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A Life in Vision

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Abstract

I was drawn into research in George Wald's laboratory at Harvard, where as an undergraduate and graduate student, I studied vitamin A deficiency and dark adaptation. A chance observation while an assistant professor at Harvard led to the major research of my career—to understand the functional organization of vertebrate retinas. I started with a retinal circuit analysis of the primate retina with Brian Boycott and intracellular retinal cell recordings in mudpuppies with Frank Werblin. Subsequent pharmacology studies with Berndt Ehinger primarily with fish focused on dopamine and neuromodulation. Using zebrafish, we studied retinal development, neuronal connectivity, and the effects of genetic mutations on retinal structure and function. Now semi-retired, I have returned to primate retinal circuitry, undertaking a connectomic analysis of the human fovea in Jeffrey Lichtman's laboratory.

THE BEGINNINGS

George Wald, Vitamin A Deficiency, and Visual Adaptation

I am often asked what brought me into vision research. Although both my father and my brother were ophthalmologists, it was a course in college that drew me into the field. Always interested in science, I was pointed toward medicine as a career, but all that changed in my junior year at Harvard University when I took biochemistry from George Wald. He was mesmerizing, especially during the second semester, which was devoted to topics in biochemistry. I can still feel the excitement he generated in me when he talked about Albert Szent-Györgyi's famous experiments with glycerinated muscle fibers. That they would contract when ATP was added seemed miraculous to me and getting at the essence of life.

Halfway through that second semester I asked George (then Professor Wald to me and for many years thereafter) whether I could undertake a senior project in his laboratory beginning that summer. I was accepted into the laboratory, and that changed my life. George proposed that I work on vitamin A deficiency in rats to determine why, after prolonged deficiency, recovery was often incomplete upon refeeding of vitamin A. Earlier studies by Katherine Tansley (1933) in England had shown that photoreceptors degenerate during prolonged vitamin A deficiency, and Ruth Hubbard (1958) in the Wald laboratory had shown that opsin (without attached vitamin A aldehyde) was much less stable than rhodopsin. George surmised that the lack of complete recovery was due to irreversible photoreceptor degeneration. So I began a series of biochemical measurements, mapping out what happens to a rat on a deficient diet. First, liver stores of vitamin A decrease, and then blood stores, at which point rhodopsin levels begin to decline. Some time later (~2 weeks), opsin levels begin to decline; thus, Wald's hypothesis seemed correct. Opsin is an important structural component of the outer segment of the photoreceptor, and degeneration of photoreceptors occurs as opsin levels decline.

But I was curious about what effect the loss of rhodopsin had on the rat's vision. How to determine this? Donald Kennedy, eventually to become head of the US Food and Drug Administration and president of Stanford University, was just completing his PhD in the biology department, recording the electroretinogram (ERG) of the frog. Don agreed to record the ERG of a rat in his setup, and it was clear that this was the way to test rat vision. I inherited much of Don's equipment when he left and moved it upstairs to a darkroom, and that began my electrophysiological studies. I found that as the visual pigment levels decline, the light sensitivity of the eye decreases, as one would expect, but it did so logarithmically! This was new and suggested a relationship between visual pigment levels in a photoreceptor and visual sensitivity, a contentious issue at the time. The next question was whether a similar relationship exists during light and dark adaptation, but those measurements were not made for another year. My first paper reporting the studies carried out as an undergraduate on vitamin A deficiency was published in the *Proceedings of the National Academy of Sciences (PNAS)* (Dowling & Wald 1958).

My senior year at Harvard was spent mainly in the Wald laboratory, and I found research immensely satisfying and fun. But I also remained determined to go to medical school and enrolled in Harvard Medical School in the fall of 1957. I soon began spending free afternoons in Cambridge. The following summer is when I examined the role of visual pigment levels in light and dark adaptation and also mapped out the exchange of vitamin A between the retina and pigment epithelium during light and dark adaptation. This resulted in a paper published in *Nature* (Dowling 1960). My second year of medical school was spent split between Cambridge and Boston, and a new observation I made led me to take a year's leave of absence from the Medical School.

This was the finding that vitamin A acid (now called retinoic acid) could prevent animals from dying from vitamin A deficiency but did not prevent them from going blind. In other words,

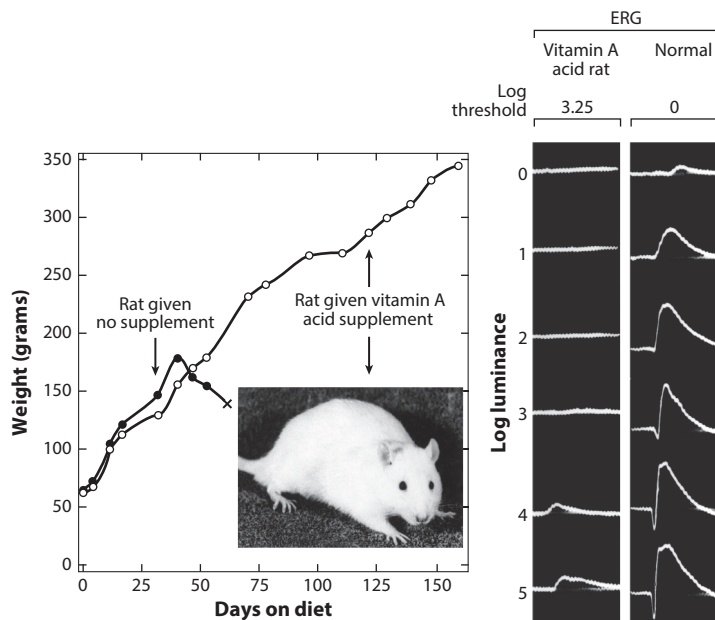


Figure 1

Activity of vitamin A acid (now called retinoic acid). Littermates were placed on a vitamin A-deficient diet or on the same diet supplemented with vitamin A acid. The rat given no supplement died on the fifty-seventh day of the diet; the animal receiving vitamin A acid continued to grow and remained in excellent condition for the duration of the experiment, a little over 5 months. The picture of this animal was taken at the end of the experiment, as were the electroretinograms (ERGs) shown at the right, which are compared with those of a normal animal. The ERGs show the rat to be highly night-blind: Its visual threshold had risen 3.25 log units (about 1,800 times) above normal, and only barely detectable ERGs could be evoked at even the highest luminances. Figure adapted from Dowling & Wald (1960) with permission.

retinoic acid can fulfill all the somatic functions of vitamin A—growth, tissue maintenance, and so forth—but cannot be reduced in the body to vitamin A aldehyde (now called retinal), which is essential for vision. Thus, with retinoic acid, it was possible to isolate vitamin A deficiency to the eye and photoreceptors (**Figure 1**). This enabled me to complete elegantly my original project. I could show that with prolonged vitamin A deficiency, photoreceptors were indeed lost and that in such retinas, complete recovery did not occur after vitamin A refeeding.

Again, though, curiosity about an aspect of the project led me to another technique that would play a major role in my research career—namely, electron microscopy. What did vitamin A-deficient photoreceptors look like? Ian Gibbons had just joined the Harvard biology department and was in charge of a new electron microscope facility. Why not learn how to do electron microscopy and find out? This I did, and thus began my anatomical studies. A *PNAS* paper reporting our retinoic acid studies included biochemical, electrophysiological, and electron microscopic observations (Dowling & Wald 1960).

Retinoic acid has become a most important molecule for understanding development, and 30 years later, we revisited retinoic acid in terms of its role in retinal and photoreceptor development (see below). But how did I come to use it in the first place? Thomas Moore's (1957) classic book on vitamin A appeared in 1957, and Ruth Hubbard read in it that although symptoms of vitamin A deficiency could be reversed in animals dosed with retinoic acid, never could one find traces of retinoic acid in the animal's tissues. This suggested retinoic acid could not be converted

back to retinal or vitamin A in biological tissues, the molecules essential for vision. She suggested I try retinoic acid in my experiments, and the results far exceeded my expectations.

An opportunity in medical school led me into yet another area of lifetime interest—namely, inherited retinal degenerations. Richard Sidman was my neuropathology instructor at the Medical School, and he had read my first paper on vitamin A deficiency. He had recently brought into this country rats with an inherited retinal dystrophy—the RCS (Royal College of Surgeons) rats—and he wondered whether they might have a deficit in vitamin A metabolism. We (Dowling & Sidman 1962) began a collaboration that resulted in a paper published in the *Journal of Cell Biology*. Although we found no evidence that the defect in the RCS rat was caused by a deficit in vitamin A metabolism, several inherited retinal degenerations in humans have now been shown to be caused by such genetic defects (Berson 1993). But I am getting ahead of my story.

During my year leave of absence from the Medical School, as the story of retinoic acid unfolded, George Wald suggested that I consider obtaining a PhD. Because I had had two years of medical school training, had been an undergraduate in the biology department, and had done, in his opinion, enough research for a thesis, George believed I could quickly qualify for the degree. I entered graduate school in February 1960, took qualifying exams in April, and wrote my thesis over the summer and into the fall. The degree was granted in January 1961!

I fully expected to return to medical school the following year, but again, George intervened. He was undertaking a new introductory undergraduate course in biology at Harvard, designed for both scientists and nonscientists, that would focus on the unity of life at the molecular level. This course was to replace the traditional botany and zoology courses that emphasized the differences among organisms. He asked whether I would join him and a small cadre of young biologists to help design and teach the course. The offer was too tempting to refuse, and I extended my leave of absence from medical school—to be 60 years in 2019!

The course, *The Nature of Living Things*, began that year, and I was appointed an instructor in the department beginning in February 1961. I was promoted to assistant professor in July and given laboratory space adjacent to the Wald laboratory. And so, my independent research career began. Initially, I followed up on and extended the research projects I had begun as an undergraduate and graduate student and completed the study on the RCS rats with Richard Sidman. With Ruth Hubbard, I looked at the formation and utilization of 11-*cis* vitamin A in eye tissues as well as the effects of brilliant light flashes on the ERG in light and dark adaptation (Dowling & Hubbard 1963, Hubbard & Dowling 1962). With Ian Gibbons, I studied the fine structure of the pigment epithelium (Dowling & Gibbons 1961, 1962), and then, when Richard Cone was visiting from the University of Chicago, I extended my observations on the mechanisms underlying light and dark adaptation, showing that there are both neural and photochemical components at play (Dowling 1963).

Up to 1963, virtually all my research had been carried out on the rat, a rod-dominated animal. What about cones? Do cones light and dark adapt like rods? How different is their fine structure? Curiosity about these questions was to lead me far beyond photoreceptors and to one of the most fruitful collaborations of my career. Ground squirrel retinas contain mainly cones, and I thought they would be ideal animals to study, but how to obtain some? Charles Lyman at the Harvard Medical School was studying hibernation in ground squirrels and was the obvious source. A call to Charles resulted in the promise of some animals, but he mentioned that a visitor to the biology department was also interested in ground squirrels and suggested we share animals. That was my introduction to Brian Boycott.

Brian was interested in synaptic plasticity and wished to follow up on an old observation that spines on cerebellar Purkinje cells change shape during hibernation. We began to take the bus over to the Medical School to pick up animals and tissues. I first recorded the ground squirrel ERG during light and dark adaptation and then began to study the fine structure of the photoreceptors.

What caught my eye were the photoreceptor terminals and that on occasion I could trace a process contacting a photoreceptor terminal back to its cell of origin. Photoreceptor–bipolar cell contacts were expected and seen, but I also identified processes from horizontal cells synapsing with the photoreceptor cells (Dowling 1964). Horizontal cells were very much of mystery then—indeed, some thought they were glial cells—but the fact that they were receiving input from photoreceptor cells clearly indicated they were neuronal.

The neuronal circuitry of the outer retina was largely unknown, and Brian and I discussed this on our trips to the Medical School. How to learn more about the synapses and synaptic circuitry there? We mused that it was first important to learn more about the horizontal and bipolar cells of the ground squirrel retina by light microscopy and Golgi staining, techniques with which Brian was expert. At the same time, Brian had found significant changes in the cerebellar (Purkinje cell) spines during hibernation at the light microscopic level, but he recognized that the next step was to study these changes by electron microscopy—something I could do. The next step was obvious: We join forces and share each other's expertise.

We made substantial progress on both fronts, but curiously we never formally published either study. [Several years later, Roger West in our laboratory revisited the ground squirrel retina and published several papers on its cellular and synaptic organization (West & Dowling 1972, 1975).] Brian returned to England at the end of the year, and the next year, I moved to the Wilmer Eye Institute at Johns Hopkins University. I had been an assistant professor in the Harvard biology department for three years, and as was then the custom, assistant professors were seldom promoted at Harvard. A tempting offer from A. Edward Maumenee, chief of ophthalmology at the Wilmer, to occupy a magnificent new space in the Woods Research Building was too good to pass up, and so I moved to Baltimore in June 1964.

THE EARLY WILMER YEARS

Retinal Circuitry and Single-Cell Recordings

During my last year as an assistant professor at Harvard, George Wald was on sabbatical leave in England, and so my teaching responsibilities were considerable. I did stay in contact with Brian, who was becoming more and more interested in the retina but also felt that to make progress in understanding retinal circuitry, the ground squirrel was not the animal with which to start; too little was known about its cells. Because Polyak's (1941) book *The Retina* provided a wealth of material on the primate retina and its cells, he suggested we should begin there. Brian visited the Wilmer in July 1964 for a few weeks, the first of many such visits over the next 10 years. During that first visit, we studied what ground squirrel material he had prepared, but also fixed some monkey retinas for both light and electron microscopy, and it was this material that set us on our course.

I first looked at the foveal cones, about which virtually nothing was known at the electron microscopic level. A paper in *Science* described not only the photoreceptor outer and inner segment structures, but also the structure of the foveal cone photoreceptor synapses, which seemed simpler than the ground squirrel photoreceptor synapses and, perhaps, easier to analyze (Dowling 1965). I thus began to focus on identifying retinal synapses in both plexiform layers. Ribbon synapses in photoreceptors were well known, but ribbon synapses were also present in the inner plexiform layer (IPL). In what cells were they located? A particularly well-fixed piece of human retina, provided to us by Ed Maumenee from an eye surgically removed for melanoma, gave us the answer and much more. Large bipolar cell terminals could be readily identified in the human IPL, and they made abundant ribbon synapses. Conventional synapses were also seen in the IPL, and the obvious

question was, What cell makes these? Again, the piece of human retina provided the answer. I could follow processes from amacrine cells into the IPL, where they made conventional synapses. Brian and I (Dowling & Boycott 1965) reported these first results, and with them a tentative diagram of the synaptic circuitry of the IPL, at the annual Cold Spring Harbor Laboratory Symposium in the spring of 1965.

In London, Brian was making new observations on the primate retina at the light microscopic level, while in Baltimore, I extended the electron microscopic observations (even carrying out some limited serial section analyses). Brian was then visiting twice a year and when he was in Baltimore, it was intense but exciting. We (Dowling & Boycott 1966) published our electron microscopy studies on the primate retina (with much grander diagrams) in the *Proceedings of the Royal Society*, but the light microscopic paper did not appear for another three years. The latter was a massive tome, 75 pages in length, published in the *Physiological Transactions of the Royal Society* (Boycott & Dowling 1969). It went through 12 drafts and had over 100 micrographs and figures.

My laboratory at Johns Hopkins was also growing. George Weinstein, an ophthalmologist, joined us and carried out a marvelous study on light and dark adaptation of the isolated rat retina, making simultaneous physiological and biochemical measurements (Weinstein et al. 1967). Helga Kolb arrived from Geoffrey Arden's laboratory in London and wanted to do anatomical studies. Brian and I suggested combining light and electron microscopy observations by studying Golgi-stained cells in the electron microscope [a technique pioneered by Bill Stell (1965) at the National Institutes of Health] was the next logical step to take, and it yielded wonderful results. An early result was the discovery of a second type of midget bipolar cell in the primate retina—the flat midget cell—which was the first hint that information from photoreceptors to bipolar cells was divided into two pathways, ON and OFF pathways (Kolb et al. 1969). But at that point we knew nothing of the physiology of bipolar cells, so that realization was some time off. Helga studied the connections of all the outer plexiform layer cells, providing for the first time quantitative data about the number of connections made between photoreceptors and bipolar or horizontal cells. Her paper in *Philosophical Transactions* (Kolb 1970) was submitted for a PhD from the University of Bristol (see **Figure 2**).

Following a lecture I gave at Johns Hopkins on the synaptic organization of the primate retina, a new graduate student, trained as an electrical engineer at the Massachusetts Institute of Technology, came to my office asking whether I thought it possible to build a theoretical model of the retina. My answer was that because we knew virtually nothing of the electrical responses of the retinal cells, it was too early to model the retina, but why didn't he, for his graduate work, make such recordings? When I was still at Harvard, I had been introduced to the mudpuppy retina by Paul Brown of the Wald laboratory, who was taking advantage of the mudpuppy's large photoreceptor cells for microspectrophotometric measurements (Brown et al. 1963). But what impressed me was that all the retinal cells were large and this might be an ideal retina from which to record the responses of single cells. Alexander Bortoff (1964) of the State University of New York at Albany had made some intracellular recordings from the mudpuppy retina, and so the project seemed feasible.

The graduate student called back a few days later to say he would like to try the project, and that is how Frank Werblin joined the laboratory. Frank was soon recording intracellularly from the mudpuppy cells, but the critical step was to stain the recorded cells. This was accomplished with the use of Niagara sky blue, and Frank identified and characterized the electrical responses of all the retinal neurons. His was a spectacular thesis reporting for the first time that there are both ON- and OFF-center bipolar cells, that bipolar cells have a center-surround organization, and that many amacrine cells respond transiently at the onset and offset of illumination. His results were published in the *Journal of Neurophysiology* (Werblin & Dowling 1969).

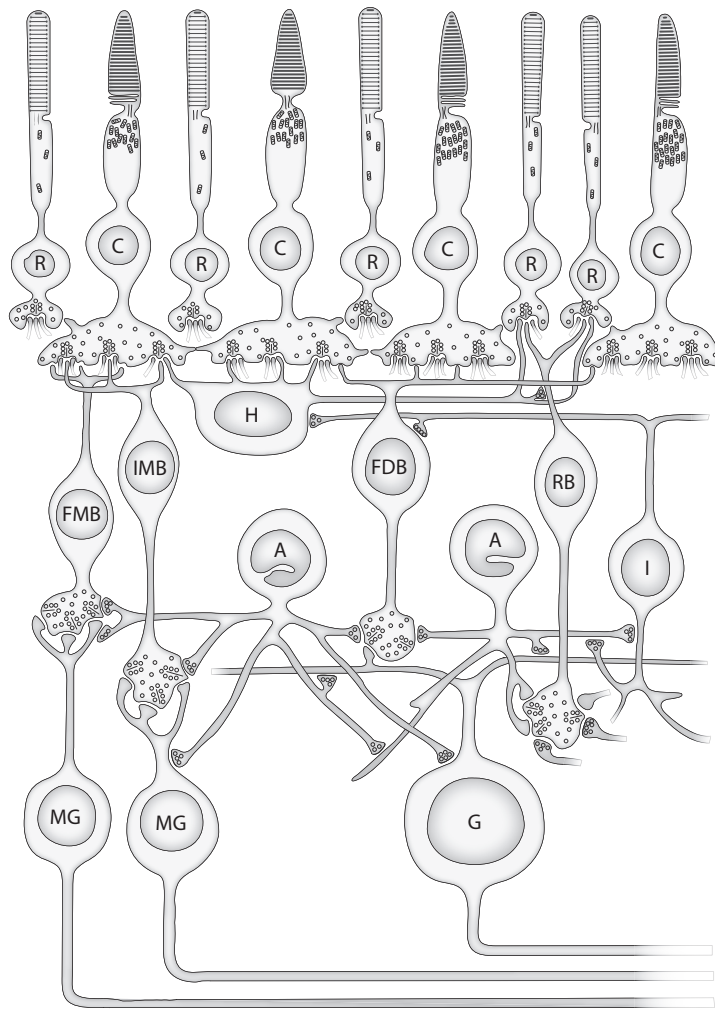


Figure 2

A simplified summary diagram, developed from the mid-1960s to the 1990s of the synaptic organization of the central (parafoveal) region of the primate retina. Rod (R) and cone (C) photoreceptor terminals make small gap (electrical) junctions with each other as well as chemical synapses with midget bipolar (MB), diffuse bipolar (DB), rod bipolar (RB), and horizontal cells (H). OFF bipolar cells [flat MB (FMB) and flat DB (FDB)] make flat (basal) contacts with the cones, whereas ON bipolar cells [invaginating MB (IMB) and RB] and horizontal cells make invaginating, ribbon-associated contacts with the photoreceptor terminals. Horizontal cell dendrites contact several cone terminals while their axons contact several rod terminals. In the inner retina, OFF and ON MB cells (FMB and IMB) contact midget ganglion (MG) cells, whereas DB cells contact the larger, parasol ganglion (G) cells, as well as amacrine (A) cells, all at ribbon synapses. The A cells make conventional synapses back on bipolar terminals and forward synapses onto G cell dendrites and other A cells. The RB cells do not contact G cells directly but through a specific type of A cell. Interplexiform (I) cells receive input in the inner retina and synapse on horizontal and bipolar cells in the outer retina. Figure adapted from Dowling (2012).

In the meantime, I was continuing my anatomical studies, first on the frog retina and then on mudpuppy (Dowling 1968b, Dowling & Werblin 1969). Clearly, retinas vary in their synaptic circuitry, and I began to explore whether the variations in synaptic circuitry could be correlated with complexity of ganglion cell responses. It had been appreciated for some time that cold-blooded vertebrates such as frogs had many ganglion cells with complex receptive field properties such as movement and direction sensitivity (Barlow 1953, Maturana et al. 1960). This must be correlated with differences in circuitry, but how?

Electron microscopy studies showed that there were many more amacrine cell (conventional) synapses than bipolar (ribbon) synapses in the frog IPL compared with primates, and that there were abundant serial and reciprocal synaptic arrangements made by the amacrine cell processes in the frog retina (Dowling 1968b). This implicated the amacrine cells in playing a pivotal role in generating complex ganglion cell responses such as movement and direction selectivity. Werblin's recordings from amacrine cells, showing that many of them respond transiently at the onset and offset of illumination (that is, they are highly movement sensitive), strongly supported this interpretation. Mark Dubin (1970), another Johns Hopkins graduate student, eventually extended these studies to a number of species, providing quantitative measurement of synaptic frequencies and densities in the IPL.

THE MARINE BIOLOGICAL LABORATORY

Horseshoe Crabs and Skates

The years at Johns Hopkins were exceptionally productive and fruitful. I did miss teaching, although I was an affiliate member of the biophysics department on the Homewood Campus and taught a graduate seminar there. One day, Francis "Spike" Carlson, chairman of the biophysics department, called to say that the Marine Biological Laboratory (MBL) wished to establish a neurobiology course and asked whether I would consider teaching such a course there. I knew little of the MBL, so Spike suggested I spend a summer in Woods Hole, Massachusetts, and become acquainted with the Laboratory. That I did, beginning in the summer of 1967, and I have been returning to Woods Hole and the MBL ever since.

That first summer, I met Michael Bennett. We joined forces and started the MBL Neurobiology course in 1970, which has been a mainstay there ever since. Typically, course directors at the Laboratory "retire" after five years, and this we did, turning the course over to Edward Kravitz in 1975. In the mid-1980s, David Papermaster and I initiated a short, two-week course called Molecular Aspects of Vision, and then in 1992, Nancy Hopkins and I started a short course called Genetics and Neural Development in Zebrafish. No longer directing either course, I have continued to teach a laboratory session for both short courses until recently.

The first summer at the MBL I decided to learn how to record intracellularly from photoreceptor (retinular) and second-order (eccentric) cells in horseshoe crab eyes and discovered a second type of discrete potential in the retinular cells. This is a regenerative potential that serves as an amplifying mechanism, ensuring that the absorption of a single photon in the retinular cell results in the generation of a nerve impulse in the eccentric cell (Dowling 1968a). I spent a second summer recording from the horseshoe crab eye, but then the following summer began another exceptionally fruitful collaboration with Harris Ripps, then at New York University and later at the University of Illinois School of Medicine in Chicago. Harris was an expert in visual pigment measurements and also had a long-standing interest in light and dark adaptation. We surmised that studying these processes in an animal that had only rods could be useful, and the early literature suggested that certain marine elasmobranchs, including dogfish, had only rods. We looked at dogfish but discovered they have some cones. However, the other common elasmobranchs in Woods

Hole, skates, did turn out to have pure rod retinas, and we spent nearly a decade of summers studying the retina of these animals and mapping out light and dark adaptation processes at all levels of the retina (Dowling & Ripps 1970, 1971, 1972, 1976, 1977; Green et al. 1975). The photoreceptors in skate, although being classic rods in the dark-adapted retina, adopt cone-like behaviors when the eye is light adapted. Many of the features of photoreceptor light and dark adaptation were first revealed in skate, and we showed that adaptation mechanisms proximal to the receptors are at play. Another important finding we made in skate was that horizontal cells hyperpolarize and lose light responsiveness when synaptic transmission from the photoreceptors is blocked with Mg^{2+} (Dowling & Ripps 1973). This provided direct evidence that the photoreceptors release an excitatory neurotransmitter in the dark and that the hyperpolarizing response of horizontal cells in the light is due to a decrease in transmitter release from the photoreceptors. Harris and I eventually published 14 papers based on our collaborative efforts during those summers.

I continued to maintain a summer laboratory at the MBL until the mid-1990s, when my laboratory began to raise zebrafish in the Biological Laboratories at Harvard. It then became difficult to justify setting up a summer laboratory at the MBL when we had more fish at Harvard (~30,000) than were available at any one time at the MBL. I continued to come to the MBL to teach and write, and for ten years (1998–2008) I was involved administratively at the Laboratory, serving as president of the corporation.

THE LATER WILMER YEARS

Functional Retinal Organization

Many students and postdoctoral fellows eventually joined the laboratory at Johns Hopkins and contributed significantly. Bob Frank, an ophthalmology resident, looked at the effects of rhodopsin photoproducts on visual sensitivity (Frank & Dowling 1968). Dwight Burkhardt (1969, 1970) discovered a new extracellular potential in the frog retina, the proximal negative response, and provided evidence that it derives from amacrine cells. Bob Miller recorded intracellularly from the glial (Müller) cells in the mudpuppy retina, found that they respond when the retina is illuminated, and provided evidence that Müller cell responses contribute to the ERG (Miller & Dowling 1970).

Leslie Fisher and Steven Fisher explored synaptic circuitry in the tadpole eye and cat eye, respectively. Les (LJ Fisher 1972) showed there are significant changes in retinal synaptic organization during metamorphosis, and Steve (SK Fisher 1972) demonstrated cat amacrine cells can make direct somato-somatic synapses on bipolar cells in the IPL. Gus Aguirre, a veterinarian, came to the laboratory to study dogs with inherited retinal degenerations, and Dick Chappell undertook a study of the dragonfly ocellus, thought to be a “simple” retina. He recorded the electrical responses of the ocellar cells, and I examined the fine structure of the photoreceptors and synapses made in the ocellar synaptic plexus (Chappell & Dowling 1972, Dowling & Chappell 1972).

Pat Sheppard had joined our laboratory shortly after I had arrived in Baltimore and served as its technician, accountant, artist, cook, and procurer of material and whatever. She cut marvelous sections for both light and electron microscopy and was responsible for all the drawings we published. She fed us well before seminars and always seemed able to find what we needed for our experiments. The only time I saw her flustered was when Brian dashed in one day to ask whether she could get him a box of rubbers. She did not know that in England, “rubbers” are erasers. Pat ended up working for me for 27 years—retiring in 1991.

The Association for Research in Vision and Ophthalmology (ARVO) meeting (then the ARO meeting) became a mainstay for the laboratory beginning in the late 1960s. Until 1968, it was a small, mainly clinical meeting, but the ARO Trustees wanted it to expand. Several of us were asked how this might be done, and we proposed organizing sections that would represent various areas

of eye and vision research. Paul Witkovsky, from New York University, who had been spending time with us learning electron microscopy (Witkovsky & Dowling 1969), and I organized a section on visual electrophysiology. The ARVO meeting eventually expanded beyond all expectations and now attracts each year about 12,000 vision researchers to its annual meeting. In 1970, I was given the Friedenwald Award by ARVO and I presented an overview of our laboratory's research to the attendees. It was well received and the published paper remains one of the most satisfying I have written (Dowling 1970).

In mid-1970, I was asked by the Harvard biology department whether I would like to return as full professor. It was a hard decision. Not only had Johns Hopkins been generous to me, but the research had been going exceptionally well and many excellent students and postdoctoral fellows were coming to the laboratory. The deciding factor was the opportunity to teach undergraduates again and to be involved in college life. I returned to Harvard in June 1971, and that is where I have been since.

THE HARVARD YEARS

1970s: Dopamine, Pharmacology, and Interplexiform Cells

Many people came with me to Harvard, including Pat Sheppard, Gordon Fain, Jochen Kleinschmidt, and Roger West. Ralph Nelson, a graduate student in the biophysics department, decided to stay in Baltimore to finish his degree and his experiments on the electrical properties of mudpuppy retinal neurons (Nelson 1973). At Harvard, Gordon recorded intracellularly from the mudpuppy photoreceptors and showed definitively that rods are about 25 times more sensitive to light than cones are (Fain 1975, Fain & Dowling 1973). Jochen examined adaptation in gecko photoreceptors recorded intracellularly (Kleinschmidt & Dowling 1975), and Roger undertook an analysis of the photoreceptors and synaptic input onto the ganglion cells in the ground squirrel retina (Green & Dowling 1975; West & Dowling 1972, 1975).

In 1973, a visitor from Sweden joined the laboratory for a two-month stay, and once again a marvelous collaboration began that added another dimension to our research that continued for many years. Berndt Ehinger, an ophthalmologist, was interested in retinal pharmacology, especially in retinal monoamines. He was an expert with the Falk-Hillarp method, which causes cells containing monoamines to fluoresce. He and others had observed what appeared to be a new type of cell in fish and New World monkeys that sits among the amacrine cells but extends processes into both plexiform layers of the retina. The color of the fluorescence suggested these cells contain dopamine. But what are their synaptic connections? Berndt came to the laboratory to find out.

To identify the processes of the cells observed with the electron microscope, we took advantage of the fact that cells containing monoamines have robust reuptake systems that do not discriminate between the natural transmitter and certain analogs that can alter the fine structural appearance of the synaptic terminals. By feeding fish retinas one such analog, we were able to identify the synapses made by these cells and show the cells are centrifugal in nature. They receive input in the inner plexiform layer, whereas the bulk of their output is in the outer plexiform layer on horizontal cells. These cells were eventually called interplexiform cells, and they and dopamine were studied in our laboratory for many years (Dowling & Ehinger 1975, 1978).

Much of our work during the 1970s was physiological or anatomical and was carried out on both goldfish and skate retinas. As the questions we were asking became more sophisticated, it became clear that we needed to know more about the molecules involved in synaptic transmission, particularly those involved in retinal neuromodulation. I was eligible for a sabbatical leave in

1978—my first at Harvard—and so I went to Cambridge, England, for the year to work in Les Iversen's laboratory. I was awarded a Guggenheim Fellowship for the year and stayed at Churchill College, where I was an Overseas Fellow. It was a marvelous year; I worked closely with Keith Watling, a young postdoctoral fellow in Les's laboratory, on the generation of cyclic AMP in the retina (Watling et al. 1979). Watling came to the other Cambridge to work in my laboratory in the early 1980s, so our collaboration continued for several years (Dowling & Watling 1981, Watling & Dowling 1981).

Dopamine acts as a classic neuromodulator on horizontal cells, binding to D1 receptors and activating adenylate cyclase through a G protein (Van Buskirk & Dowling 1981). The resulting increase in cyclic AMP activates protein kinase A (PKA), which modulates both gap junctional and glutamate channels in horizontal cells (Knapp & Dowling 1987, Lasater & Dowling 1985). Since those early days, the study of dopamine in the retina has become a virtual industry. Every retinal cell type responds to dopamine, and there are a variety of dopamine receptors in the retina whose activation can either increase or decrease cyclic AMP levels (see Dowling 2012). The story gets more complicated every year, and we still do not have a complete grasp of dopamine's overall role in the retina. Indeed, it appears dopamine plays multiple roles.

Work in the laboratory during the 1970s was not focused entirely on dopamine and dopaminergic mechanisms. Curiosity about other neuroactive substances in the retina led us to study amino acids as the principal excitatory and inhibitory neurotransmitters in the retina. Sam Wu (Wu & Dowling 1980), Mickey Ariel (Ariel et al. 1984), Randy Glickman (Glickman et al. 1982), Stewart Bloomfield (Bloomfield & Dowling 1985a,b), and Ido Perlman (Perlman et al. 1989a,b) contributed here, as did Berndt Ehinger (Ehinger et al. 1988), who for many years paid us an annual visit. David Pepperberg and Stuart Lipton continued the work on photoreceptor adaptation, studying the effects of retinal, Ca^{2+} , and the cyclic nucleotides on these cells (Lipton et al. 1977a,b; Pepperberg et al. 1976), while Geoffrey Gold, a physics graduate student at Harvard, carried out beautiful experiments on the electrical coupling between photoreceptors (Gold 1979, Gold & Dowling 1979).

When I arrived back at Harvard in 1971, it was understood that I would teach a course in neurobiology. There were no neurobiologists in the department, but faculty from the Medical School did teach an advanced introductory neurobiology course for juniors and seniors. I decided, however, to teach a course for freshmen and sophomores who had little college science experience, so that they could explore neurobiology more deeply in their later years. Called Biology 25, it became quite popular and I ended up teaching it for 31 years, until Josh Sanes and Jeff Lichtman came to Harvard. Initially, David Hubel and Dick Sidman from the Medical School taught with me, but first Dave dropped out and then Dick; so I taught it by myself for many years. Harvard Medical School faculty did teach some upper-level neurobiology courses as did some junior faculty members in the department, so interest in neurobiology began to grow among the undergraduates.

I was elected a member of the National Academy of Sciences (NAS) in 1976 and was soon asked to join the Assembly of Life Sciences, the committee that oversaw the studies of the life sciences carried out by the National Research Council (NRC). In 1985, I was asked to chair the committee, now known as the Commission of Life Sciences, and subsequently was elected a member of the Academy's Council (1993–1996). I was also, from 1994 to 1997, a member of the governing board of the NRC, and so for several years I was going to Washington, DC, about once a month.

The 1980s: White Perch and Neuromodulation

As my laboratory's interests became more pharmacological, we needed a system simpler than the whole retina to understand how neuroactive substances were affecting neurons at the cell and

molecular levels. Other laboratories were isolating and culturing retinal neurons, and this seemed to be a promising approach. We first isolated neurons from goldfish or carp retinas, but the results were disappointing. Although the neurons would survive in culture for several days, they would usually round up and it was difficult to distinguish subtypes of cells. Nevertheless, we were able to make a number of important observations with them. Rick Lasater, for example, showed that cultured carp horizontal cells respond selectively to L-glutamate but not to L-aspartate, providing some of the early evidence that the photoreceptor transmitter is L-glutamate (Lasater & Dowling 1982). Robert Van Buskirk made partially purified carp horizontal cell preparations by velocity sedimentation procedures that enabled him and others in the laboratory to study the effects of dopamine, vasoactive intestinal peptide, and other substances on the generation of cyclic AMP in these cells (Lasater et al. 1983, Van Buskirk & Dowling 1981). At the MBL, Lasater, Ripps, and I isolated skate retinal neurons and recorded from both horizontal and bipolar cells, but cultured skate horizontal cells, like carp horizontal cells, tended to round up in culture (Lasater et al. 1984).

In the summer of 1981, I decided to spend my time at the MBL seeking a fish whose neurons would culture better. On my first day in the laboratory, I cultured neurons from the retinas of fish abundant in the pond on which we lived. I'll never forget my first look at the cultured white perch neurons; they were spectacular! I could, for example, identify four types of horizontal cells, and the cells maintained their shape for days to weeks. I spent the rest of the summer trying other fish, but none worked as well as the white perch (Dowling et al. 1985).

The white perch retina became the mainstay preparation in our laboratory for more than a decade. We would journey down to Woods Hole and collect 200–300 fish each fall from Oyster Pond to use throughout the winter and spring. Several important observations were made in the 1980s and early 1990s both with isolated retinal neurons and with the intact retina. Rick Lasater and I showed that strong electrical coupling occurs between overlapping pairs of horizontal cells of the same morphological type but not between overlapping pairs of cells of different morphological types, and that dopamine decreased the conductance of the electrical junctions of the coupled cells (Lasater & Dowling 1985) (**Figure 3**). Subsequently, Douglas McMahon and Andrew Knapp demonstrated that the reduced conductance induced by dopamine was the result mainly of a reduced open time of the gap junctional channels (McMahon et al. 1989).

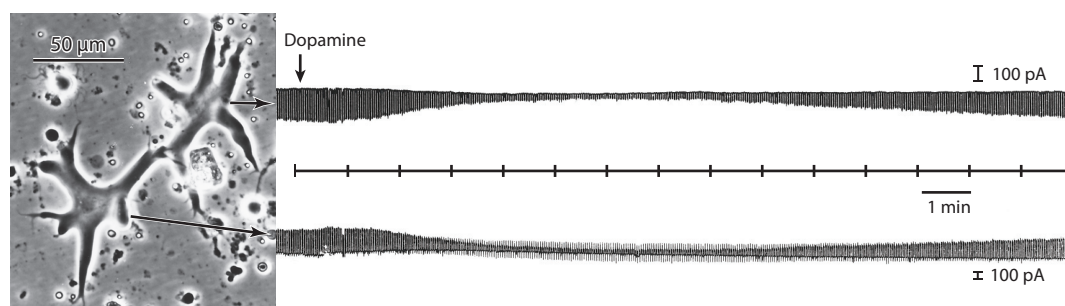


Figure 3

Effects of dopamine on an electrically coupled pair of white perch horizontal cells maintained in culture (*left*). Both cells were voltage-clamped at -60 mV with patch electrodes, and current pulses were applied to the driver cell (*lower trace*) to shift the membrane potential $+20$ mV. Ringer solution containing dopamine was applied briefly (0.5 s) to the cell pair. The cells uncoupled, as shown by the decrease in magnitude of the current pulses required to depolarize the driver cell by 20 mV (*lower trace*), which reflects the increase of resistance of the driver cell; and the decrease in magnitude of the current pulses passed into the follower cell (*upper trace*), which reflects the decreased conductance of the junctional membrane. Figure adapted from Lasater & Dowling (1985) with permission.

In the mid-1980s, it was generally believed that the principal effect of dopamine on horizontal cells was to modify the electrical coupling between adjacent cells. However, first Bill Hedden and then Stuart Mangel in our laboratory showed that dopamine reduced the responsiveness of horizontal cells to light in the intact fish retina when full-field illumination was used (Hedden & Dowling 1978, Mangel & Dowling 1985). This effect of dopamine cannot be explained by reduced coupling between cells, and so Andy Knapp looked to see whether dopamine affected the horizontal cells' responsiveness to the photoreceptor transmitter, L-glutamate. He found that dopamine greatly enhances L-glutamate-gated conductances in cultured white perch horizontal cells, the first direct evidence for dopamine modulation of excitatory amino acid neurotransmission in the vertebrate central nervous system (Knapp & Dowling 1987). Subsequently, Andy Knapp and Karl Schmidt (Knapp et al. 1990) showed that dopamine exerts this effect on the glutamate channels by increasing the channel opening probability in response to a given concentration of agonist, and that dopamine also increased the duration of the channel open times somewhat. At about the same time, Emily Liman, as a rotating graduate student, showed that the enhancement of the excitatory amino acid currents in the horizontal cells was mediated via a cyclic AMP-dependent kinase (PKA) (Liman et al. 1989).

The work of Stuart Mangel and subsequently of Xiong-Li Yang, Kristina Tornqvist (Yang et al. 1988), and William Baldrige (Baldrige et al. 1995) stimulated another line of research that continues to this day. Following prolonged dark adaptation, horizontal cell responses are suppressed, and light is needed to sensitize the cells. The extent of dark suppression of horizontal cells is influenced by the time of day, and from these observations, Mangel has demonstrated in his own laboratory circadian clock regulation of rod and cone input to horizontal cell responses and other retinal neurons as well as retinal circuitry (Mangel et al. 1994, Ribelayga et al. 2002). The effects of dopamine on retinal cells are many and complex; indeed, effects of dopamine on every retinal cell type have been reported.

Two other studies from our laboratory utilizing white perch neurons deserve mention. First, using cultured neurons, Haohua Qian discovered a novel GABA response in the rod (H4) horizontal cells of the white perch (Qian & Dowling 1993) and later in bipolar cells (Qian & Dowling 1995). This non-desensitizing, bicuculline-resistant GABA response was subsequently shown to be the result of activation of ligand-gated channels made up of rho (ρ) subunits. These ligand-gated channels have been called GABA_C receptors and appear to play an important role in the visual system. Isolation and cloning of the genes for the rho receptors in the white perch was accomplished by Qian, first working in our laboratory and later with Harris Ripps in Chicago (Qian et al. 1997, 1998). Second, George Grant used slices of the white perch retina to study the generation of ON bipolar responses. It has long been known that the ON bipolar cell response generated by cones in fish is different from the ON bipolar cell response generated by rods and cones in other animals. The latter response is the result of activation of a metabotropic glutamate receptor that through a G protein keeps cation channels in the bipolar cell membrane closed. In the light, as glutamate release from the photoreceptors decreases, the channels open and the cells depolarize. But the fish cone ON bipolar cell response is different; glutamate released in the dark hyperpolarizes the cell and the ON light response results from relief of the hyperpolarization. Grant found that glutamate hyperpolarizes the bipolar cells by activating a glutamate transporter linked to a Cl⁻ channel (Grant & Dowling 1995, 1996). In the dark, Cl⁻ enters the bipolar cell, thus hyperpolarizing it. When the transporter is no longer activated by glutamate (i.e., in the light) and Cl⁻ no longer enters the cell, it depolarizes. This is a novel mechanism of generating a postsynaptic response, and it will be of interest to see whether this mechanism occurs elsewhere in the brain. Kwoon Wong, a graduate student in the laboratory, followed up and extended Grant's

work (Wong & Dowling 2005), eventually publishing three papers on the subject (Wong et al. 2004, 2005a,b).

In the mid-1980s, I was eligible for another sabbatical and decided to use the time to write a book on the retina—namely, about where we were in understanding this model piece of the brain. My wife, Judith, was in the East Asian studies graduate program at Harvard, focusing on Japan, and so the leave was taken in Okazaki, Japan, where two outstanding retinal researchers worked, Ken-Ichi Naka and Aki Kaneko. I much enjoyed my time there and writing the book *The Retina: An Approachable Part of the Brain*, published by Harvard University Press (Dowling 1987). I also had the opportunity in Naka's laboratory to participate in two interesting projects, one that demonstrated ganglion cell dendrites in the catfish retina are presynaptic in the IPL (Sakai et al. 1986) and one that demonstrated cultured catfish horizontal cells form synapses (Hidaka et al. 1989).

In the 1980s, I was also becoming more involved in Harvard College administration. Following a stint as chair of the biology department in the mid-1970s and election to the Faculty Council, I was asked by the dean of the faculty, Henry Rosovsky, to serve as associate dean for the Natural Sciences, which I did from 1980 to 1984. However, the longest and most satisfying administrative post I held at Harvard was as Master of Leverett House, one of the residential houses for undergraduates that included 360 undergraduates and about 150 faculty and administrators. Harvard students spend three of their four years in the same House, so it gave me and Judith, Co-Master, the opportunity to get to know well many undergraduates, some of whom are friends to this day. We served as Co-Masters from 1981 to 1998.

Writing also consumed time. There being no suitable textbook for my introductory neurobiology course, Biology 25, I wrote *Neurons and Networks: An Introduction to Behavioral Neuroscience*, which was reasonably successful (Dowling 1992).

1990s: Zebrafish, Genetics, and Development

Toward the end of the 1980s, the white perch in Oyster Pond began to disappear, and so we cast around for a substitute fish. The closest relative to the white perch readily obtainable was the hybrid striped bass. These fish, a cross between striped bass and white bass (essentially landlocked white perch), were being raised for commercial purposes, and a large fishery raising them operated in western Massachusetts. When we began to use them in our experiments, I was astonished how consistent our results became. Why? The obvious answer was that all these fish were raised under identical conditions, were of the same age, and were of the same genetic stock. It seemed clear to me that carrying out experiments on animals whose genetics, age, and environment could be controlled, rather than on animals from the wild, was the way to go.

Zebrafish as an experimental model were introduced in the 1970s by George Streisinger at the University of Oregon, but it was not until the mid-1980s that several groups recognized their potential. We began to examine the eyes of zebrafish at that time, first looking at retinal development (Schmitt & Dowling 1994, 1996, 1999) and then at the effects of retinoic acid on eye development. The latter work found that retinoic acid is critical for early retinal development, especially the ventral retina (Hyatt et al. 1992, 1996; Marsh-Armstrong et al. 1994); too much retinoic acid at an early stage of eye development results in an apparent duplication of the retina, whereas block of retinoic acid synthesis early on results in an eye with no ventral retina. These experiments were some of the first to show that the ventral and dorsal parts of the retina are distinct with regard to development.

A collaboration with Walter Gilbert's group at Harvard was undertaken to determine whether we could mutagenize zebrafish using insertional viral methods. In this we failed, but in the early

1990s, efficient methods for chemically mutagenizing zebrafish had become available and Susan Brockerhoff, James Hurley, and Jim Fadool began to look for functional and developmental mutations in zebrafish that were eye specific. To this end, Sue (Brockerhoff et al. 1995) developed a behavioral test, based on the optokinetic reflex, that enabled her to examine visual function in five-day-old larval fish. She eventually isolated many mutants that were completely, partially, or even color-blind (Brockerhoff et al. 1997). Jim Fadool isolated several developmental mutants (Fadool et al. 1997), a number of which were worked on subsequently by newer members of the team, including Brian Link and Tristan Darland (Link & Darland 2001; Link et al. 2000, 2001). A second behavioral test, based on the escape response, was developed by Lei Li, another postdoctoral fellow, that enabled us to examine visual behavior in adult fish (Li & Dowling 1997). Fish with slow inherited retinal degenerations were found by Brian Perkins with this test (Perkins et al. 2005), which also permitted Lei to study dark adaptation and the effects of the circadian clock on visual responsiveness in zebrafish (Li & Dowling 1998).

In the late 1990s, I wrote a second edition of *Neurons and Networks* (Dowling 2001), but by then, other undergraduate textbooks had appeared and so I decided to focus on writing more for the general public. That resulted in *Creating Mind: How the Brain Works* (Dowling 1998), which remains in print to the present time and has done quite well. I followed that with *The Great Brain Debate: Nature or Nurture?* (Dowling 2004b).

2000 Onward

Zebrafish physiology and color vision. We continued to work intensively on zebrafish until 2015, and they had much to teach us. Not only can the ERG be recorded from the zebrafish eye, but Farida Emran succeeded in recording single-unit responses from the ganglion cells in five-day-old fish (Emran et al. 2007). The animals are only 3 mm long at this stage of life and the eyes only 250–300 μm in diameter. When we first began working on the mudpuppy, I was concerned by their small eyes—about 4 mm in diameter. We were now recording from single retinal neurons in an animal that could fit inside the mudpuppy eye! A number of papers by Brenda Allwardt (Allwardt et al. 2001), Jeffrey Gross (Gross et al. 2005), Yuk Fai Leung (Leung et al. 2008), Jonathan I. Matsui (Matsui et al. 2006), Daisuke Kojima (Kojima et al. 2008), and Pamela Kainz (Kainz et al. 2003), among others, came from our work (**Figure 4**).

Another attraction of zebrafish is its magnificent color vision. Zebrafish have four cone types that absorb maximally in the red, green, blue, and ultraviolet (UV) regions of the spectrum (Robinson et al. 1993). Further, the cones are arranged in a precise mosaic; rows of blue- and UV-sensitive cones encompass alternating rows of double red- and green-sensitive cones. This enabled Yong Li to work out the precise circuitry among the four types of cones and three types of cone horizontal cells (Li et al. 2009), and then the circuitry between the photoreceptors and bipolar cells (Li et al. 2012). And what do the animals use their UV photoreceptors for? Young zebrafish use their UV receptors to avoid UV light, which damages them. Indeed, if exposed to UV light, up to 70% of wild-type fish die before they reach 10 days of age as shown by Saul Nava (unpublished data).

I had another sabbatical coming in 2008 and spent a delightful semester in Santa Barbara in Steven Fisher's laboratory. My main objective was to write the second edition of *The Retina* (Dowling 2012). In 2008, I was approached by Alfred Sommers, former dean of the School of Public Health at Johns Hopkins and distinguished ophthalmologist, who asked whether I would consider chairing a new initiative on vision, jointly sponsored by the Lasker Foundation of New York and the International Retinal Research Foundation (IRRF) of Birmingham, Alabama. The idea was to examine major eye diseases from a multidisciplinary point of view and to see whether

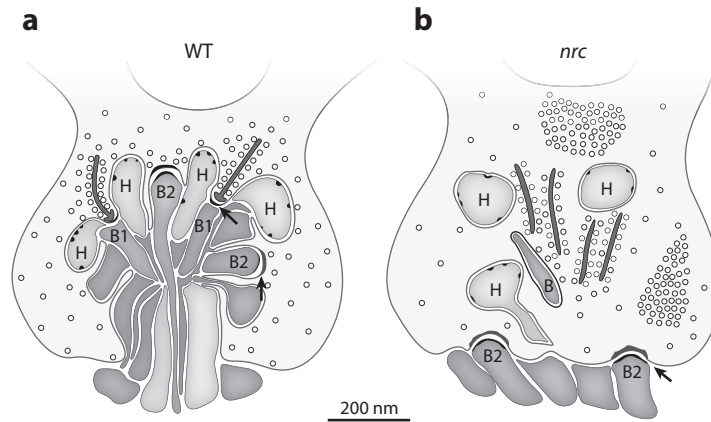


Figure 4

Drawings of cone photoreceptor terminals in (a) a WT control and (b) a mutant zebrafish. The processes from second-order bipolar cells fail to penetrate into the terminal to form the classic triadic ribbon synapses (see **Figure 2**). Thus, no ON bipolar cells are activated by the terminal but OFF bipolar cells that receive input at the flat contacts are. Interestingly, in the normal photoreceptor, the flat contacts are found within the single large invagination in the cone terminal, but in the mutant, the flat contacts are present along the base of the terminal as is the case in mammals. No other significant alterations in the mutant retina in either the outer or the inner plexiform layers were observed. Recordings from the retinas of many animals indicate that ON bipolar cells are activated at the ribbon synapses, whereas the OFF bipolar cells are activated at the flat, basal contacts. Recordings from the mutant retina confirm this dichotomy—more than two-thirds of the ganglion cells respond to light with only an OFF response, whereas in controls, only about 15% of the ganglion cells show only an OFF response. Interestingly, the animals behaviorally do not show the OKR, indicating that ON bipolar cells and ON ganglion cells are required for the fish to detect the movement required for the OKR. Abbreviations: B, bipolar cell dendrite; H, horizontal cell process; OKR, optokinetic reflex; WT, wild type. Figure adapted from Emran et al. (2007) with permission.

understanding and therapies of major visual disorders could be advanced. The initiative was to last for 10 years. We first studied glaucoma and the possible involvement of reactive astrocytes in the disease. Two workshops were held in Woods Hole with a diverse group of scientists and were followed by a plenary session with the same group and others at the Janelia Farm Center of the Howard Hughes Medical Institute the following spring. Our first report was published in 2010, and a second report, on diabetic retinopathy in 2012. Our third study, “Restoring Vision to the Blind,” was our most ambitious, and it was published in 2014. Our final report on amblyopia was published in 2017. All these reports are available on the Lasker Foundation website (<http://www.laskerfoundation.org/programs/lasker-irrf-initiative-innovation-vision-science/>).

These studies introduced me to clinical ophthalmology, about which I knew little, and encouraged me to join forces with my brother, an ophthalmologist, to write a book titled *Vision: How It Works and What Can Go Wrong* (Dowling & Dowling 2016). It is intended for the public, the basic scientist who would like to know more about major eye problems, and the clinician who wishes to catch up on our present understanding of how we see.

While involved with the Lasker/IRRF Initiative, I was asked by Marty Friedlander whether I would join the Board of Scientific Governors of the Lowy Medical Research Institute, which is concerned with a rare type of macular disease called macular telangiectasia, or MacTel. This experience has also expanded my experience with clinical ophthalmology and is leading me to a study of the disease.

CONCLUDING REMARKS

I closed my laboratory in 2015, and I am now a research professor at Harvard, which means I can do pretty much what I want (Harvard no longer pays me). I continue to teach a freshman seminar called *The Amazing Brain*, and I am writing the second edition of *Creating Mind*.

But what has me most excited is a research project I am undertaking with Jeff Lichtman and his colleagues at Harvard, along with Dennis Dacey and Rachel Wong of the University of Washington, to reconstruct the human fovea. Jeff and his colleagues have developed connectomic methods to reconstruct neural tissue down to the synapse level, and the fovea is an ideal place to do such a reconstruction. So far, we have been reconstructing a fovea from a normal young man, but Charles Zucker and I are also reconstructing eyes from MacTel patients (with support from the Lowy Medical Research Foundation). I am returning, if you will, to my early days at the Wilmer, when Brian Boycott and I were studying the central primate retina. Back then, we could do little in the way of reconstruction because we were limited in the number of serial electron microscopic sections we could successfully image and analyze (20–50). Today, with the methods developed in the Lichtman laboratory, we can cut, image, and analyze up to 10,000 sections (Kasthuri et al. 2015)!

LESSONS LEARNED

What words of advice, if I may be so bold, can I offer to young investigators? I have enjoyed enormously my life in vision, and I have lived it in a golden time—when resources were plentiful and wonderful students and collaborators were many. I also feel I have been lucky in many ways, but when I hear from young investigators that today jobs are few, resources are limited, and the field overcrowded, I always say, “Yes, but there is always room for another good person in a field.” But how does one become good? Here is my list.

1. Be curious. Keep asking questions about a scientific observation, puzzle, or problem: How, what, where? Muddle over the possibilities: how to confirm something, what does it mean, where might it fit in?
2. Learn and use different methods and techniques to attack a problem. I began as a biochemist and then learned some electrophysiology. Anatomy (electron microscopy) followed, and then pharmacology, genetics, and behavior. Seek out the best way to solve a problem.
3. Have good collaborators, postdoctoral fellows, and students. In this regard I have been blessed. How does one attract such colleagues? Go to meetings and lectures, and meet people who interest you. Be open with them. Encourage and take advantage of their expertise, and join forces if possible.
4. Teach. It keeps you up to date. Reading and writing is important too; it broadens your horizons. Write to and respond to those doing interesting things.
5. Know when to start a line of research, but equally if not more important is to know when to abandon a line of research and move on to new ventures. After a satisfying result, it is tempting to continue extending that research, but too often the returns decrease. This, though, is a difficult decision to make, and I have a list of projects I continued for too long or stopped too early.
6. Ask big questions, but questions that can be approached. Dip your feet in with a new project, and try to decide early whether it might work.
7. Give postdoctoral fellows and graduate students the freedom to try new things with or without your approval. If they stumble, intervene to get them back on track, but treat them as independent collaborators, encouraging them continuously.

8. Enjoy what you are doing in the laboratory, when teaching or even writing. Your enthusiasm is sensed by colleagues and collaborators and makes the enterprise fun and satisfying.
9. Take advantage of opportunities you might be asked to undertake in scientific administration. For example, I have learned much about clinical problems and met so many interesting people over the past nine years while overseeing the Lasker/IRRF Initiative. And my years on NAS committees and Harvard committees also resulted in making new friends, and broadening horizons.

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