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JOHN E. DOWLING

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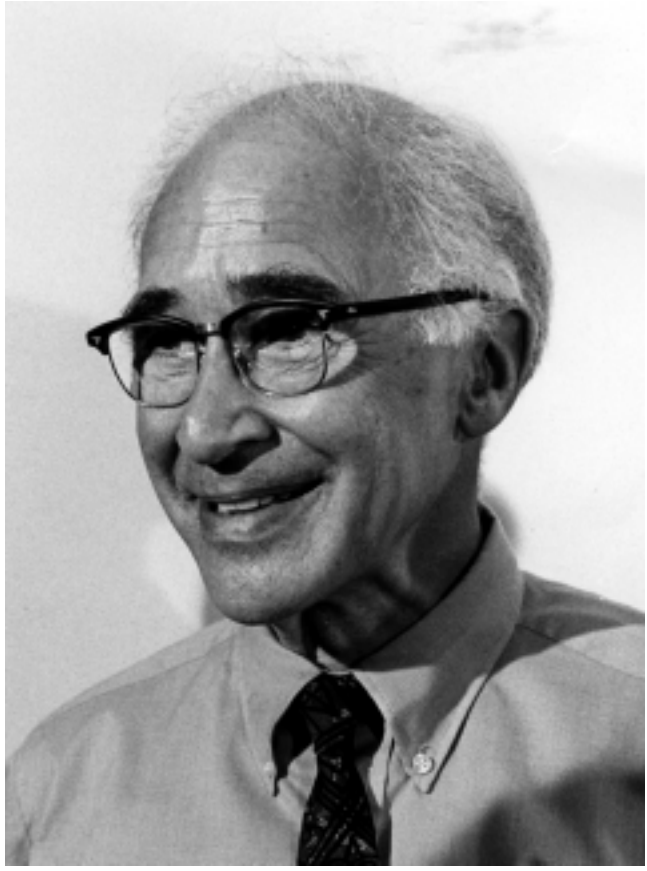

George Wald

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GEORGE WALD

November 18, 1906–April 12, 1997

BY JOHN E. DOWLING

BIOLOGY LOST ONE of its towering figures of the twentieth century with the passing of George Wald. A student of Selig Hecht, the major researcher in visual physiology of his generation, Wald unraveled the nature of the light-sensing molecules found in photoreceptor cells and was the dominant force in his field for over forty years. Beginning with postdoctoral research in the early 1930s, Wald showed that the visual pigment molecules consist of a protein (termed opsin) to which is bound a derivative of vitamin A (vitamin A aldehyde, now termed retinal). Retinal serves as chromophore for these molecules, absorbing the light and initiating conformational changes in the protein that lead eventually to the excitation of the photoreceptor cells. Wald's findings represented the first instance that a biochemical role for a fat-soluble vitamin was established and were widely recognized. Wald was elected to the National Academy of Sciences in 1950 and was awarded the Nobel Prize in physiology or medicine in 1967 for his monumental contributions to our understanding of the molecular basis of photoreception.

In addition to being a superb scientist, Wald was a marvelous teacher, lecturer, and writer. *Time* magazine named

him "one of the ten best teachers in the country" in a cover story published in 1966. He wrote and lectured on a wide variety of topics from the "Origin of Life" and "Life and Mind in the Universe" to political issues. The Vietnam War horrified him and, beginning in the mid-1960s until shortly before his death, he was deeply involved in anti-war and anti-nuclear activities. He considered his political actions as part of being a biologist: one who is concerned with life.

George Wald was born in New York City on November 18, 1906. The son of immigrant parents, he grew up in Brooklyn in a working-class neighborhood. His mother was from Germany, his father from Poland. He showed an aptitude for mechanical things and science from his youngest days. An early triumph was the successful construction of a crystal detector radio that enabled him and his neighborhood friends to listen to the 1919 World Series.

George went to Manual Training High School, now the Brooklyn Technical High School, which trained students to use their hands and to build things. He later felt this training was especially useful for his scientific career, as it enabled him to design and even to help build a variety of specialized equipment. Two interests stand out from his high school days: electricity and vaudeville. For a while he thought of electrical engineering as a career but a visit to Western Electric in New Jersey soured him on that path. With a high school friend, he organized a vaudeville act that they took to nearby Jewish community centers. His success as a performer suggested law as a possible career and so he entered college as a pre-law student at Washington Square College of New York University.

College was especially exciting for George; it introduced him to art, classical music, and literature and he became enamored of them all. In later years, he gathered a first-class collection of Rembrandt etchings and much indigenous

art from Africa and Central and South America. His college years were also broadening in another way: for two summers he worked onboard a passenger ship that traveled between New York and Buenos Aires. His pre-law studies, however, did not interest him. He felt he needed something "more substantial, more natural, more organic," and so he became a pre-medical student. By the time George was a college senior, medicine as a career also had lost its luster, but he happened upon Sinclair Lewis's *Arrowsmith* and was smitten by the possibility of doing biological research. He applied to Columbia University for graduate studies in zoology and was accepted.

The first year as a graduate student was again a watershed year for George. He took a genetics course with T. H. Morgan and met Selig Hecht, his future mentor. Hecht was well known for his studies on photosensory systems of both simple organisms, such as the worm *Ciona* and the clam *Mya*, as well as man. His quantitative measurements of the effects of light and dark on various organisms demonstrated that visual mechanisms conform to photochemical laws. Hecht (1919) introduced the notion that in photosensory systems, a photosensitive substance S is decomposed by light into products P and A (light adaptation) and that in the dark, P and A combine to reform S (dark adaptation). Wald and his co-workers would eventually set many of Hecht's concepts into precise molecular terms.

Not only did Hecht introduce Wald to vision but he had a profound influence on him. Upon receiving the Proctor Medal from the Association for Research in Ophthalmology in 1955, eight years after Hecht had died, Wald remarked,

> Hecht was a great teacher and physiologist. Also, he was one of those rare persons who sets a standard both at work and at leisure. I was fortunate in

having his instruction and later his friendship. I saw too little of him after leaving his laboratory, but I felt his presence always. What I did or said or wrote was in a sense always addressed to him.

As a graduate student, Wald worked on the visual performance of *Drosophila*. He found that in many ways fruitfly visual function resembles that of other animals, including man. With Hecht, he also investigated human dark adaptation. Although Hecht's research was concerned with the essential features of the photoreceptor process, he was not especially interested in the underlying molecules themselves, only their physicochemical relationships. Wald, on the other hand, very much wanted to lay his hands on these substances and for postdoctoral work chose to go to the laboratory of Otto Warburg in Berlin. Warburg was one of the great biochemists of the day and had just won a Nobel Prize.

Supported by a National Research Council Fellowship, Wald and his wife, Frances, arrived at Warburg's laboratory in 1932. This was the beginning of his *Wanderjahre*, which would take him to three distinguished laboratories and provide him the first and key insights into the structure of the visual pigments. Franz Boll had discovered the rod visual pigment in 1876. Boll (1877), as well as Willy Kühne (1878) in Heidelberg, described the effect of light on the substance. They showed the native pigment has a reddish-purple color, termed visual purple by Kühne and later called rhodopsin. In light the pigment bleaches to a yellowish-orange product (visual yellow) and then with time it fades to a colorless substance (visual white). Kühne also solubilized rhodopsin, with bile salts and showed it was a protein.

In Warburg's laboratory, Wald surmised that rhodopsin is a carotenoid-linked protein based on its absorption spectrum. He, therefore, took some retinas, extracted them with chloroform, and reacted the extract with antimony trichlo-

ride. The solution turned a bright blue color and had an absorption curve typical of vitamin A. Earlier work had established a link between vitamin A deficiency and nutritional night-blindness, but the nature of the link was unknown. Could it be that vitamin A played a direct role in the chemistry of rhodopsin and, thus, in the visual process?

Upon seeing these findings, Warburg suggested that Wald should go to Paul Karrer's laboratory in Zürich to confirm the result. Karrer had just elucidated the structure of vitamin A and β-carotene, showing that β-carotene consists of two end-to-end molecules of vitamin A minus two water molecules. In Zürich, Wald collected retinas from cattle, sheep, and pigs; extracted them with organic solvents; and with Karrer confirmed the presence of vitamin A in all of them. In three months the job was done and it was time to move on, now to Otto Meyerhof's laboratory in Heidelberg. Meyerhof was an expert in muscle biochemistry and had been awarded a Nobel Prize in 1922.

The Germany Wald returned to was fast becoming a hostile country, especially for Jews, and both Meyerhof and Wald were Jewish. Hitler had come to power at the end of January 1933, and the National Research Council soon decreed that George must return to the United States by the end of the summer. In the middle of the summer, however, a fortuitous situation arose that enabled George to make a quantum leap forward in the understanding of visual pigment biochemistry.

Everyone was away on holiday when a shipment of 300 frogs arrived in the laboratory. The assistant was about to release the frogs when George asked for them. Extracting the retinas with various solvents, he found that from dark-adapted retinas and retinas bleached to the visual yellow stage, he could detect a novel carotenoid that was similar to but distinct from vitamin A; for example, it was yellow in

color and when reacted with antimony trichloride had a different absorption spectrum. This substance he called retinene. From retinas in the visual white stage, no retinene was found; rather, there was abundant vitamin A. He then proposed a visual cycle: that retinene was bound to protein in native rhodopsin and was released by light to yield the visual yellow product. He further surmised that retinene was gradually converted to vitamin A, resulting in visual white, and that regeneration of rhodopsin represented the reverse process. He wrote a note to *Nature* suggesting these relationships and returned to the United States for a second year of fellowship in the Department of Physiology at the University of Chicago.

Wald assumed his first academic position as tutor in biochemical sciences at Harvard in 1934. He remained at Harvard his entire academic career, becoming instructor and tutor in biology in 1935, faculty instructor in 1939, associate professor in 1944, and professor of biology in 1948. His research at Chicago and initially at Harvard was to confirm in other vertebrates the visual cycle he had found in the frog. Wald was aware that Kühne and others had observed that the dark-adapted retinas of certain fish were a darker purple than were frog retinas, and so in the mid-1930s he began to study this and other questions in the summers at the Marine Biological Laboratory at Woods Hole. He returned to Woods Hole virtually every summer, teaching for many years in the famous physiology course and becoming eventually a trustee of the laboratory.

In Woods Hole, George found that the rod visual pigment of marine fishes is similar to that of frogs: their retinas contain rhodopsin and, when exposed to light, the rhodopsin releases retinene that is converted to vitamin A. Freshwater fish, he discovered, were somewhat different. Their rod visual pigment absorbed maximally at longer wave-

lengths of light and, when bleached, yielded a different form of retinene and vitamin A. He called this novel visual pigment porphyropsin, and the new carotenoids, retinene$_2$ and vitamin A$_2$.

From this work came an exploration of fishes that go back and forth between fresh and salt water. Salmon live in salt water but spawn in fresh water, whereas eels do the opposite. The result he found was that the vitamin A used and the visual pigment produced goes with the spawning environment. Salmon use vitamin A$_2$ and have porphyropsin in their retinas, whereas eels use vitamin A$_1$ (the more usual form of the vitamin) and make rhodopsin. Frogs, which spawn in freshwater but live on land, appeared to be different: their retinas contain rhodopsin. When George looked at tadpoles, he discovered that their retinas contain vitamin A$_2$, which is changed over to A$_1$ at metamorphosis. These experiments led him to start thinking about biochemical evolution and the molecular transformations that occur during metamorphosis, and about the origin of life. In later years, he wrote provocative articles on "The Significance of Vertebrate Metamorphosis," "Life in the Second or Third Periods; Or Why Phosphorous and Sulfur for High Energy Bonds," and "The Origin of Optical Activity."

Also in the mid-1930s, Wald turned his attention to cone vision. How do cone pigments differ from the rod pigments? Using chicken retinas, which have abundant cones, he was able to extract a visual pigment that absorbed maximally at longer wavelengths: a red-sensitive visual pigment. He called it iodopsin, but because it was always mixed with rhodopsin, he could not show unequivocally that iodopsin bleached to retinene and opsin. It was not until the mid-1950s that Wald and co-workers showed that iodopsin bleaches to retinene$_1$ and opsin. The conclusion could then be drawn that this cone pigment, like rhodopsin, uses vitamin A$_1$ and ret-

inene$_1$; it must differ from rhodopsin, therefore, in its opsin protein.

Wald's experiments on the visual pigments were interrupted by World War II, during which time he worked with Donald Griffin and others on applied vision research projects for the U.S. Army Board of Engineers. Infrared viewing devices were being developed to allow soldiers to see in the dark, but the prototype infrared searchlights gave off a dim red glow. Were the filters used in the searchlights defective or could humans see in the near-infrared? They discovered that, although human visual sensitivity falls rapidly at wavelengths beyond 700 nm, humans can see intense infrared light. At about 1000 nm, a warming of the skin is felt at the same time that the red glow is seen! Wald and Griffin also studied the spherical and chromatic aberration of the human lens.

At the conclusion of the war, Wald returned to studying visual pigment molecules. He was joined in this work by two individuals who were to play essential roles in his laboratory until he retired and who themselves became distinguished investigators; Ruth Hubbard joined the laboratory as a graduate student and was eventually to become George's second wife and Paul Brown became Wald's research assistant and long-time co-worker.

The next major advance in the visual pigment story came from the laboratory of R. A. Morton in Liverpool, who first surmised and then showed that retinene is vitamin A aldehyde (Ball et al., 1946). Eventually, retinene was renamed retinal and vitamin A retinol, the terms we now use. Shortly thereafter, Hubbard in Wald's laboratory worked out the enzymatic interconversion of retinal and retinol as her Ph.D. thesis, while Brown showed that rhodopsin could be generated simply by mixing retinal and opsin. This was a spontaneous reaction; no enzymes or energy source were required.

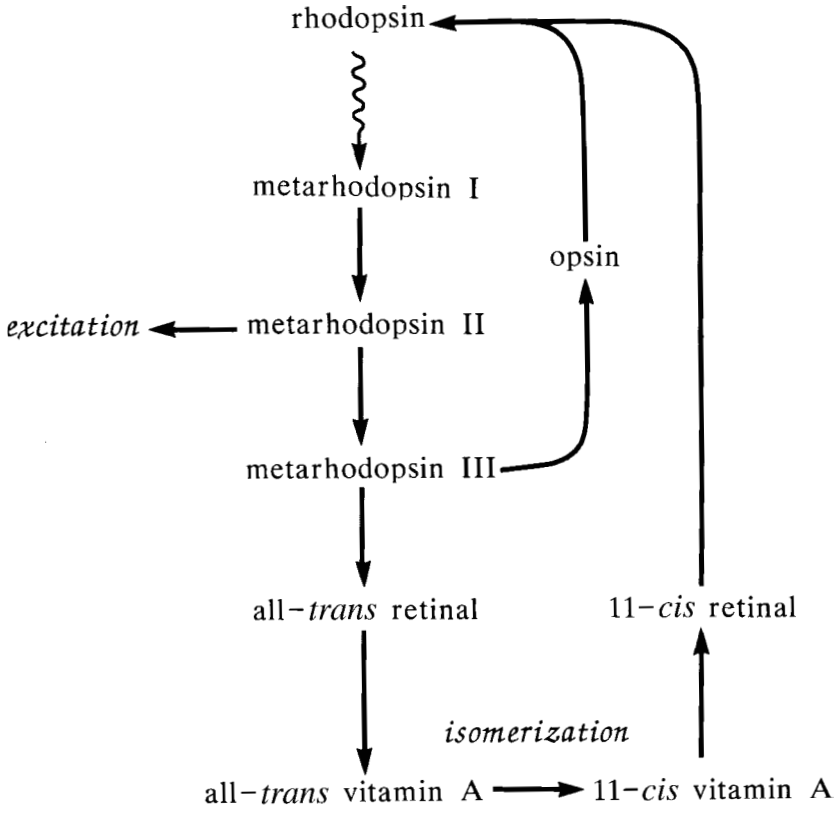
At this point, it was possible to assemble the components needed to synthesize rhodopsin in a test tube, including retinol, opsin, and the appropriate enzymes. An immediate puzzle was observed: whereas a light-sensitive, rhodopsin-like pigment was produced when retinol from fish oil was used, nothing happened when synthetic retinol was tried. What is different between retinol in fish oil and synthetic retinol? The answer turned out to be *cis-trans* isomerization. Carotenoids can assume different shapes depending on whether their double bonds are in a *cis* or *trans* configuration. Adding a trace of iodine to synthetic vitamin A in light promotes isomerization, and such retinol would form a light-sensitive pigment with opsin.

Wald, Hubbard, and Brown, working with several organic chemists, were able to show that one *cis* isomer, the 11-*cis* isomer, was precursor to all visual pigments. This isomer is not only bent, it is sterically hindered and twisted, which makes it particularly light sensitive and optimal as a visual pigment chromophore. A second *cis* isomer, 9-*cis*, will form a light-sensitive pigment, but with lower light sensitivity and a different absorption maximum. No other isomer works at all. This part of the story was completed by 1955 and was satisfying. Not only did it represent the first instance of a role for *cis-trans* isomerization in biology, it also meant that rhodopsin and other visual pigments could be quantitatively synthesized in the laboratory.

The focus of the Wald Laboratory then turned to the bleaching of rhodopsin. What does light do to rhodopsin and how does it excite the photoreceptor cell? Hubbard led the research team studying these problems, working first with Robert St. George and then with Allen Kropf. By studying rhodopsin cooled to low (down to liquid nitrogen) temperatures, they showed that what light does in the visual process (and the only thing it does) is to isomerize

11-*cis* retinal to the all-*trans* form. Thus, a cycle of stereoisomerization is part of the visual cycle, as all-*trans* retinal or retinol must be isomerized back to the 11-*cis* form for regeneration of rhodopsin to occur. These experiments also demonstrated that rhodopsin goes through a series of molecular transformations as illuminated rhodopsin is warmed in the dark from liquid nitrogen to room temperature. These transformations reflect conformational changes in the protein, and we now know that one of these bleaching intermediates, metarhodopsin II, leads to excitation of the photoreceptor. A summary of the sequence of events that occurs from the absorption of a quantum of light by rhodopsin to its resynthesis is shown below.

How does metarhodopsin II lead to excitation of the photoreceptor cell? This was not solved until the mid-1980s, nearly a decade after Wald's retirement in 1977. It was, however, a question that vitally interested him. His mentor Hecht had shown in the late 1930s that the absorption of a single photon was sufficient to excite a rod. This suggested that a large amplification must occur when rhodopsin is excited. In 1965 Wald wrote a prescient paper, published in the journal *Science*, suggesting that light-activated rhodopsin might trigger a cascade of enzymatic reactions, much like those occurring in blood clotting, to account for the amplification. We now know this is exactly what happens: metarhodopsin II interacts with a G-protein, transducin, which activates phosphodiesterase molecules that regulate cyclic GMP levels in the photoreceptor cell (see Stryer, 1986). Membrane voltage of the photoreceptor cell relates to cyclic GMP levels and modulates neurotransmitter release from the cell. The amplification factor between one light-activated rhodopsin molecule and changes in numbers of cyclic GMP molecules is about 10^6. The story is now virtually complete and represents one of this century's triumphs of



Scheme of the sequence of events that occurs following the absorption of a quantum of light by the rod visual pigment, rhodopsin. Light initiates the conversion of rhodopsin to retinal and opsin through a series of metarhodopsin intermediates. Metarhodopsin II is the active intermediate leading to excitation of the photoreceptor cell. Eventually, the chromophore of rhodopsin, retinal, separates from the protein opsin and is reduced to vitamin A (retinol). For the resynthesis of rhodopsin, the vitamin A must be isomerized from the all-*trans* to the 11-*cis* form, and this isomerization takes place in the pigment epithelium overlying the receptors. Vitamin A is replenished in the eye from the blood.

biochemistry. Receptor molecules that interact with G-proteins and enzymatic cascades are ubiquitous in biology, and rhodopsin is arguably the best understood of these proteins.

As the rhodopsin biochemistry story began to wind down in the early 1960s, George turned much of his attention to color vision. Using a modification of psychophysical methods developed by W. S. Stiles in England, he determined the spectral sensitivity functions of the red-, green-, and blue-sensitive cones in normal and color-blind human subjects. At the same time, Paul Brown built a microspectrophotometer in the laboratory that enabled the measurement of the absorption spectrum of the human fovea and then of single cones. Since all of these pigments could be regenerated with 11-*cis* retinal, this showed that all had the identical chromophore but were different in their opsin structure. Jeremy Nathans and his colleagues (1986) eventually described the precise differences in the amino acid composition of the three opsin types.

I joined the Wald laboratory in 1956 as an undergraduate. It was an exceptionally lively and heady place for an undergraduate. In addition to George, Ruth, and Paul, Timothy Goldsmith was there, working on insect visual pigments, along with Norman Krinsky, who was studying the esterification and storage of retinol in tissues. Patricia Brown, Paul's wife, was also in the laboratory helping both Paul and George with various experiments. Allen Kropf joined the laboratory a year or so later.

My research dealt with vitamin A deficiency and night blindness, an old interest of George's. Indeed, George had carried out two studies on vitamin A deficiency in humans in the late 1930s, but a number of questions remained, particularly the question of whether prolonged vitamin A deficiency caused loss of opsin and degeneration of photo-

receptor cells. Thus, he proposed I map out the course of vitamin A deficiency in rats, focusing on the ocular manifestations of the deficiency. The project eventually formed the basis of my Ph.D. thesis and led to the discovery that vitamin A acid (now retinoic acid) could substitute for all the functions of vitamin A, except for its role as precursor to the visual pigments. Retinoic acid now appears to be a key molecule in the development of many tissues and is under active investigation the world over.

Lunch in the Wald Laboratory was an event. We took turns buying bread, deli meats, cheese, cookies, and drinks. At 12:30 p.m. we gathered in the lunchroom to be joined by John Edsall, Alex Forbes, Don Griffin, and occasionally Jim Watson, as well as their colleagues and students. George presided and we discussed science, politics, or whatever, and all joined in, from undergraduates like myself to professors emeriti such as Alex Forbes. The discussions were entertaining, provocative, and invariably stimulating.

George was one of Harvard's best teachers. He introduced biochemistry to generations of undergraduates, teaching always with great wit and clarity. In 1960 he began his famous introductory biology course entitled "The Nature of Living Things," which he taught until his retirement. This latter course was part of the general education program at Harvard, and was taken by both students intending to concentrate in biology as well as non-concentrators. He started the course with his marvelous "Origin of Life" lecture and the second semester with an "Origin of Death" lecture. Thousands of undergraduates were enthralled by his excursions into cosmology, atoms, and molecules and, of course, all aspects of contemporary biology. More than one student altered direction to become a biologist or physician because of the fascination of Nat Sci 5, as the course was called and numbered. From the course came a popular

laboratory manual that George titled "Twenty-six Afternoons of Biology." George gained national attention from the course, and as noted earlier was named one of the country's 10 best teachers by *Time* magazine in 1966. Wald was also a superb writer. A manuscript given to him for review invariably came back with more red pencil marks on it than typed words. But it was remarkably better, and those of us in his laboratory always strove to write as elegantly as did he.

The Vietnam War had a profound effect on Wald and was to lead him away from science. He was one of the first in academia to speak out against the war and was one of the signers of an open letter to *The New York Times* protesting the war in 1965. He won the Nobel Prize in 1967, and that provided him the recognition to speak out effectively on political issues. In 1969 he participated in a teach-in at the Massachusetts Institute of Technology and gave a speech called "A Generation in Search of a Future" that was published in the *Boston Globe*, *The New Yorker* magazine, and numerous other newspapers and publications. It eventually was translated into over 40 languages and was even released as a phonograph album.

From that moment on, politics became his primary interest: He was a forceful spokesperson against the Vietnam War, nuclear arms proliferation, and the military-industrial complex. In this effort, his wit and clarity served him well. When challenged that the arms race and the peacetime draft were "facts of life," he retorted, "No, those are the facts of death. I don't accept them and I advise you not to accept them." After his retirement from Harvard, Wald gave up laboratory research to devote his time entirely to political causes. He traveled widely until the last two years of his life.

Wald is survived by four children: Michael and David from his first marriage to Frances Kingsley in 1931 and

Elijah and Deborah from his second marriage to Ruth Hubbard in 1958. At the time of his death, there were nine grandchildren and three great-grandchildren.

Over the years, Wald won numerous awards in addition to the Nobel Prize, including the Eli Lilly Award in 1939, the Lasker Prize in 1953, and the Rumford Prize of the American Academy of Arts and Sciences in 1959. The opening lines of his Nobel Prize lecture typify his approach to science and are a fitting close to this memoir.

> I have often had cause to feel that my hands are cleverer than my head. That is a crude way of characterizing the dialectics of experimentation. When it is going well, it is like a quiet conversation with Nature. One asks a question and gets an answer, then one asks the next question and gets the next answer. An experiment is a device to make Nature speak intelligibly. After that, one only has to listen.

TIMOTHY GOLDSMITH, DONALD GRIFFIN, and particularly Ruth Hubbard and Elijah Wald provided material for this memoir. The piece that Ruth Hubbard and Elijah Wald wrote for the Novartis Foundation Symposium held in Japan in 1998 in honor of George Wald was particularly helpful (R. Hubbard and E. Wald. 1999. George Wald Memorial Talk. In *Rhodopsin and Photransduction*, pp. 5-20. Chichester: Wiley [Novartis Foundation Symposium 224]). Ruth Hubbard read the memoir and made many useful comments. The memoir was drafted while I was a visiting fellow at the Bellagio Study and Conference Center of the Rockefeller Foundation.

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