potentials that has been useful in olfactory bulb studies ever since.

In brief, the study demonstrated self and lateral inhibition of mitral cells. We established this first for antidromic activation from the lateral olfactory tract, and then for orthodromic activation after I devised a new method for activating orthodromic volleys by delivering somewhat longer electrical shocks to the olfactory nerve bundles in the dorsal recess of the nasal cavity. At the time it wasn't known that fine (0.2 μm diameter) unmyelinated fibers were electrically excitable. Based on recordings from presumed granule cells, I inferred from those images of Cajal that the inhibition was mediated through the granule cell superficial process. I reported the first recordings at a Physiological Society meeting in January 1961, joining the many who have been through that ordeal by fire (with Hodgkin, Huxley, Katz, and others sitting in the audience, whose murmur of doubt about a result could crush any aspirations toward a career in science—or so it felt).

Three papers reporting these results were published in the *Journal of Physiology* in 1963, the year after I had left Oxford. I made explicit the inhibitory feedback circuit through the granule cell with a circuit diagram. The only precedent for such a diagram was by Eccles in the spinal cord (this was before the cerebellar studies of Eccles et al.), so I assume this must have been one of the first circuit wiring diagrams for a region in the vertebrate brain. The advantage of the diagram was that it provided testable hypotheses for the connectivity mediating the physiological properties. The connectivity for the granule-to-mitral inhibition seemed strong, though it required thinking of the dendrite as being "axon-like," as well as having a prolonged inhibitory action in the absence of action potentials, unlike a Renshaw cell.

The connectivity for the mitral-to-granule excitatory activation was postulated to occur through deep collaterals of the mitral cell axons.

Those were halcyon years in Phillips' laboratory. Not only did I have the freedom to pursue my own project, but I had freedom from a formal thesis program. This may seem antisocial, but I had had four intense years in medical school, and just wanted to get into a laboratory and do electrophysiological experiments. I recall on one occasion a visitor from the United States, Hermann Rahn, I believe, who was conversing with department members at afternoon tea, curious about comparing Ph.D. programs. What kind of course work do you have? None. What kind of seminar program do you have? None. What kind of prelims do you have? None. What kind of social support for the students do you have? None. He was stunned. I just sat there, quite content with my nonexistent program.

There were giants for inspiration. Francis Crick, Louis Leakey, and Peter Medawar gave talks; I visited Niko Tinbergen to ask about ethological studies involving smell; Gilbert Ryle spent an evening with us at the Osler Society; Eccles came by on one of his trips; there were tea time chats with Maurice Pirenne, the pioneer visual psychophysicist; my first seminar was to le Gros Clark and his department.

In the spring of 1962 I passed my "viva" (the Oxford oral exam), carried out as a conversation for a couple of hours with George Gordon of the department and J. A. B. Gray of UC London. Meanwhile, Grethe was succeeding in her examinations for her B.A. in English Literature.

National lnstitutes of Health

During the last year I looked for a job in the United States I had some correspondence with Donald Griffin, the well-known auditory physiologist, with the idea of learning more about sensory physiology of another system, but in the end he had no position. I had met Torsten Wiesel and thought that it would be great to work out the circuits underlying their simple and complex cells, but they were not taking students at the time (life was too exciting for them!). Through Tom Powell I contacted Mountcastle to pursue the circuits in the columns in the cortex, he wrote back that he wished he could take me, but he already had 10 in the laboratory and just couldn't handle any more. Things were looking a bit bleak.

In the spring I had run across theoretical papers by Wilfrid Rall on currents and potentials around dendrites. Since dendrites were now my field, and I had an underlying interest in applying theory to experiments, I wrote to him about the specific field potentials correlated with different layers and different physiological actions, asking whether he would he be interested in applying his methods to them to obtain a rigorous relation between the field potentials and the neuronal elements that had generated them.

Wil wrote back that he was interested. It then depended on finding a position quickly, which he was able to do when Wade Marshall and Karl Frank offered us a slot in the Laboratory of Neurophysiology at NIH. Until then Wil had worked mainly on the motoneuron, then the model neuron for intracellular studies, so again I was taking advantage of the expertise of a motor system laboratory to apply it to the olfactory bulb.

In late August Grethe and I sailed on the Nieuw Amsterdam for New York, and on to Bethesda. I then had to take and pass the exams for admittance to the Public Health Service, to serve my 2 years in the uniformed services, and to start the new job. It was a long month to be without a salary, but nothing ventured, nothing gained.

As with Phillips, I was Wil's first postdoctoral student. It was early in his career, at a time when he was attempting to establish the new field of computational neuroscience in the face of considerable opposition, not least by his former mentor, John Eccles. I learned at first hand how unduly harsh criticism can bring hardship to a young investigator and deny deserved recognition. Through it all Wil was a gentleman, and he has remained so, one of the finest people I have known.

I spent 2 years with Wil, leaving experimental work to undertake with him a computational reconstruction of the activation of mitral and granule cells. Our project was to see whether we could simulate the field potentials from the intracellular potentials more accurately than had been done previously in other systems, by taking advantage of the symmetry of the olfactory bulb layers and the correlation with the single-cell recordings and the simplified anatomy. Wil had figured out how to simulate the intracellular potentials using his new compartmental method, and how to simulate the extracellular potentials using a potential divider model. Fortunately my recordings were sufficient to provide the needed physiological data, as well as a very tight correlation with laminar depth due to the methods with Powell.

By August of 1964 we had the simulations of mitral cell followed by granule cell responses. While discussing one day how the granule cells might be activated, the "aha" moment occurred. We hit on the idea that it must be through the same mitral cell lateral dendrites that were then inhibited. Wil's protocol book contains our speculation that these "dendrodendritic synapses" provide a mechanism for "lateral inhibition" in the olfactory bulb. There was no evidence for this kind of interaction between dendrites at the time. However, I had come to know Tom Reese and Milton Brightman, who were about to undertake an electron microscopical study of the olfactory bulb, so I told them to be on the lookout for such synapses.

Shortly after I had left for a further fellowship in Stockholm, Reese and Brightman found synapses between mitral and granule cell dendrites oriented in opposite directions. Wil attended their seminar and immediately

told them how the synapses fit with our model. It was a case of the model predicting the fine structure and explaining the physiology, rather than the other way around as is the usual case with models. Over the next few months we put together a paper on this multidisciplinary study, probably the first to combine electrophysiology, electron microscopy, and compartmental modeling. We submitted it to *Science*, who promptly rejected it as "not of general interest." It was published in *Experimental Neurology* in January 1966 and opened up several new lines of investigation as described later in this chapter.

Karolinska

Meanwhile, at the Karolinska Institute in Stockholm, I had joined David Ottoson to learn about olfaction, in order to apply this knowledge to understanding how the bulbar circuits mediate smell perception. Ottoson was widely known for his discovery in 1956 of the electroolfactogram (EOG), the summed potential response of the olfactory epithelium to odor stimulation. He had then worked with Stephen Kuffler at Woods Hole, where he and Charles Edwards discovered the site of impulse initiation far out on the axon initial segment in the crayfish stretch receptor, one of the classical studies on the integrative organization of the neuron. He had returned to Stockholm intending to pursue studies of the receptor, but crayfish were not then obtainable, so he was forced to develop a new preparation of the isolated muscle spindle of the frog.

I worked with David, also as his first postdoctoral student, for the next 2 years on that preparation. Although it was a diversion from my main interest in brain mechanisms, it gave me an extensive background in sensory reception in general, as well as an introduction to the broad field of olfactory studies, summarized in a review (Ottoson and Shepherd, 1967).

We had a great time in Stockholm, living in the new Wenner-Gren Center and enjoying the ready access to the rich culture of that city. The proximity to Grethe's home in Denmark was also a big plus. At the end of our stay, in the summer of 1966, I worked with Grethe's 85-year-old father, a master carpenter, and her brother, an engineering student, to build a summer house near her home in Humlum where the family could stay when we visited. It is on a site called Toftum Bjerge (Toftum Mountain), one of the highest peaks in Denmark—50 meters above sea level! Toftum has been a summer home for us ever since.

At that point I could look back on 7 years of postdoctoral training after graduating from medical school. It was a rich experience, with training in a series of different but interrelated experimental and theoretical approaches to neural organization and mechanisms. I often tell my students to take advantage of these opportunities in your early training; it is the time when you build up the capital that you will invest throughout your career.

Yale

During my time at NIH I had visited with my good friend from Oxford, John Nicholls, at Woods Hole where he was working with Stephen Kuffler. I discussed with Kuffler my interest in finding a job on returning to the United States and my aspiration to create a multidisciplinary unit emulating his neurobiology department at Harvard. He put me in touch with both his close colleague and friend, Cuy Hunt, who was the new chair of physiology at Yale, and John Gergely at the Retina Foundation in Boston. The Retina Foundation seemed like a better prospect for setting up my multidisciplinary unit, so with the enthusiasm and naiveté of youth I arranged to return to the United States to a position there in September 1966. Unfortunately, it turned out not to provide the expected opportunities. Through Pat Wall I moved to MIT for the remainder of the year and was fortunate to be reinvited by Cuy to Yale. We moved there in July 1967.

My time with Ottoson, though rewarding in many ways, was for starting my career a mixed blessing, because he had become the target of heavy criticism by Lloyd Beidler and his students in the United States, who questioned whether the EOG was an artifact. This had little justification scientifically and had severely set back Ottoson's career in Sweden. Again I saw the unfortunate effects of overly harsh criticism. It meant that when I returned to the United States I was out of favor with the field of olfaction.

To start with, this didn't matter to me very much, because I considered my field to be cortical organization. My first RO1 grant, awarded in September 1966 while at the Retina Foundation, was entitled "Basic Mechanisms of Cortical Integration"; my site visitors were Carlos Eyzaguirre and Larry Kruger. That grant has served as the foundation for the laboratory, providing 43 years of continuous funding and counting. I also received a Research Career Development Award (RCDA)—site visitor David Lloyd, a former colleague of Cuy Hunt. I came with no startup package, which as far as I knew didn't exist; I was just happy to land at Yale on my feet. With a $30,000 grant from NINDS and $14,000 salary I had enough to start a laboratory.

It was in an atmosphere of challenging new ideas that I set up the new laboratory in the Physiology Department at the medical school at 333 Cedar Street at Yale in 1967. It was an exciting time there, because the school was going through a transformation in the 1960s from the old school to the new. Five of the six departments were seeking chairs, so it had the feeling of a new school inventing itself. The department was an exciting mix of outstanding young people: among the neurophysiologists were membrane physiologists (Knox Chandler had trained with Hodgkin; Larry Cohen had coinvented voltage-sensitive dyes) and cell physiologists (Bob Martin had trained with Katz, John Nicholls with Kuffler; Charles Michael did Hubel-Wiesel studies).

Starting out was greatly facilitated when in the first few months Lew Haberly came to the laboratory as my first graduate student. His impeccable skills and thoughtful analysis set the bar for everyone that followed, which continued in earnest after I returned from a year at Penn, first with Tom Getchell, then John Kauer and Bill Stewart.

This started a tradition in the laboratory of matching the talents of every new person to a new direction in our research. I'll attempt to organize the discoveries that ensued over the years, thanks to over 60 outstanding students and visitors.

Dendrodendritic Synapses

During 1967 I made several trips to NIH to finish the study with Wil, which was published at the end of 1968 in the *Journal of Neurophysiology*. Surprisingly, the paper was immediately of broad interest for several reasons.

First, our study was among the first wave of reports of the circuit organization of different parts of the brain. Dowling and Boycott, followed by Werblin and Dowling, provided parallel evidence for the circuit organization of the retina, also involving reciprocal dendrodendritic-like synapses. Soon dendrodendritic synapses were reported in the different nuclei of the thalamus by Ralston (1969), Famiglietti and Peters (1971), and Morest (1971). Eccles and his associates published their studies of cerebellar circuits (Eccles et al., 1966). It was interesting to be contributing to the new ideas brought forth by these and other laboratories. An opportunity to attempt a synthesis came with a year's sabbatical as the visiting scientist of the Neurology Institute at Penn in 1971–1972, at the new Monell Institute and with my friend Sol Erulkar; out of it came a course and then a book on *The Synaptic Organization of the Brain*.

A second reason for wider interest was that we had solved the puzzle of the granule cell—how could a cell in the central nervous system be a neuron if it lacked an axon? The cell received synaptic input onto its dendritic spines, like other spiny neurons, and sent its synaptic output from the same spines. It therefore had a synaptic output like all other neurons. Similar evidence was obtained in the retina for the reciprocal synapses between bipolar and amacrine cells.

A related reason was that the dendrodendritic mechanism posited a specific role for the granule cell spine: feedback and lateral inhibition. This was I believe the first specific function for a dendritic spine; 40 years later it is still one of the clearest roles for a spine.

The mechanism posited a specific role for an action potential spreading into the lateral dendrite: activation of the dendrodendritic synapses to bring about feedback and lateral inhibition. More recently similar backpropagating action potentials have been assumed to play important roles in the dendrites, though their functions are still being elucidated.

The dendrodendritic synapses also required revision of the functional concepts of the neuron doctrine. Revisions had been started by a seminal paper by Ted Bullock in 1959, summarizing the multiple ways that neurons were being shown to interact. Since Cajal the concept of the neuron doctrine had included the idea that neurons receive their input in their soma and dendrites and send their outputs through their axon. The dendrodendritic synapses showed that this no longer held: dendrites could be sites of output as well as input. Furthermore, these input-output operations could occur locally, as semi-independent integrative units, without involving the entire cell. This resulted in a paper in 1972 on "The Neuron Doctrine: A Revision of Functional Concepts," the first of a series of papers and a book on the conceptual foundations of modern neuroscience.

Finally there was the fact that our study involved the earliest use of Wil's compartmental approach to build computational models of neurons. Wil deserved all the credit for this great contribution to neuroscience. My role in our collaboration was to help fine-tune the models and match them precisely to my experimental studies of the anatomy and physiology of the olfactory bulb. The principles of dendritic electrotonus and active properties involved have guided my work ever since. We often discussed how we envisaged the time when it would be possible for physiologists to carry out computational analysis in the laboratory of the cells they were working on, in parallel with experimental analysis, so that each approach could test the hypotheses developed by the other. It took a generation for that to begin to happen. One feels fortunate to see that prediction realized and to have contributed to it.

Glomerular Dendrodendritic Interactions

One of my first studies in the new lab was to obtain physiological evidence for dendrodendritic synapses in the olfactory glomerulus, which seemed pretty impenetrable—a literal "Gordian knot." However, a strategy of using very weak peri-threshold paired volleys in the olfactory nerves produced evidence for inhibitory actions between mitral and PG cells that appeared to be mediated between glomerular dendrites. When detailed EM studies of the synaptic connections in the glomerulus were carried out by Price and Pinching, I was able to reconstruct their findings, even from their 1970 abstract, and fit them precisely into a circuit consistent with the physiology. That provided a "basic circuit" diagram of the olfactory glomerulus to go with the mitral-granule interactions and the initial overall circuit diagram from my Oxford days. This was published in a review on the synaptic organization of the olfactory bulb commissioned by Eccles in *Physiological Reviews* in 1972. These diagrams have been used by others and greatly modified and extended by work in the field ever since. When Tom Getchell joined the lab, we produced two *Journal of Physiology* papers with this approach

in 1975. Physiological analysis of the glomerulus then lay fallow in the field for a quarter of a century.

Olfactory Cortex Basic Circuit

Lew Haberly came to the lab with recordings of spike responses in rat olfactory cortex to odor stimuli, so it was natural to launch a study of the circuit organization of the cortex. We thought the dog would be an optimal preparation for this study, but a dog undergoing anesthesia was too hard on our sensibilities. We opted instead for the opossum, with its large nose, olfactory bulb, and olfactory cortex—one of many new preparations introduced over the years. As a tune-up we recorded local evoked field potentials in the olfactory bulb to focal stimulation of the lateral olfactory tract, showing that there is a topographical relation between the tract and the bulb. This study also showed how Wil's field potential model facilitated the interpretation of local field potentials. This model still awaits more general use, as local field potentials are increasingly employed in analyzing neural systems.

Lew then turned for his doctoral thesis to an in-depth analysis of the functional organization of the olfactory cortex, using intracellular, extracellular, and field potential responses evoked by LOT shocks. His correlation of the field potentials with the cortical layers is still used today. He was midway through documenting the lateral inhibition implied by Walter Freeman's earlier linear systems analysis when Maria Biedenbach, working with Chuck Stevens in Washington, reported recordings implicating inhibitory interneurons activated by pyramidal cell axon collaterals. Undaunted, Lew carried out an early current source density analysis of the field potentials. He was one of the first to include a conductance shift between layers in CSD (current source density) analysis, which revealed a hitherto unrecognized excitatory collateral feedback system. Almost concurrently, Joe Price's anatomical studies revealed the axon collaterals for this system, which came to be called the "long association fibers." When added to the LOT input and the inhibitory interactions, it completed a new basic circuit for the olfactory cortex. This study was published in three papers in the *Journal of Neurophysiology* (Haberly, 1973a, 1973b; Haberly and Shepherd, 1973).

This basic cortical circuit was central to the account of cortical organization soon published in the first and succeeding editions of the synaptic organization book. Lew then used the circuit, particularly the long association fibers, to introduce the concept of the cortex functioning as a "content addressable memory" for processing complex odor stimuli, in analogy with the face area of the visual neocortex (Haberly, 1985). A similar basic circuit was then invoked by Connors and Kriegstein (1985) in their study of the organization of turtle dorsal cortex. Several papers have pointed out the key features of this circuit, which may have been a fundamental plan for the emergence of neocortex, a concept still being developed.

Dendrodendritic Interactions and Lateral Inhibition

Despite the attractions of the cortex, a high priority for the lab was obviously testing the mitral-granule cell dendrodendritic model. I tried to get further evidence with Sol Erulkar during my stay at Penn in 1972, but the in vivo preparation was too unstable. It was frustrating, because we were not keeping up with the work on circuit organization of the retina, cerebellum, and other regions. The introduction of in vitro slices of hippocampus in the early 1970s showed the way we had to go. The opportunity came when Martha Nowycky and Kensaku Mori joined the laboratory in the late 1970s. In thinking about an in vitro preparation, I had been impressed by hearing from my friend Denis Baylor that in his study of the turtle retina he could work on one retina one day and take the other retina out of the refrigerator and work on it the next day. There must be something about the turtle that made for a good in vitro preparation!

Martha was initially interested in the dopamine projection from the brainstem, so we removed the entire turtle brain and made a hemi-brain and brainstem preparation for in vitro study, which enabled one to stimulate the brainstem as well as the olfactory tract and olfactory nerves and record from the olfactory bulb. At about the same time Rodolfo and his colleagues were reporting a perfused preparation of the brainstem. I was very concerned about the viability of our unperfused preparation, but Kensaku carried out an initial intracellular study showing long-lasting inhibitory postsynaptic potentials (IPSPs) in mitral cells following lateral olfactory tract (LOT) stimulation, just what I had found in the rabbit 20 years earlier. He and Martha then did a thorough study showing the calcium component of the action potential, successive short-term IPSPs, and a very long-lasting IPSP in the mitral cell, reported in three papers in the *Journal of Physiology* in 1981. Two more papers in the *Journal of Neurophysiology* used pharmacological manipulations to characterize long-lasting synaptic excitation, including autoexcitation, in the distal tuft of the mitral cell. After Kensaku returned to Japan we published two more papers from his studies, on fast prepotentials and on excitatory and inhibitory interactions in the distal dendrites, so the turtle was a productive innovation, thanks largely to Kensaku's consummate intracellular recording skills.

Martha's first abstract on the isolated turtle brain preparation at the SFN meeting in 1978 prompted Roger Nicoll and Craig Jahr in San Francisco to exploit the turtle olfactory bulb too. An interesting sidelight is that they were able to demonstrate feedback inhibition after current injection into a recorded mitral cell, which we could never get. A few years later, after NMDA receptors had been characterized, we all realized, chatting together one day, that this was due to the fact that they had used a Mg2+ free Ringer solution, whereas we had used the standard Ringer containing Mg2+. According to Roger and Craig, when they started they checked for what

Ringer fluid to use from an old publication of Katz's on muscle, where he happened to be working in Mg2+ free Ringer! Such is the life of the laboratory.

Topographical Relations between Epithelium and Bulb

For carrying forward the study of the intrinsic circuits of the olfactory bulb, we realized we needed to know how the input related to them. In the 1950s le Gros Clark used degeneration in the nose after local ablations of the olfactory bulb to reveal a rough topographical organization from epithelium to bulb. Adrian had then showed that multispike recordings from the anterior and posterior part of the bulb showed differential responses to different odors, suggesting a spatial representation of odor molecules.

One of the most used tools for demonstrating axonal projections of that time was the Nauta degenerating method. A colleague, Bob Eager, pointed out that it had never been proved that one could stain fine unmyelinated C fibers, such as in the olfactory nerve. A biology graduate student, Lanay Jordan Land, undertook the project, and with focal ablations of the olfactory nerve bundles in different parts of the nasal cavity was able to show degenerating terminals restricted to subsets of olfactory glomeruli. We developed a flat map method for representing the localization of these projections in the glomerular layer. This became the prototype for flat maps used later by ourselves, and now generally adopted in the field, for representing functional activity in the olfactory glomerular layer.

The topographical organization of the projection was further documented by the use of radioactively labeled amino acid pledgets placed in different locations in the olfactory cavity. In the retina this approach had produced dramatic images of tightly organized projections from retina to lateral geniculate nucleus. The organization in the bulb was less dramatic, due to the fact that it was related to the molecular identity of the receptor cells rather than the location in the nasal cavity. These and other anatomical mapping experiments became obsolete with the discovery of the olfactory receptors by Buck and Axel in 1991, and their use in precisely mapping the projection by Buck and Axel, Peter Mombaerts, and others. Nonetheless, the mapping of the olfactory projection, by both anatomical and functional methods, gave ample evidence of some kind of underlying organization, so that the new results were received by prepared minds.

Functional Mapping of Odor Responses with 2DG

As I was finishing my doctoral studies at Oxford in 1962 I paid a visit to Adrian to discuss how my results might relate to his ideas about the representation of odors by spatial patterns of mitral cell activity in the olfactory bulb. What was the mechanism underlying the spatial patterns? I don't

remember the details of our conversation, but I do remember his final advice: "Look to the glomeruli."

During the late 1960s and early 1970s, David Moulton and others tried various approaches to this problem in mammals. John Kauer, during his doctoral studies with Moulton, introduced the salamander olfactory bulb for this purpose. But the electrophysiological approach was difficult without knowledge of the spatial organization of the input as one had in the visual system that was exploited so brilliantly during this time by Hubel and Wiesel. What chance did we have!?

The solution came from a chance encounter with Ed Evarts, another pioneer of motor cortex. On a visit to Yale he was chatting with John and myself in the corridor, and said, by the way, there is a new activity marker called 2-deoxyglucose (2DG) that Frank Sharp in his laboratory was working on in collaboration with the founder of the method, Lou Sokoloff. It wasn't certain how useful it would be because it mainly labeled active synapses, not cell bodies. John and I looked at each other in another "aha" moment: this was exactly the tool we needed to label activity elicited by odor stimulation in the synaptic-rich olfactory glomeruli, at a distance from the mitral cell bodies.

In December I visited Frank at NIH and we carried out the first experiments on waking rats injected with 2DG and exposed for 45 minutes to different odors, including the most natural odors we could put our hands on at the time, cheese from the local supermarket. Frank did the histology and autoradiographs, and after the holiday he called excitedly that it had worked! There were dots and spots of activity over the olfactory bulb in the films. John joined us for further experiments at NIH, and we soon had the first publication of the application of functional localization in the olfactory bulb. This was true localization, virtually to the level of single glomeruli or groups of glomeruli, a significant step from the multispike unlocalized gradients reported by Adrian. We had "looked to the glomeruli" and found the mechanism! Once again, a motor laboratory had contributed to the olfactory bulb model for basic mechanisms of cortical integration; Frank's efforts were monumental, and Ed's support crucial.

Nowadays we would have insisted on publication in a high-profile journal, but we couldn't preempt the first paper on the Sokoloff method that hadn't yet been submitted to *Science*. So we submitted ours to *Brain Research*, and it came out in the same year (Sharp et al., 1975). The impact was muted, for several reasons. There were few laboratories interested in the olfactory bulb; the 2DG isotope was expensive; few in the brain imaging field were interested in olfactory imaging. Nonetheless, we had the excitement of opening the new field of functional imaging of the olfactory bulb, as well as contributing to the new field of functional brain imaging using positron emission tomography (PET). Again, the use of the olfactory bulb as a model system had produced results of general interest.

Follow-up studies established the basic properties of the patterns. The most intense activity was localized to the glomerular layer (Sharp et al., 1977). The patterns in the glomerular layer were displayed using the flat-map representation of the glomerular layer introduced in our previous topographical study. The patterns with different odors were overlapping but distinct. The patterns increased in extent with increasing odor concentration (Stewart et al., 1979). From these properties it could be suggested that the patterns could contribute to the encoding of odor identity as well as odor concentration. These basic properties have been confirmed by many subsequent laboratories, using many different methods in many different species.

The 2DG method also led to the discovery of a new subsystem in the olfactory pathway. This started with a suggestion by a medical student, Marty Teicher, who had worked on the suckling pheromone in rat pups for his Ph.D. at Princeton with Elliott Blass, to see what the 2DG method would show in the suckling pups. Bill Stewart led this project, which showed an intense 2DG spot of activity in the posterior olfactory bulb. We first suspected this might be in the accessory olfactory bulb, but correlation of the 2DG activity with the anatomy revealed that the focus was over a group of glomeruli that we called a "modified glomerular complex" in the medial posterior aspect of the main olfactory bulb, tucked up against the side of the accessory olfactory bulb. We set this unexpected finding aside for several months, not knowing whether to believe it or not, and finally invited a reigning expert on olfactory anatomy, Jim Hinds, to come to give advice on whether it was real. We decided it was (Teicher et al., 1979). The MGC has subsequently been shown to be a part of the "necklace glomeruli" surrounding the AOB, with its own special properties within the main olfactory pathway.

This finding occurred at about the same time as the discovery of the "macroglomerular complex" in the antennal lobe of insects, correlated with pheromone activation. Up to that time there was little recognition of similarities between vertebrate and insect olfactory pathways, despite an early suggestion that they were analogous. Our contemporary studies laid out the case for considering the modules in the insect as true glomeruli, which was rapidly adopted by the field, and is a central concept today in analyzing the underlying principles of glomerular organization. This led to many interesting interactions between our lab and many labs involved in insect olfaction, including John Hildebrand in Arizona, Jurgen Boeckh in Regensburg, and Barry Ache in Florida. The fundamental cross-phyla role of the glomeruli in olfactory processing was summarized by Hildebrand and Shepherd (1997).

With the 2DG method there was much to do for the lab, in addition to the ongoing electrophysiological studies of the dendrodendritic synapses noted earlier. For a decade or more there were only two other labs doing functional imaging, both with 2DG: Michael Leon and Andre Holley. This was characteristic of the early days of olfactory research; only one or a few

labs doing a particular approach, which left the field open, but impoverished of colleagues, concepts, and competition.

Fortunately we had outstanding students to do the work. In addition to Bill Stewart and John Kauer, Charles Greer came in the late 1970s, and soon after Doron Lancet and Patty Pedersen. Charlie first focused on the physiological basis of the activity labeling, recording the 2DG labeling in the olfactory bulb in response to volleys in the olfactory nerve bundles. In both turtles (Greer and Shepherd, 1982) and rats (Greer et al., 1983), this showed that only a few hundred volleys could give intense labeling. He then carried out a developmental study in rat pups, showing the emergence of odor-specific patterns in the second postnatal weeks (Greer et al., 1982). Patty Pedersen focused on the suckling-induced patterns and found evidence for 2DG activity there in utero (Pedersen et al., 1983).

With Pavel Jastreboff, a recent émigré from Poland, a major effort was made to identify the receptor cells projecting to the MGC, using retrograde labeling of HRP after injections into the MGC area. The labeled cells were in restricted areas of the main olfactory epithelium (Jastreboff et al., 1984) and showed evidence of radial and laminar clones within the epithelium, a finding that still deserves follow-up. A more complete study of the topographical relations between bulb and epithelium followed (Pedersen et al., 1986), consistent with a similar study by Astic and Saucier.

With Doron we made a major effort toward improving the resolution of the 2DG method. The use of tritiated 2DG gave the first clear localization of odor-induced activity to individual glomeruli (Lancet et al., 2000, 2002). A subsequent study used rapid freezing combined with electron microscopy, carried out with Dennis Landis at the MGH in Boston, gave the first evidence of 2DG localization at the cellular level (Benson et al., 1985). We then turned our attention to new projects, returning to odor mapping with new methods later in the 1990s (see later discussion).

Finally, of course, all this work predated the discovery of the olfactory receptor molecules. The lab also helped to take the first steps in that direction, after weathering some transitional challenges.

Transition Years

By the mid 1970s, into my 40s, the lab was thus alive with new projects and new people working on odor maps and cell electrophysiology. One might assume that all was running smoothly, but in fact it was a period of uncertainty for myself and indeed for the future of funding for this kind of research.

Funding through the physiology study section at NIH was extremely tight. We were now focusing on problems in the sense of smell, and there was not much interest in the neurology institute in this tiny subject. The future

of research in olfaction was in fact so dire that an NSF/NIH committee was formed in the late 1970s to consider how to ensure its survival. Out of this came the recommendation to set up a new society, called the Association for Chemoreception Sciences (surely the most sibilants you could pack into a society's name), shortened to AChemS. The first meeting was held in 1978, with Max Mozell as the chair. Linda Bartoshuk was the second, I was the third, and Bruce Halpern was the fourth. Our goal was to be as successful as ARVO, whose annual meeting in Florida had helped to boost the field of vision research.

The early membership of AChemS was predominantly psychophysicists in taste and smell, all from colleges, universities, or institutes; to begin with I was the only investigator from a medical school. It was symptomatic of how taste and smell were not yet in the mainstream of modern cellular and molecular science, with the resources possible in a medical school setting. Fortunately, within a few years we began to attract other anatomists and physiologists, so that by the time Linda Buck and Richard Axel discovered the olfactory receptors in 1991 the society was ready to receive a big influx of molecular biologists and patch electrophysiologists, many from medical schools, and to assume a central role in the rise of modern studies in taste and smell.

During this time the new "National Institute for Deafness . . . " was set up. Taste and smell, along with somatosensation, were transferred to the new institute under the humbling added words " . . . and Other Communicative Disorders." It was rather demoralizing to become an anonymous "other," but there was no other home. My main grant barely made it through renewal, for only 3 years, in 1977, and I was lucky to get funded through Terry Dolan at NSF for 3 years to support the new 2DG work. So it was a relief when the R01 grant was renewed for the first time for the full 5 years in 1980, and we could look forward to a little stability and long-term planning. A Javits Award in 1985 was welcome recognition for that highly productive period of the lab.

In addition to funding problems, the place of integrative neuroscience in physiology at Yale, focused as it was on nonneural membrane physiology, was also uncertain. This was resolved with the recruitment of Pasko Rakic in 1978 to head a new Section of Neuroanatomy, together with Pat Goldman-Rakic. My position was shifted to the new section to help give it a critical mass. In 1980 we moved the lab to new quarters on the clinical side of Cedar Street, nearer the labs of the Section of Neurosurgery under Bill Collins, a staunch supporter of our 2DG work. In return we provided leadership for the Neurosurgical Research Laboratories, through Bill Stewart, John Kauer, and ultimately Charles Greer. Charlie has been a rock of support for both neurosurgery and ourselves, as well as becoming the director of the Interdepartmental Neuroscience Program for graduate studies at Yale. Life

with Pasko and Pat and the new faculty was immediately rewarding, and it has been ever since. I couldn't have asked for a more supportive chair than Pasko, and a more loyal and inspiring colleague than Pat.

A dash of uncertainty was added in 1978 when I was invited to take the chair of Neurophysiology in Copenhagen, Denmark. Being married to a Dane, with a summer house in Denmark, didn't make this seem impossible as a career and life move. However, the visit revealed that the building housing the Institute of Neurophysiology was being abandoned, and the neurophysiology department in it absorbed into the new Panum Institute along with all the other medical science departments. Moreover, it was a strongly anti-authoritarian period in Danish life, when the chairmanship of a department was supposed to rotate among all the staff, including secretaries and other staff! Although we had to turn down the invitation, we have remained close to Jørn Hounsgaard, Henrik Jahnsen, Jens Midtgaard, and others through annual visits during our summers in Denmark.

Also attractive was an invitation in 1982 to take a chair at Oxford. I felt a strong pull to return to the place where we had had such a good student life together, but reality quickly set in when we learned of a salary far below the modest salary I was making at Yale. My Yale dean, Bob Berliner, quipped that he "didn't know whether he could lower Gordon's salary enough to meet the Oxford offer!" So that too had to be declined. However, we have had continuing rewarding contacts with Oxford, through our daughter Kirsten's and her future husband Alastair's D.Phils. in the mid-1990s, a mini-sabbatical with Julian Jack during that time, Kirsten becoming a don at St. Catherine's, and a recent sabbatical with Kia Nobre in the fall of 2009 as an Astor Visiting Lecturer.

Dendritic Spines

The dendritic spines of olfactory granule cells were central to the dendrodendritic model for lateral inhibition and stimulated new research by Wil and myself. Wil, with colleague John Rinzel, drew attention to the ability of the spine neck to control the electrical coupling between the synapse on the spine head and the dendritic trunk as a possible basis for activity-dependent change that could underlie learning and memory. I pointed out that it could control metabolic coupling as well. These suggestions, from theoretical studies, helped to stimulate a new field searching for the cellular changes that might underlie long-term potentiation (LTP).

Our dendrodendritic model was based on separate models for the mitral and granule cell. To complete the model, I carried out a computational study with friend Bob Brayton, then at the IBM Watson Research Center, in which we connected the two cells and reproduced the feedback and lateral inhibition (Shepherd and Brayton, 1979). It was possibly the first synaptic circuit simulated computationally.

At about the same time *Scientific American* invited me to contribute an article on our work. I had been following the news of the development of the first integrated computer chips and took the opportunity to title the article "Microcircuits in the Nervous System," applying the term to the specific synaptic circuits that had been identified in the olfactory bulb, retina, and several other brain regions. Eric Kandel, Jack Byrne and colleagues used the term at about the same time to refer to the reflex circuit under study in *Aplysia*. The term stuck, and is now in common usage to refer to circuits at many levels of organization in the brain.

A new chapter in spine studies opened with the postulate that spines may have active properties. Wil led the way with collaborators John Miller and Idan Segev, showing how active properties in a spine boosted the response in the dendrites (Miller et al., 1985; Segev and Rall, 1987). Concurrently, Brayton and I showed how the active properties could confer logic gates on synaptic interactions in distal dendrites of pyramidal cells (Shepherd et al., 1985; Shepherd and Brayton, 1987). Subsequently we showed computationally with Ted Carnevale that logic gates were also formed with active properties confined only to the dendritic shaft (Woolf et al., 1989). This work helped stimulate a study by Softky (1994) on exquisite coincidence detection by active spines, and more recently the two-layer network of Poirazi et al. (2003).

The early work on spines was summarized in an invited review (Shepherd, 1996), well before any direct experimental evidence was available. It has been pointed out that these early computational studies from the 1970s to 1990s helped lay the basis for understanding spine functions, a conceptual foundation leading to the dramatic results obtained since the late 1990s by direct microscopic observations linked to new genetic and optical recording approaches.

During this time we didn't forget granule cell spines. These continued to be, and perhaps still are, the only spines with a specific input-output function: mediation of feedback and lateral inhibition of the mitral cells, as proposed in our model and supported by the experimental evidence. A key question was how the local function of a spine related to the global function of the dendritic tree. To answer this, Tom Woolf carried out a thesis study beginning with the fine structure of the granule cell and its spines with Charlie Greer (Woolf et al., 1990). He generated Golgi-stained granule cells which he simulated computationally, and analyzed how excitatory postsynaptic potentials (EPSPs) in individual spines would summate within the dendritic tree to communicate with each other and generate action potentials in the cell body (Woolf et al., 1991). Finally, he analyzed the movement of Ca^{++} in and out of a spine (Woolf and Greer, 1992). The study has provided a basis for subsequent experimental analysis of these questions. My review (Shepherd, 1996) listed some 30 possible functions of spines, few as well documented as those of the granule cell.

Olfactory Transduction

By the 1980s we had an idea of how the olfactory receptor cell responses were represented in the activity patterns of the olfactory glomeruli. The next step was to understand the nature of the transduction mechanism in the receptor cells themselves.

As explained earlier, the olfactory bulb for us began as a model for cortical integration, and for the first decade of work in the 1960s I kept that as a focus. However, it was obvious that it was going to be necessary to understand the natural stimulus—odors—for this system. I had hoped to begin this study with Ottoson, but his experimental work was devoted exclusively to the muscle spindle. I then got in touch with David Moulton, the reigning expert on olfactory bulb physiology, who had just joined the new Monell Center for Chemical Senses in Philadelphia, and arranged to spend part of my sabbatical year 1971–1972 at Penn with him. It was another thing I tell my students: always be willing to travel to acquire new methods and expertise.

As the Monell Center was getting off the ground, it was exciting to interact with Morley Kare, and with Tom and Marilyn Getchell just arrived from Northwestern, and John Kauer and Michael Meredith as graduate students with Moulton. Tom had just carried out studies of olfactory receptor cell responses with Bob Gesteland, using the new carbon-coated electrode for this purpose, and Marilyn had carried out the first studies of the nature of the olfactory receptors using protein-blocking agents.

The most important result of my visit was that Tom elected to withdraw from his faculty position at Penn and join the lab as a postdoctoral fellow for further electrophysiological training. Together we carried out the study of the glomerular responses mentioned earlier. John soon joined the lab too. We further developed his system of quantitatively controlled odor stimulation through a solenoid-triggered three-concentric nozzle device, which allowed step pulses of odor to be delivered and cleared from the head space over the exposed epithelium. The result was one of the first classifications of olfactory bulb odor responses, into excitatory, excitatory-inhibitory, and inhibitory responses (Kauer and Shepherd, 1976).

Tom then used this step-pulse nozzle system to analyze responses of salamander olfactory receptor cells (Getchell and Shepherd, 1978a, 1978b). This showed that there is a response latency of several hundred milliseconds, and that virtually all the responses were excitatory. The mainly excitatory responses were an important step away from the bewildering variety and complexity of receptor cell odor responses that had been reported up to then. This was confirmed by subsequent intracellular and patch recordings in vertebrate receptor cells. The long latency was eventually explained by the second messenger cascade activated by the G-protein coupled receptors.

The next step was to develop an isolated epithelial preparation, which was undertaken with John and new recruits Leona Masukawa and Britta Hedlund. This resulted in several papers, showing the high input resistance of receptor cells, which would make them extremely sensitive to low levels of odor concentration, and the low input resistance of supporting cells due to high K conductance and gap junctions between them (Masukawa et al., 1985). A study of patch recordings of the receptor cells to odor stimuli was begun by an undergraduate, Jessica Hopfield, which produced some of the first patch recordings in the receptor cells. On this basis, I suggested to Jeff Gold, a retinal physiologist at Yale, that we should collaborate on carrying forward this project.

My interest in the nature of the olfactory receptors had been piqued by many stimulating conversations with Doron Lancet. He had come from a background of molecular immunology, with the long-term goal of attacking this problem. Before he left the lab in 1981 I made him compose a list of comparisons between the immunoglobulins and the predicted olfactory receptors. That list hangs in the lab today, with the key prediction that the receptors would be numerous in number. After setting up his own lab in Israel, Doron took the first step into the modern era of olfactory receptors by showing that a cell-free preparation of the cilia was stimulated by odors to produce cAMP, suggesting a G-protein coupled receptor activating a cAMP second messenger cascade (Pace et al., 1985).

Nature asked me to write a commentary, where I thought it would be useful to compare this proposed cascade with the cyclic G cascade that had just been shown in photoreceptors by Fesenko. In consultation with Jeff, I suggested that the olfactory receptors could lead to activation of the sensory channel either by adenylate cyclase or by cyclic AMP itself. To my knowledge, it was the first explicit suggestion of this mechanism. Jeff then carried out the study with his student Nakamura confirming this prediction that cyclic AMP directly activates a cyclic nucleotide gated channel (Nakamura and Gold, 1987); they kindly acknowledged I had stimulated them to do the study.

The race was then on to identify the receptor. The route lay through the intermediates of the cascade, identified in outstanding studies in several laboratories, those of Doron, Randy Reed, and Benjamin Kaupp. This was biochemical work outside our own expertise. However, we continued to be interested in the physiological approach, which received a big push when Stuart Firestein came to the lab. Stuart had trained in a retinal lab with one of the pioneers of retina functional organization, Frank Werblin, and had just obtained the first odor responses, recorded with patch pipettes in salamander receptor cells. He joined the lab in the late 1980s. The first study with Stuart showed the time course of the receptor current in response to odor applied directly to the cilia; this was the first demonstration that the cilia are the site of odor transduction. Stuart was on the lookout for others

to join in the fun, and soon Frank Zufall from Hans Hatt's lab in Munich and then Terese Leinders-Zufall arrived to launch a new era of work on odor transduction. We had just begun with the first characterization of the pharmacological properties of the second messenger pathway (Darrow et al., 1990) and the membrane properties of the cyclic nucleotide gated channels (Firestein et al., 1991) when, in 1991, Buck and Axel reported the finding of a large family of G-protein coupled receptors (GPRCs) that appeared to be the long-sought olfactory receptors. We immediately began interacting with Richard, who visited the lab in February, and with Linda, who made her first trip to AChemS in April.

Although there was much excitement over the discovery, there was initially no functional evidence that these receptors were odor sensitive. Furthermore, they showed up in other tissues, especially testes. However, the receptors were received positively by the olfactory community largely because they fit with several expectations. First, they were a large family, as predicted by Doron. They belonged to the GPCR family, as predicted by the studies of the components of the cascade. They provided a binding pocket similar to that of other GPCRs, as indicated by studies by Catherine Strader. I had discussed these possibilities in my Wright lectures in Vancouver in 1987, and subsequently in a conference on the olfactory bulb as a model system in 1990, published in 1991. Later that year Stuart and I attended a conference in Paris on olfactory transduction, in which we together with Doron introduced the idea that a single cell could express a single receptor with a broad response spectrum. Stuart and I also suggested that a new pharmacology of the receptors could arise with characterization of odor agonists and antagonists. The first idea has become one of the cornerstones of the molecular biology of olfaction (all the credit to the brilliant experiments of Axel and Buck and others); the second is being pursued by Stuart and several laboratories for its possible contribution to complex processing at the transduction level.

Expression of the receptors in heterologous cell systems immediately was pursued by several laboratories, but with no success. This turned out to be an exasperatingly difficult problem, due apparently to the receptors hanging up in the endoplasmic reticulum on their way to the membrane. To obtain evidence regarding the functional nature of the receptors, we carried out a study based on a report many years previously by Frank Margolis and subsequently documented by us (Hedlund and Shepherd, 1985) that a cholinergic blocker could bind selectively to the olfactory epithelium. We found that the receptor potentials were blocked by cholinergic antagonists, but not by other neurotransmitter receptor blockers (Firestein and Shepherd, 1992). This appeared to be the first physiological evidence for the GPCR nature of the olfactory receptors.

Stuart and Frank, soon joined by Trese, produced a series of fundamental studies of the odor transduction mechanism. This included inhibition of

the CNG channels by intracellular calcium (Zufall et al., 1991), voltage-dependence of the odor response (Firestein and Shepherd, 1995), and modulation of the CNG channels by carbon monoxide (Leinders-Zufall et al., 1995) and by cyclic GMP (Leinders-Zufall et al., 1996). Charlie Greer, established with his own laboratory as head of research in neurosurgery, joined us to identify odor-induced calcium transients in single olfactory cilia (Leinders-Zufall et al., 1997, 1998). Trese's key role in these experiments is obvious.

By then these guys were moving on to new faculty positions. Before leaving, an outstanding graduate student, Haixing Zhao, joined Stuart; with John Carlson they set out to obtain physiological evidence that the olfactory receptors were really odor receptors. The project moved with Stuart when he took up his new position at Columbia, where they used transfection with adenovirus to show that the I7 receptor was sensitive to octanal and related aldehydes (Zhao et al., 1998). This landmark study opened up the new field of olfactory receptor physiology. John has gone on to become a leader in insect olfaction.

Minghong Ma, who trained with John Koester at Columbia, joined the lab in the late 1990s to carry on the physiological study of the receptors. Most studies to that date, including our own, had been done on freshly dissociated cells. To develop a more physiological prep, and one that would retain the anatomical relations between the cells, we developed an in vitro preparation of the olfactory epithelium, a segment of epithelium we called a "swatch" (like a swatch of cloth) (Ma et al., 1999). Utilizing both patch recordings from the receptor knobs and Ca^{++} imaging, Minghong characterized the preferential cell responses within populations of up to several hundred cells (Ma and Shepherd, 2000). With a new postdoctoral fellow, Xavier Grosmaitre from Paris, she next characterized for the first time the response properties of cells in the septal organ (Ma et al., 2003). This led to a collaboration with Anne Vassalli and Peter Mombaerts, using swatches from gene-targeted mice to characterize the odor specificity of the MOR23 olfactory receptor (Grosmaitre et al., 2006), work completed after Minghong had moved to her new position at Penn. According to Peter, it was the first demonstration of the physiological properties of a singly expressed olfactory receptor.

Our saga with the receptors had an additional chapter. In a discussion with a modeler, Ralph Linster, in the early 1980s, I suggested a collaboration on a model of olfactory encoding, to which he replied: "To get started, what are the primitives?" I had to admit nobody knew. I began to discuss this in a short review given to AChemS in 1985, entitled "A Molecular Vocabulary for Olfaction," which involved comparisons between the immune and olfactory systems along the lines of my discussions with Doron. The primitives of the olfactory molecules appeared to be individual atoms, much smaller than the amino acids and peptides of immune antigens. In analogy

with pharmacological determinants, I suggested we call them determinants or odotopes, to distinguish them from the much larger immune epitopes. In the end, it is probably best to call them determinants.

With the discovery of the receptors, and assuming expression data would soon follow, I initiated a computational modeling study with an outstanding Yale undergraduate, Michael Singer. This was focused on answering the question about the primitives of the odor stimulus: how is the information contained in the odor molecule transferred to the olfactory receptors? The receptor model was built on the rhodopsin coordinates. The first results showed a close correlation with the expression data of Heinz Breer for the O5 receptor (Singer and Shepherd, 1994). Subsequent studies explored the nature of the odor molecule–odor receptor interaction. Michael's study of I7 gave a close fit with the experimental data of Firestein and Zhao (Singer, 2000). Another study with Bill Goddard's dynamic modeling group at CalTech gave close correlations with other receptors (Floriano et al., 2000).

Without strong expression data these modeling studies were another example of a methodology preceding the means to utilize the results. Nonetheless, it gave us a clear idea that the primitives of the olfactory system are the determinants of the odor molecules that are transduced by their interactions with specific amino acid residues within the binding pocket of the receptors. It is a working hypothesis that continues to be useful in current studies by many new laboratories drawn to this great challenge in receptor biology.

Olfactory Bulb Dendritic Physiology Again

In the early 1990s we again took up the physiology of olfactory bulb dendrites. Paul Trombley, from Gary Westbrook's lab, joined us to carry out several studies of synaptic interactions between olfactory bulb cells in tissue culture. We then carried out a study on our old friend, the isolated olfactory bulb of the turtle. Amazing as it is, at that late date the neurotransmitter of the olfactory receptor cell axons was still unknown. David Berkowicz and Paul used the isolated turtle olfactory bulb to demonstrate for the first time that glutamate is the neurotransmitter of the olfactory nerves onto the mitral cells (Berkowicz et al., 1994).

During the late 1980s and early 1990s I began receiving increasing inquiries from Chinese students to join the lab, which ran up against my policy to interview all candidates, or have a colleague I could consult who knew the candidate. The opportunity to meet colleagues in China came with a trip to Japan in 1993, to which we added a week in China. Grethe and I were warmly received in Beijing by Renji Zhang. He gave us a guided tour of the Great Wall, and he and his wife Lily and daughter entertained us in their home. With Xiaocheng Gu we toured the Secret City and Tiananmen

Square. We then visited the Brain Institute in Shanghai, hosted by Ching Ping Wu, who had studied with Charles Phillips in Oxford soon after I left. I gave a chalk talk to a large group of graduate students, led by one of them, Wei Chen. Getting to know the great Chinese electrophysiologist Hsiang-Tung Chang was especially memorable.

Among all the students I met, Wei made the strongest impression. Fortunately, he soon wrote me inquiring about a postdoctoral position and joined us in 1994. After a year of trying several different projects in the lab, he came to me one day and said: "Gordon, I have decided to devote my career to the olfactory bulb." It was the same spirit in which I had made a similar decision in 1959.

Our first task was to develop a tissue slice of the rat olfactory bulb, which we did building on our experience with the in vitro turtle bulb and the recent introduction of the rat olfactory bulb slice by Nickell and Shipley. Wei first carried out a study characterizing some membrane and synaptic properties of mitral cells (Chen and Shepherd, 1997). About that time it was reported, using the new dual patch technique, that action potential initiation in the initial axonal segment, with backpropagation into the dendrites, is the rule in all nerve cells. However, Per Andersen had provided extracellular evidence back in the late 1950s that forward spike propagation occurs in hippocampal dendrites. With its synaptic excitatory input confined to the most distal dendritic tuft, the mitral cell was the perfect model to test the rule. Joined by my colleague Jens Midtgaard from Copenhagen, Wei carried out dual patch recordings and determined that the rule held at low levels of distal dendritic activation, but the initiation site shifted toward the distal site with higher levels. The report was published in *Science* (Chen et al., 1997) and stimulated a number of studies in other systems, with similar results. We subsequently carried out a computational study with Gongyu Shen and Michael Hines in which we could precisely model this shift (Shen et al., 1999). A further study showed how the site could shift back and forth in a "ping-pong" fashion, also modeled computationally (Chen et al., 2002).

Wei then turned to the dendrodendritic synaptic interactions. Using caged glutamate, he and Wenhui Xiong obtained evidence that the release of GABA from the granule cell spine onto mitral cell lateral dendrites could occur in the absence of voltage-gated Ca channels, suggesting that the Ca^{++} for vesicle release came from the influx into the spine due to the neighboring dendrodendritic excitatory synapse from the lateral dendrite (Chen et al., 2000). This innovative finding also stimulated follow-up studies from other laboratories.

A question unresolved since our original dendrodendritic model was whether the action potential generated at the cell body of the mitral cell spreads into the lateral dendrites passively or by active invasion. Wei and Wenhui attacked this problem with brilliant results: with patch recordings and Ca^{++}

imaging they showed that the action potential could spread through the entire lateral dendrite, up to a millimeter in length (Chen and Xiong, 2002). They also showed that the invasion could be blocked by stimulating at a point in the granule cell layer. This also gave rise to follow-up experiments in other laboratories, suggesting that the amount of invasion is controlled by the amount of feedback inhibition along the way. This finding had great significance in showing how long distance communication could occur within the olfactory bulb microcircuit.

With Wei in the lab we could rely on a steady stream of students from the best schools in China. Wei seemed to know them all! Changping Jia came to study the synaptic organization of the rat accessory olfactory bulb (Jia et al., 1999). Gongyu Shen carried out the detailed mitral cell modeling mentioned earlier. Zhishang Zhou analyzed dendritic excitability and Ca^{++} signaling in the mitral cell dendritic tuft (Zhou et al., 2006) and plateau potentials in juxtaglomerular cells (Zhou et al., 2006). For building our two-photon setup Andong Xia joined us from China for several extended stays. After Wei had become an assistant professor in neurobiology, Max Fletcher from Don Wilson's lab and Shin Nagayama from Kensaku Mori's lab joined our combined labs, introducing new methods for visualization of activated dendrites in the glomerulus. After 14 fruitful years, Wei moved on to join the faculty at the University of Texas in Houston, in 2008.

Odor Mapping with High-Resolution Functional Magnetic Resonance Imaging

Our odor mapping studies during the 1970s and early 1980s were exciting in opening a new field of study, but they were also frustrating, because the 2DG patterns were another example of a discovery predating the technological means to exploit it. In particular, pseudo-color representation of spatial patterns was not generally available until the 1990s. More efficient activity markers operating over shorter time periods were also needed. In the early 1980s John Kauer and I advised Larry Cohen and his colleagues on launching the use of voltage-sensitive dyes for this purpose, which John then used to great advantage in the salamander. Being optically based, observations were limited to the dorsal surface of the olfactory bulb, which John exploited brilliantly in the salamander because of the way the laminae open onto the dorsal surface. In the 1990s other optical methods were introduced, especially intrinsic imaging and Ca imaging, both providing what appeared to be glomerular resolution.

I was eager to take up our study of odor maps again, but was looking especially for a successor to 2DG that would allow multiple trials of different odors in the same animal, with labeling throughout the glomerular layer, at a glomerular resolution. I had been impressed with the resolution down to 10 micron pixels in anatomical magnetic resonance imaging (MRI) images of

the brain in rodents. Fortunately we had a leading center for fMRI at Yale, so Charlie Greer and I went to Bob Shulman and Doug Rothman to ask whether they would be interested in a collaboration on the olfactory bulb using functional imaging. They certainly would! And they showed us a recent result of imaging a single activated barrel in barrel cortex in the rat. They brought great enthusiasm and consummate expertise to the project. Our initial study showed patterns centered on the glomerular layer similar to those with 2DG (Yang et al., 1998). At this point Fuqiang Xu joined the lab from Tim McClintock's lab in Kentucky and worked with Fahmeed Hyder and the Shulman team to demonstrate resolution at the single glomerular level using a 7.4 Tesla magnet.

Fuqiang and I pursued the odor mapping project, focusing on mice with a view to bringing in gene-targeted animals eventually. The mouse olfactory bulb is a very small structure, but Fuqiang succeeded in getting laminar resolution, which enabled us to delimit the olfactory glomerular layer in each slab and reconstruct the entire glomerular BOLD pattern for a given odor stimulus. Our first study showed that an aldehyde series from C4 to C8 produced extensive glomerular activity patterns which were overlapping but different, confirming the basic properties we had identified with 2DG back in the late 1970s, but all trials in the same animal and at shorter odor exposures (Xu et al., 2003). It also confirmed that the main activity for many odor stimuli is in the medial and lateral aspects of the olfactory bulb.

We next asked whether so-called pheromones activate only the accessory olfactory bulb, a common belief in the field that I had long doubted. Fuqiang, with Diego Restrepo and his student Michelle Schaefer in Denver, carried out these experiments beautifully, showing that a "pheromone" molecule could activate the main olfactory bulb as well as the accessory olfactory bulb, and ordinary odor molecules could also do both (Xu et al., 2005). This was consistent with several other studies then and subsequently. This has further significance in implying that humans also process "pheromone" odors through their main olfactory bulb, because we lack a functional adult vomeronasal organ (see Commentary in Shepherd, 2006).

In revealing the patterns where the responses are strongest, on the medial and lateral surfaces, the results provide a necessary complement to the more easily obtained, but weaker, optical activity of the dorsal glomeruli. Fuqiang achieved recognition for his work when he returned to China in 2008 as one of the select "100 outstanding young scientists" of China.

It was particularly rewarding to have olfactory studies contribute to the development of high-resolution fMRI, pushing from 7 to 9 and 11 Tesla magnets and beyond. Olfactory studies should be able to continue to play this role in the future, aiming at glomerular spatial resolution and subsecond time resolution.

Lateral Connectivity and Distributed Dendrodendritic Inhibition

The fMRI patterns left no doubt that odor stimulation leads to extensive activation in the glomerular layer. This posed the problem of how lateral inhibition mediated by granule cells could operate over such spread-out patterns.

A possible mechanism emerged from a project by postdoctoral fellow David Willhite involving tracing connectivity in the olfactory bulb using pseudorabies virus. The expectation had been that following an injection in the glomerular layer one would see diffuse labeling within the mitral and granule cell populations around the injection site. Surprisingly, discrete columns of labeled cells were seen, widely distributed in a mosaic pattern (Willhite et al., 2006). An individual column appeared to be centered on a single glomerulus, suggesting a "glomerular unit," each unit containing the granule cells synaptically connected to the mitral cells connected to the single glomerulus. Though connectivity induced by the virus cannot be ruled out, the formation of the columnar pattern remains unique. The functional implication is that lateral inhibition could be mediated through these distributed connections, in contrast to a local center-surround organization.

There was no precedent for this type of organization. As it happened, independent support for this new idea came from a computational modeling study carried out by Michele Migliore. Michele had begun to collaborate with us on analyzing dendritic active properties in the early 2000s, coauthoring two reviews on comparing integrative properties of dendrites across different neuron types (Migliore and Shepherd, 2002, 2005). We then launched a computational study to begin to build a model of the mitral-granule processing network, building on the Shen 1999 mitral cell model and adding a granule cell model. We purposely began with a reduced three-mitral-cell model, in order to work through all the possible constraints on the network. In doing so, Michele reported that the only way to get strong lateral inhibition over long distances was to have the granule cells activated by action potentials propagating throughout the length of the mitral cell lateral dendrites, which of course was just what Chen and Xiong (2002) had shown.

It was another "aha" moment, bringing together the experimental and computational results with the connectivity findings to adapt our original model to provide for distributed lateral inhibition in the processing of distributed odor images. Keeping up traditions, this new model was rejected when submitted for publication, forming a kind of bookend to the rejection of the original model 40 years earlier, as noted earlier. It was finally published (Migliore and Shepherd, 2007), initiating a series of studies still in progress on scaling up to a full realistic simulation of the mitral-granule cell interactions. Combined with the evidence for the determinants transduced

by the binding pocket of the olfactory receptors, and the basic circuit of the olfactory cortex for a content-addressable representation of the images, one has a logical sequence for understanding the neural basis of the perception of smell up to orbitofrontal cortex, as earlier hypothesized (Shepherd, 1991).

Human Smell and Human Evolution

In the 1980s I was asked for a quote for the *National Geographic* article on smell, and I began to think about how our animal research related to human smell. During a sabbatical with Jacques Glowinski at the College de France in Paris, I became acquainted with Jean-Didier Vincent and through him came my first contacts with French wine producers and connoisseurs. This led to participation in a French radio program on smell by Jean-Didier and Alan Prochiantz in the early 2000s; several interactions with the wine industry, including private tastings at Petrus and Château d'Yquem (heady stuff for a kid from Iowa); and participation in several international meetings on food and flavor. The field of olfaction had been focused on orthonasal smell produced by sniffing in, but taste physiologists like Bruce Halpern and flavor physiologists like Terry Acree and Andrew Taylor knew about food in the mouth as the source of flavor, and they knew that most of flavor is due to smell, specifically retronasal smell, by breathing out through the nasopharynx. When this message sank in, I became convinced that the olfactory field had been missing the importance of smell for humans; it was retronasal, not orthonasal, smell. The problem was that the smell component in flavor is almost entirely hidden, and ascribed to "taste" because it appears to come from the mouth.

At the Weurmann Flavor Research Symposium in 2001, I suggested that odor images are formed in humans, that these must play an important role in the perception of human flavor, and that smell must therefore have played an important role in the evolution of human cuisines. This was directly opposed to the traditional view of the decline of smell during human evolution, which appeared to be confirmed by the research on the olfactory receptor genes, which showed that the number of functional olfactory receptor genes declined in number within vertebrates from over 1000 in rodents to only 350 in humans. This assumed that our sensory and cognitive capacities are determined by our peripheral receptors. But a better hypothesis is that the enormous overgrowth of the cerebral cortex during evolution endowed the human with an accordingly enhanced ability for complex processing of its inputs, including the elaboration of much more complex flavors by humans compared with other species.

During this time Richard Wrangham was developing his well-known theory that the early control of fire enabled a complex cuisine that played a large role in the enhanced nutrition that literally fueled the larger brain of

Homo erectus. He kindly invited me to give a seminar at the Harvard anthropology department in 2003 where I presented my hypothesis. This was developed in an article for *PLoS Biology* in 2004 entitled "The Human Sense of Smell: Is It Better Than We Think?" My colleague Avery Gilbert sent me an amusing e-mail with the comment that what I really meant was: "The human sense of smell: is it better *because* we think?" That was exactly the point! Support for this idea soon came from human fMRI experiments by Dana Small, showing that combined taste and retronasal smell stimuli recruited additional association cortical areas. Odor images and the extensive brain regions involved in flavor perception were brought together in an Insight article for *Nature* in 2006 entitled "Odor Images and the Flavor System of the Human Brain."

Obviously, the role of the olfactory system needs to be reassessed for its importance in primate and humans. A pioneer has been Matthias Laska, who spent several years with us as a visiting scientist. His earlier results in the monkey suggested that primates, including humans, should be classified as "macrosmats" rather than "microsmats" (and this was only for orthonasal smell). This reassessment needs to be extended not by simple measures of sizes of different regions, but rather by the increasing knowledge of genetic makeup, microcircuit organization, brain imaging, and behavioral testing. A major challenge in food science as well as for any theory of the role of nutrition in evolution is therefore to understand the relation between the brain, the flavor of a food, and its nutritive value. This new field could be called "neurogastronomy".

Neuroinformatics

Our experience over the years with computational modeling led us into an entirely new field. In the 1980s molecular biology surged forward, critically aided by the gene and protein databases produced by the new field of bioinformatics. Neuroscience in this respect remained a digital backwater. The Institute of Medicine formed a committee in 1990 to bring neuroscience into the new age, chaired by Joseph Martin. Among the working groups, I cochaired with Vint Cerf, an Internet pioneer, a subcommittee on databases for cell structure and function. The final report was entitled *Mapping the Brain and Its Functions: Integrating Enabling Technologies into Neuroscience Research* (Pechura and Martin, 1991). Discussions began on a funding program to create a new field of neuroinformatics. Several of us urged that it be called the "Human Brain Project," with a vision of transforming neuroscience in the way the "Human Genome Project" was transforming molecular biology.

The program started in 1993, with a dozen or so laboratories among the first funded. We had a great advantage at Yale in Perry Miller, who had set up a Yale Center for Medical Informatics in the 1980s to support research in

molecular biology. He and I had interacted a bit before, and he enthusiastically joined the new effort. We entitled our grant "SenseLab: Integrating Multidisciplinary Sensory Data," with the aim of creating databases of neuronal data to support building computational models to aid experimental analysis of olfactory cells and circuits, with extension to other brain regions as well.

We began by responding to a request by several labs to provide a database to assist them in cloning and sequencing the thousand or more olfactory receptor genes. Thus was created Olfactory Receptor Database (ORDB). With the completion of the Human Genome Project around 2000, several labs produced their own terminology, with different nomenclatures for the same genes. This problem was discussed at a meeting at Cold Spring Harbor in 1991 on the "Molecular Biology of Chemosensory Receptors: The First Decade." The recommendation was for ORDB to organize the several nomenclature schemes so that the different names could be identified for the same gene/protein. Michael Singer and Chiquito Crasto took responsibility for initiating this, Chiquito building it up to the present inventory of over 14,000 chemical sensory genes, receiving some 200,000 Internet hits per month.

To support our research on dendrites, we decided to archive key membrane properties: transmitter receptors, membrane channels, and transmitters. For this we invented a format for canonical dendritic trees with proximal, middle, and distal compartments, enabling identification of the combinations of membrane properties that contribute to the integrative operations of a given neuron. A unique tool enabled searches for arbitrary families of properties across neurons, much as blast searches reveal families across sequence banks. The initial construction of this multidomain database was carried out by a recent Yale graduate, Jason Mirsky, with key input from the informatics group (Mirsky et al., 1998). Over the years it has grown to comprise over 30 principal neurons and interneurons in over a dozen key brain regions, receiving some 60,000 hits per month.

In 1996 Michael Hines joined our research group, bringing his deep experience in creating and maintaining the simulation program NEURON. Like all other compartmental approaches to modeling neurons, it was in the direct lineage from Wil Rall's original methods that we used in our olfactory bulb study. Just as in my work with Wil, I've benefited from the quiet expertise that Michael brings to the modeling enterprise, and the focus on interpreting experimental results. Michael made possible two new ventures in SenseLab. One was the opportunity to bring neuron modeling back into the lab, with the results noted earlier. The other was the construction of a new database, ModelDB. This has enabled us to address one of the most critical problems for computational modeling as a field: Models traditionally were constructed and published by a student in the lab, who then moved on in his or her career, so that testing the results by others required creating a new

model from scratch, which was rarely done. Without this capability, computational modeling lacked the credentials that every scientific field must have: rapid testing of published results.

For this purpose we created ModelDB. Tom Morse soon joined the lab and took over responsibility for this project. It has grown to comprise over 600 computational models at this writing, with over 100,000 hits per month. Some of the models are of circuits, which have been moved to a new MicrocircuitDB to make them more easily accessible as interest increases in building realistic network models.

As molecular biologists identify genes expressed in different cells, it is convenient to have a database where they can be archived. Cell Properties Database (CellPropDB) was created for that purpose. It is complementary on the one hand to NeuronDB, and on the other to brain atlas databases such as the Allen Brain Atlas, enabling users to determine quickly the types of genes expressed in a given cell type, or to go from CellPropDB to an atlas to see other genes expressed in the cells of that region.

For olfactory research, in addition to ORDB is OdorDB, archiving the range of odors that have been shown to activate different specific olfactory receptors, and OdorMapDB, archiving 2DG and fMRI maps from the lab. The latter was created by postdoctoral fellow Nian Liu, who also built software (OdorMapBuilder and OdorMapComparer) for constructing the odor maps in the work with Fuqiang.

Our most recent project is a new database called BrainPharm, aimed at expanding NeuronDB to include molecular properties involved in neurological disorders such as Alzheimer's disease.

The early years of the Human Brain Project involved a struggle for recognition. The director, Steve Koslow, organized numerous panels at national and international meetings to spread the word about the importance of sharing data in common databases but experimental neuroscientists were skeptical; at some meetings we panelists outnumbered the audience! A big boost came in 2004 when Huda Akil made neuroinformatics a signature focus of her presidency of the Society for Neuroscience. It came at a propitious time when, after a decade, the HBP was folding. In its place was put the Neuroscience Database Gateway (NDG), initiated by our SenseLab project, that was a portal to all the HBP project Web sites. This in turn led to an NIH Blueprint program funded by NIDA called the Neuroscience Information Framework (NIF), chaired first by Dan Gardner of Cornell and currently by Maryann Martone of San Diego. SenseLab is one of the five groups charged with creating this portal to the extraordinary range of neuroscience data. Also supporting the growth of neuroinformatics and data sharing is the International Neuroinformatics Coordinating Facility (INCF) in Stockholm, in which we also play a part.

At this stage in my career, focusing on the spread of effective databases in support of neuroscience research seems like one of the most important

contributions I can make. Sharing data is at the heart of the collegiality I believe is essential for the scientific enterprise. Its effectiveness is shown by the rise of molecular biology; we need that same spirit for a surge in shared data in neuroscience to achieve an integrated understanding of brain and mind.

Cognitive Neuroscience

In 1984 the McDonnell Foundation convened a meeting to discuss how to support the formation of a new field of cognitive neuroscience. We recommended starting by setting up a summer school in the subject, expecting a couple of dozen students. Over 300 applied! The first summer school was held at Harvard, with the course directors Steve Kosslyn, Michel Posner, and myself. We continued to put on the summer school over the next 4 years at Dartmouth, hosted by Michael Gazzaniga, with similarly high numbers of students. I'm still meeting cognitive neuroscientists who remember that summer school as the start of their careers in the new field.

History of Neuroscience

Notwithstanding my father's injunction against being distracted by history, I had developed a deep interest in the historical origins of neuroscience from my first encounter with Cajal in Oxford. In 1985 I suggested to then Society for Neuroscience president, Bill Willis, that the society should have a committee on the history of neuroscience led by neuroscientists themselves. I was joined by Ted Jones in presenting the proposal at the next council meeting, which, after a vigorous debate, led to setting up a Committee on the History of Neuroscience, with myself as the first chair, followed by Ted. The annual Lecture in the History of Neuroscience was first given in 1985 by Julius Axelrod, which completely bowled us (and Julie) over by attracting an audience of some 2000. The lectures have continued to be among the most popular at the meetings, belying the received wisdom that modern young neuroscientists aren't interested in anything more than a week old! The present series of autobiographies under Larry Squire continues that tradition.

Conceptual Challenges

The focus in this account has been on the original research, experimental and computational, that has driven the work of the lab. Part of the fun of doing the research has been to see how it can enlarge the conceptual basis of our understanding of brain function.

The implications of our dendrodendritic study for revising the neuron doctrine led to stimulating interactions with Sandy Palay, Ted Bullock, and others. My review on this subject, published in 1971 in the *Yale Journal of*

Biology and Medicine, not what one would now call a high-profile journal, nonetheless brought over 500 reprint requests! This led to a full account in 1991 of the classical work in *Foundations of the Neuron Doctrine* on the centenary of Waldeyer's original review in 1991. (Some have assumed that I was blindly supporting the neuron doctrine; rather, I was laying out its full history in order to suggest how to revise it, as was done in the final chapter).

In 1985 a volume was published to celebrate the career of Carl Pfaffman. I used the opportunity to suggest the idea that the glomerulus constitutes a "labeled line," albeit a broadly tuned one, in odor processing (most believed that a labeled line had to be responsive to only one ligand).

I'm not a Proust scholar, but you can't work on the olfactory system and avoid him. The more I had read the famous passage about the instant memory evoked by the cookie and the cup of tea, the more I doubted it. The result was an essay with a scholar of modern English literature which pointed out that in fact it took Proust a page and a half of concerted effort to dredge up the memory from the past. We provided the reader with a tour of the brain pathways and mechanisms that would have been involved (Shepherd and Shepherd-Barr, 1989, 2009).

My work with Wil Rall instilled a lifelong commitment to realistic modeling of nerve cells and circuits. A direct challenge was neural networks, which came on the scene in the 1980s. John Hopfield sought me out to discuss his new approach at the same time that David Rumelhart and Jay McClelland were popularizing parallel circuits. My response has been that devices that can simulate functions similar to those of the nervous system are greatly to be welcomed, for their practical use and for the insights they can give into functions at the system level. However, networks that represent nerve cells as simple nodes with all-to-all connectivity are extremely un-neural in their architecture, as explained in a review (Shepherd, 1989) and numerous talks since. The power of the brain lies in the computational depth of its dendrites and microcircuits. When these get incorporated into neural nets, the revolution will really start!

In addition to introducing new concepts, one also has the opportunity to introduce new terms required by one's research. "Dendrodendritic synapses," "odor images," and "microcircuits" seem to have entered the general vocubulary; perhaps "human brain flavor system" and "neurogastronomy" will too! New fields to which this work has contributed have included computational models of dendrites, dendritic spines, dendrodendritic synapses, odor images, olfactory receptor models, synaptic organization, microcircuits, and neuroinformatics.

Books

With so many challenges in the lab, one may wonder why one would take out time to write books. However, it's been a particular privilege to be able to publish several books giving new syntheses of our own and others' work.

Most have been with Oxford University Press, starting with my editor and long-time friend Jeffrey House in 1974, and including Fiona Stevens and recently Craig Panner.

The Synaptic Organization of the Brain (1974) as noted was based on a course on the newly breaking studies, taught while a visiting professor at Penn in 1972. I began teaching the subject as a graduate course at Yale in 1976 and have just finished using the fifth edition to teach the most recent class 34 years later. *Neurobiology* (1983) was written to introduce undergraduate students to the new ways of understanding the functional organization of the brain. Although not dislodging Kandel et al. from its well-deserved popularity, the book nonetheless has been translated into five languages, and the third edition is still being sold. *Foundations of the Neuron Doctrine* (1991) was my homage to all the classical histologists I studied in my early work at Oxford, with much help from Grethe on the translations. *Creating Modern Neuroscience: The Revolutionary 1950s* (2010) has been my tribute to all my teachers, colleagues, and other great figures from the 1950s. The collected papers of Wilfrid Rall, with commentaries by his colleagues, was published as *Theoretical Foundation of Dendritic Function* (1995) with coeditors Idan Segev and John Rinzel. *Handbook of Brain Microcircuits* (2010), coedited with Sten Grillner, is the continuance of the main message in *The Synaptic Organization of the Brain*, distilled to focus on basic microcircuits and extended to over 50 brain regions.

Various Offices

A scientist rightly tithes time to various offices to support his or her field. My efforts included various contributions. The main ones were 6 years as editor-in-chief of the *Journal of Neurophysiology*, followed by the same office for 4 years for the *Journal of Neuroscience*. The former occurred as e-mail was becoming widespread, the latter as the Internet age began, so the times were exciting. My main focus in running a journal was getting quality editors who in turn get the reviewers who are the best possible fit with the subject matter of the article. Given a good fit, collegial criticism will bring the field forward in the best possible way.

At Yale, my main contributions were as director of medical studies for our department, followed by director of graduate studies for the nascent Interdepartmental Neuroscience Program, followed by Deputy Provost for Biomedical Sciences. The latter provided fascinating experience and insights into the governance of a university. I enjoyed the job greatly, while at the same time was relieved to return unscathed to the lab! Bart Giamatti once asked me to be master of Pierson College, which would have been stimulating, but too much of a diversion from the lab.

Among other duties, serving as advisor to programs and institutions in the United Kingdom, France, Germany, Denmark, Sweden, and Switzerland, as well as in the United States, has been particularly interesting and I hope useful.

Friends and Awards

The rewards of a life of research have been in having many great colleagues and in enjoying the intellectual stimulation of opening new fields. The additional awards listed at the start of this essay have been icing on the cake, for which I am grateful to the brave souls who put up my name for them. Visiting appointments have been especially rewarding. Warm friends and colleagues around the world, in addition to those already mentioned, have been Pierre-Marie Lledo, Alain Prochiantz, JacSue and Phillip Ascher, Serge Charpak, and Henri Korn in Paris, Tomas Høkfelt in Stockholm, and Yoshi Yoshihara in Japan. Among the recognition, I especially appreciated the honorary degrees in Copenhagen, reflecting my connection through Grethe and to colleagues in Denmark, and Pavia, reflecting my connection to the origins of neuroscience and to Golgi, through Paolo Mazzarello, Golgi's outstanding biographer.

Family

An active life running a lab and writing has to be balanced with family life. Grethe, a reference librarian and gardener, has made it all possible, maintaining our homes in Hamden and Toftum and leading us all with the right values. Gordon M. G. is making his own career in neuroscience at Northwestern. Kirsten is a don at Oxford in English literature and theater. Lisbeth cofounded Unis-Cité, a youth service corps in France, and now runs a green nonprofit in the U.S.. The ideals that they and their spouses and our seven grandchildren live by give hope for the future.

I've also had plenty of stimulation from my four younger siblings. Geoffrey has published 15 books in economics and Margaret 17 as a calligrapher; I'm still trying to catch up! Alison was chief of staff to the Alameda County CA Supervisor for many years. Doug was a caring husband and father, bravely battling asthma all his life.

Also close to me growing up were cousin Dave Murray, who became President of the American College of Surgeons, and Jean Murray Sutherland, Elizabethan scholar and a pillar of strength as her husband Tom survived 6 years as a hostage in Lebanon, which helps to put one's own strivings in perspective.

Students

It seems appropriate to end this essay with one of the most important contributions a lab can make, as a training site for the next generation of scientists. I was hugely fortunate in the talented young people who joined me. There were two rules in taking them on. I took responsibility for mentoring them toward independent positions when they left, and they were free to

pursue whatever subjects they wished, including what they had worked on in the lab. As a result, I've had great times with a growing family of colleagues. The reward has been to see them make successful lives in neuroscience as well as other walks of life. The list speaks for itself. I thank them all.

On my 75th birthday some 80 students, collaborators, family, and friends gathered from 11 countries for an all-day symposium. It was the best lab meeting ever!

Students

Graduate Students

1967–1971	Lewis Haberly, Ph.D.
1969–1972	Lanay Jordan Land, Ph.D.
1985–1990	Thomas Woolf, Ph.D.
1986–1990	Ben Strowbridge, Ph.D.
1991–1994	David Berkowicz
1994–1998	Paul Kingston, Ph.D.
1995–2000	Michael Singer, M.D., Ph.D.
2005–2007	Janna Nawroth
2006–2007	Johannes Richter
2006–2009	Arjun Masurkar, M.D., Ph.D.
2007–2009	Aurelie Pala
2007–2011	Matthew Phillips, Ph.D.

Postdoctoral Fellows and Research Associates

1972–1973	Lanay Jordan Land
1973–1974	Thomas V. Getchell
1973–1976	John S. Kauer
1976–1978	William B. Stewart
1977–1982	Martha C. Nowycky
1977–1978	Ulrich Waldow
1978–1980	Kensaku Mori
1978–1981	Charles Greer
1980–1981	Doron Lancet
1981–1985	Patricia Pedersen
1982–1985	Thane Benson
1982–1985	Leona Masukawa
1982–1984	Britta Hedlund
1987–1989	Masato Higashima
1987–1988	Joan Hamilton
1988–1990	Stuart Firestein
1988–1991	Ferenc Pongracz
1990–1991	David Berkowicz
1990–1995	Paul Trombley
1990–1995	Anne Williamson
1990–1997	Frank Zufall
1994–1997	Trese Leinders-Zufall
1994–1996	Bret Peterson
1995	Mark Rand
1996–1999	Emmanouil Skofous
1997–2000	Changping Jia
1994–2000	Wei Chen
1996–2003	Minghong Ma
2000–2001	Andong Xia
2000–2004	Zhishang Zhou
2000–present	Thomas Morse
2001–2002	Buqing Mao
2000–2002	Andrew Davison
2001–2003	Xavier Grosmaitre
2002–2004	Fan Jia
2002–2005	Shaoquin Zeng
2001–2005	Nian Liu
1998–2006	Luis Marenco
1998–2007	Fuqiang Xu
2000–2007	Chiquito Crasto
2003–2010	David Willhite
2005–2008	Shin Nagayama
2005–2008	Max Fletcher
2009–present	Tom McTavish
2011–present	Yuguo Yu

Programmers and Technicians

1996–1998	Jason Mirsky
2002–2003	Jian Liu
2004–2010	Hetal Petal

Yale Undergraduates

1985–1986	Jessica Hopfield
1987–1988	Rob Rosenberg
1988–1989	Pratik Mukherjee
1989–1990	Bruce Darrow
1989–1990	Karen Rosewater
1993–1995	Michael Singer
1995	Winnie Au
1995–1996	Uzman Rabbani
1996–1997	Jason Smith
1999–2000	Jasen Yang
2000–2001	Rishikesh Dalal
2004–2006	Catherine Nguyen
2005–2006	Dipa Joshi
2006–2008	Andrew Chang
2007–2008	Hayley Ryan
2007–2008	Maria Thomas
2008–2010	David Kim
Also:	
2002–2004	Peter Bail

Visiting Scientists

1980–1981	Norbert Halasz
1981	Burton Slotnick
1982	Dennis Lincoln
1982–1984	Pawel Jastreboff
1983	Norihiko Onoda
1984–1986	Anker Hansen
1985	Hinrich Sass
1996–2000	Jens Midtgaard
1998–2000	Gongyu Shen
1999–2000	Michael Meredith
2001–present	Michele Migliore
2003–2006	Matthias Laska

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