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ANNUAL REVIEWS

Annual Review of Vision Science

Fifty Years Exploring the Visual System

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Annu. Rev. Vis. Sci. 2020. 6:1–23

First published as a Review in Advance on April 22, 2020

The *Annual Review of Vision Science* is online at vision.annualreviews.org

https://doi.org/10.1146/annurev-vision-121219-081824

Keywords

color vision, photopigments, retinal physiology, visual pathways, melanopsin

Abstract

We as a couple spent 50 years working in visual psychophysics of color vision, temporal vision, and luminance adaptation. We sought collaborations with ophthalmologists, anatomists, physiologists, physicists, and psychologists, aiming to relate visual psychophysics to the underlying physiology of the primate retina. This review describes our journey and reflections in exploring the visual system.

PROLOGUE: A PERSONAL INTRODUCTION

Vision science arose with traditionally separate studies of temporal vision, spatial vision, movement, adaptation, and color vision. In part, this segregation reflected different needs of those seeking information about the visual process (industry, ophthalmology, etc.), but it was reinforced by the growing specialization and complexity of psychophysical research. The significance of our work lay in our attempt to view and analyze visual processes within the larger framework of established physical and biological principles.

Student Days

As a teenager, Joel was interested in electronic design and had worked in a radio and TV repair shop (in the 1950s, broken home electronic devices were actually repaired rather than discarded!). He started at Middlebury College in 1958 as a physics major, but when taking a Sensation and Perception course, he became interested in colored afterimages. Hunt Ewell, a social psychologist with textbook knowledge of afterimages, was excited by Joel's interest. He was happy to dive into the vision literature with Joel, where they discovered Clarence H. Graham. Joel graduated Middlebury College in 1962 and moved to Columbia University to study visual psychophysics with Clarence Graham.

Vivianne received a B.S. from the Columbia University School of General Studies. She took a course taught by Samuel Sutton in Sensation and Perception; Sutton introduced her to Ragnar Granit's pioneering work on vertebrate retinal processes (Granit 1947). This induced Vivianne to pursue graduate work studying sensory systems. We enjoy recalling the influences of Hunt Ewell and Sam Sutton. Both were fine undergraduate mentors. They inspired interests and then pursued them with us.

We first met at Columbia University in 1962. We discovered that we both were fascinated with the visual system. We also found that we shared many common interests, e.g., classical music, ethnic food, European movies, and sports cars. We were TAs in graduate classes and soon spent every day working side by side in the TA shared office.

Clarence Graham emphasized four processes: knowledge of the literature, equipment and calibration, psychophysical methods, and mathematical analysis. Over 70 Ph.D. recipients performed their dissertation research under his direction, and he and his students had a profound influence on the direction of vision science (Brown 1996, Riggs 1975).

Joel entered Columbia University with an interest in color. Graham suggested Joel follow up on some work he had done while on sabbatical in David Wright's laboratory at Imperial College London on grating acuity for different wavelengths. Joel was ushered into Yun Hsia's office, which contained the classical optical instruments of Selig Hecht's days at Columbia, the Hecht, Shlaer and Pirenne apparatus for measuring rod absolute threshold (Hecht et al. 1942) and the Shlaer acuity apparatus (Shlaer 1937). The acuity apparatus was massive and cleverly designed, with an early version of what today we would call a projection zoom system. Joel and fellow graduate student Bob Lanson collected data and published combined results from Imperial College and Columbia (Pokorny et al. 1968). Later, with minor alterations of the optical system, Joel did his dissertation on the effect of target area on grating acuity (Pokorny 1968).

Vivianne had no preconceived idea of an area in vision that she wished to pursue. In a meeting with Graham, he asked her if she might be interested in doing research on a motion phenomenon. She said yes, and he handed her a 63-page article in early twentieth-century German (Cermak & Koffka 1922). Two weeks later, they discussed the paper and agreed that a modern extension of the 1922 findings was in order. Saying, "I think this will help you," Graham walked into a laboratory, climbed on a chair, and retrieved a large motor and a Varimax speed controller. Vivianne's

dissertation research concerned band movement thresholds (distance/threshold velocity at the transition from perception of a moving luminous circle to perception of a filled moving band of light) (Smith 1969a,b). Graham was generous with his time and oversaw us just enough to ensure that things were done right.

We have always followed Graham's precepts. We immediately realized that we needed to learn optical design. We found a course in engineering optics at the Columbia School of Engineering. Edwin Bechtold allowed us in and became another important mentor. We learned about ray tracing, lens design, optical aberrations, apertures, stops, pupils, vignetting, and instrument design for visual experiments (Maxwellian view). Joel's background in electronics became important when we put both the optical equipment and the psychophysical measurement under computer control. It was also important for designs using LEDs to allow complex temporal modulations. It was at this time that the newly published Wyszecki & Stiles (1967) book *Color Science* become our permanent companion. As we started to analyze the data, we realized the necessity for analysis to be consistent with the known physical and biological properties of the visual system.

In the fall of 1965, we had been in the graduate program for three years and were close to completing our dissertation data collection. Clarence started forwarding letters to Joel about available academic positions. One day, he walked into our office with a letter from Alex Krill, an ophthalmologist at The University of Chicago. Clarence knew of Alex's clinical color vision work and thought highly of him. Clarence was not sure that a clinical department provided an ideal environment for a basic scientist but thought that it should be considered.

Alex Krill was an academic ophthalmologist specializing in inherited retinal and choroidal dystrophies. Alex's clinical expertise attracted referrals from ophthalmologists throughout the Midwest, and he ran a busy clinic. He remembered every retina that he ever looked at. He was committed both to defining genetic patterns of retinal and choroidal diseases and to understanding the biological bases of the visual defects. His specific interest was in X-linked retinal disease and its expression in the female carriers. His interests matched ours, and we both thought that this was a unique opportunity. He wanted us to study visual function in his patients and to develop an independent research program in color vision.

Early Years in Chicago

We married in December 1965 and set off for Chicago. There was one two-year soft money position, but we wanted to work together and accepted living on a single $14,000 salary. There was gender discrimination at that time, but we handled it, and it did not affect our science. To maintain independent identities, we decided that Vivianne would use her maiden name professionally. Our arrangement with Alex was to spend half-time on clinically relevant issues and teaching residents and half-time on basic research. Initially, the clinical time was like postdoctoral study in functional testing. We learned about clinical syndromes and later developed protocols to help distinguish retinal and optic nerve origins of visual loss. We discovered that we enjoyed working with both clinical patients and residents. Initially, the major thrust of our basic science studies involved characterizing the cone spectral sensitivities and discriminative capacities of normal and color-deficient observers.

Our son Charlie was born in April 1968 and our daughter Julie in July 1969. We had these two marvelous children, completely different in personality but both fitting perfectly into our lives. We managed to deal with the stress of active research and child rearing.

We regularly attended meetings of the Optical Society of America, the Association for Research in Vision and Ophthalmology, and the International Research Group on Color Vision Deficiencies (now the International Color Vision Society). These were really important for us, since we met so

many interesting researchers who became the sources of our collaborations. Dean Judd, Günther Wyszecki, and Bob Boynton became new advisors and friends. We also want to acknowledge Guy Verriest, an erudite ophthalmologist from Ghent, Belgium. He persuaded us to collaborate with him and Fred Pinckers on a book about clinical color vision deficiencies. This became a major project that was published in early 1979 (Pokorny et al. 1979).

Tragically, Alex Krill died on December 8, 1972, in a jet airliner crash in Chicago. He was returning from Washington, where he had lectured that morning at the National Eye Institute. His death was a great personal loss to us. We were fortunate that Dr. Frank Newell, the Ophthalmology Department chair, was supportive of our research, and we were able to continue our research and collaborations with departmental ophthalmologists.

In 1978, Steve Shevell joined the Psychology Department at the University. Steve rapidly became a valued colleague and friend. When the Ophthalmology Department moved offices and laboratories into the newly renovated Visual Sciences Center building, Steve moved in, and students and postdocs shared common office space. For many years, the three of us ran a seminar, Advanced Topics in Color Vision. Interactions were lively, and many good ideas originated in these sessions.

In 1979–1980, we spent a year in off-site research in the Netherlands. Our interests arose from discussions with Dutch scientists at the Institute of Perception in Soesterberg. Dirk van Norren had interests very similar to ours in the visual photopigments, and he and Jan van der Kraats, his technician and collaborator, had recently designed a retinal densitometer to study human photopigments in situ (van Norren & van der Kraats 1981). We had also met Loe Went, a human geneticist interested in pedigree analysis of families with congenital color vision abnormalities. The Netherlands was an ideal place to study pedigrees, since the country is small, and many families tend to live near each other. We put 25,000 miles on the car driving to clinics and family homes. Charlie and Julie attended sixth and fifth grades in a friendly Montessori school, biking back and forth. Since we were driving home in the evening, after the shops closed, they became friendly with our neighborhood shopkeepers.

Later Years in Chicago

A new collaborative venture arrived in the 1990s with Barry Lee, a physiologist at the Max Planck Institute in Göttingen, Germany. Barry was engaged in extracellular recording of primate retinal ganglion cells (RGCs). At that time, we had been using LEDs for psychophysical work in temporal processing. Barry was interested in our poster with Bill Swanson at the 1986 ARVO meeting. Joel designed similar equipment for Barry. This was our introduction to extracellular retinal recording and the spike-trains of cells in the magnocellular (MC-) and parvocellular (PC-) pathways. We listened to the spikes over a loudspeaker for hours. There was minimal response variation in a cell: The cells sounded like little machines. We realized that the retinal input to the visual cortex is just the beginning of vision. Additionally, Barry and his wife Daphne welcomed us into their home, and a long-lasting friendship developed. During our first spring trip to Göttingen, Barry asked if we liked baroque music. The town holds an annual Handel music festival. We love baroque music; even today, we return annually for a week of listening to Handel and spending time with Barry and Daphne.

Our work with Barry also led us to studies with Dennis Dacey on intracellular responses in horizontal cells of the primate retina. Dennis Dacey received a Ph.D. in anatomy from The University of Chicago, followed by a postdoctoral position working on primate retina with Bob Rodieck in Seattle. He then developed an extracted retina preparation, attached to the pigment epithelium and oxygenated. It was ready for intracellular recording. He wanted to interface a photostimulator

with the microscope in his retinal physiology recording system and came to Chicago to see John Troy at Northwestern. John suggested that Dennis should visit us. At the time, Barry was a visiting professor at The University of Chicago, and Dennis met with the three of us. Barry agreed that he would help Dennis with recording techniques, and we agreed to provide a LED photostimulator that could be directed through the camera port of the microscope. We sent him a "Baby Box" with analog dials to control two LED outputs.

We went to Seattle quite often, 2–4 times a year, enjoying our time with Dennis, his wife Kate, and their delightful daughter Erin. This led us to a study of intracellular recording of horizontal cells.

Finally, we became involved with a collaboration with Dennis and Paul Gamlin looking at a newly described RGC containing a visual photopigment in its dendrites. This work was exhausting. Following stimulus termination, the responses to bright stimuli lasted for 10 minutes or longer. This necessitated long recording sessions for individual cells, on the order of 1–2 hours. At 2:00 A.M., and as Dennis was finishing recordings from a cell, he said, "Great! Let's do one more cell!" When that was done, it was 4:00 A.M., and we received a similar response from Dennis. We were exhausted and left for a few hours of sleep. Dennis arrived for breakfast, excited by the cells that he had recorded after we left.

Below, we turn to a review of our research, which is summarized in sections titled The Cone Fundamentals, Interobserver Variability, Color Defects, Temporal Processing, Chromatic and Luminance Modulation, and Intracellular Recording. This range might give an impression of a somewhat disparate research approach. But all this work was interconnected and evolved from the precepts learned in our student days and from our opportunities for collaboration.

THE CONE FUNDAMENTALS

We first concentrated on the spectral sensitivities of the human cone photopigments. Rod photopigments (Rhodopsins) found throughout the animal kingdom showed a broad spectral sensitivity, with peaks near 500–520 nm. Cone photopigments showed greater spectral variation, with a group with peaks at short wavelengths (400–450 nm) and a group with peaks at longer wavelengths (540–560 nm).

One early psychophysical approach was to measure increment thresholds on chromatic adapting backgrounds. These studies yielded variable results (Stiles 1953, Wald 1964). An additional complication was that Dartnall (1953) had measured Rhodopsin pigments in solution and proposed that visual pigment spectra were invariant when plotted on a wavenumber axis. At the time, the only measured cone photopigment spectrum was from chickens (Wald 1937), but this was not compared with Dartnall's nomogram. We compared the spectral sensitivities of X-linked dichromats (Hsia & Graham 1957, Pitt 1935) with the then-available spectra of extracted cone photopigments in the animal kingdom. On a wavenumber axis, the protanopic and deuteranopic data and the pigment data shared a common spectral shape, narrower than the Dartnall nomogram (Smith & Pokorny 1972). Subsequently, it was determined that the spectral shape narrowed slowly but continuously with change in peak wavelength (Ebry & Honig 1977, Govardovskii et al. 2000).

The second psychophysical approach was to derive the human cone photopigment spectra from color-matching data. The linking hypothesis was that, when a color match between two fields was achieved, the rate of quantal absorption for each cone type was exactly the same for the two fields. Therefore, the spectral sensitivities of the human cone photopigments were a linear transform of the color-matching data. However, there were infinitely many possible transforms, so we needed additional constraints. The modern approach developed slowly, starting in German

physiological optics in the 1880s. An early idea from König & Dieterici (1886) was that the two forms of X-linked human color defect reflected a deficiency or loss of two classes of photopigment. Color-matching data from X-linked dichromats could be used to constrain the transformation, and to this day, the solutions are termed "König fundamentals." Measurement of spectral sensitivity in X-linked dichromats should be consistent with the L- and M-cone fundamentals. A third color defect, tritanopia, was thought to be a failure of S-cone function. An added critical test was that König fundamentals should predict tritanopic color matching.

The accepted color-matching database was developed by a committee of the Commission Internationale de l'Eclairage (CIE). The CIE 2° Standard Observer (CIE 1932) combined color-matching data with a standard luminosity curve, the V(λ) (CIE 1926). However the luminosity function was not directly related to color matching and must involve a physiological function determined following photopigment absorption. Dean Judd, part of the original colorimetry committee, realized that the V(λ) underestimated sensitivity at short wavelengths. He proposed a revised Standard Observer that included a revised luminous efficiency function and the colorimetric data of the 1931 observer (Judd 1951). We used this Judd observer. Furthermore, we postulated that the Judd luminosity function was determined only by activity in the L- and M-cones (Smith & Pokorny 1975). This assumption places the L- and M-cone isolating primaries on the inverse diagonal and the S-cone isolating primary on the x axis (the so-called alychne) of the Judd (x,y) diagram.

Our König fundamentals showed agreement with dichromatic sensitivities and prediction of tritanopic color matches. Vos & Walraven (1971) had proposed a similar set of receptor fundamentals using the CIE(Judd) observer but with all three cone types contributing to luminosity. Their fundamentals did not predict the tritanopic color matching data reported by Wright (1952). Finally, our fundamentals matched the cone photopigment shape (after corrections described below). The Smith-Pokorny fundamentals remain widely used in the literature (Smith & Pokorny 1975).

INTEROBSERVER VARIABILITY

As we reviewed the literature on color matching, we became interested in interobserver variability. Possible sources of variability include the λmax of the visual photopigment, the optical density of the visual pigment in situ, and prereceptoral filtering. Our first approach to individual differences was to evaluate variability in a renormalized system that eliminated the effects of prereceptoral filters. Stiles & Burch (1959) noted that observer differences expressed in this coordinate system exceed observer repeatability and must be attributed to receptoral variability (Smith et al. 1976). Predictions for shifts in λmax of 7–10 nm for the L- and/or M-cones were within the range of color-matching variability across observers. A parallel analysis of optical density variation allowed an optical density range of 0.2–0.3. More recent molecular genetic studies identified amino acid polymorphisms that provide variation in the spectral peaks of the L- and M-cone photopigments of up to 5–7 nm and show psychophysical correlates (Neitz et al. 1995, Sharpe et al. 1998, Winderickx et al. 1992).

Photopigment Optical Density

In the human retina, the photoreceptors are oriented toward the exit pupil of the eye. Light therefore enters along the long axis of the photoreceptor. In particular, the foveal photoreceptors show lengthened outer segments, the portions containing photopigments. When extracted photopigments are measured in vitro, they are dilute without orientation. The measurement is called an

extinction spectrum. The psychophysical measurement produces an absorption spectrum, with a greater probability of absorption near the λmax of the photopigment. When the relative absorption and extinction spectra are compared, the absorption spectrum is broader. The greater absorption is measured in units of optical density. To assess the effective optical density of human cones, we measured dichromatic heterochromatic flicker photometric (HFP) matches as a function of retinal illuminance. Once bleaching levels are reached, the optical density should decrease, approaching the extinction spectrum. More longwave light is needed for a flicker photometric match. The data suggested optical densities of 0.3–0.4 for a 2.5° test field (Smith & Pokorny 1973).

There were also indications that the effective optical density varied with change in field size. We measured Rayleigh matches for field sizes ranging from 0.5° to 10°. Observers required more long-wavelength light in their match as field size increased. We termed this the color-match-area effect (Pokorny et al. 1976). We also could account for receptoral spectral sensitivity differences in the Stiles (1955) 2° and Stiles & Burch (1959) 10° color matching with variation in optical density (Pokorny et al. 1976).

Our final approach to photopigment optical density was to measure regeneration using densitometry with Dirk van Norren and Jan van der Kraats. With optimized optics interfacing the densitometer and the observer, the change in measured density between a fully bleached and a fully dark-adapted retina was for most subjects between 0.25 and 0.40, values higher than in previous densitometers. The radiance response function, which could be measured precisely, was steeper than the function predicted by a simple first-order kinetic equation. Statistical analysis of the regeneration data revealed a highly significant nonlinearity. We developed a model in which the rate of regeneration increases as the proportion of bleached photopigment decreases; this is required to explain both the radiance function and the regeneration data (Smith et al. 1983). Deviations from first-order kinetics were subsequently confirmed psychophysically (Burns & Elsner 1985). Dirk and Jan kindly built a copy of their compact densitometer (van Norren & van der Kraats 1989) for us to use in Chicago.

Prereceptoral Filtering

Prereceptoral filters include the macular pigment and the human lens. The macular pigment shows considerable interobserver variability in peak foveal density and retinal extent. The story on the lens is more interesting, since lens density is age dependent. Stiles & Burch (1959) published 10° color matching data from 53 observers ranging in age from 16 to 55. In our laboratory, Margaret Lutze collected spectral sensitivity with chromatic adaptation on 60 observers with an age range of 13–68 (Lutze et al. 1987). We compared the age changes to published data for the density of the human lens. The age effect was not a simple scalar multiple of a single absorption spectrum. We proposed a two-factor lens-density spectrum to describe the nonlinear course of lens aging, one to represent an age-stable portion and the other an age-dependent portion (Pokorny et al. 1987). Ten years later, we assessed the lens density of 27 observers from reflectance spectra measured off the optic disk with a retinal densitometer (Xu et al. 1997) and confirmed the two-factor model with a physical technique. Van der Kraats & van Norren (2007) reviewed the substantial data on ocular media absorption that has appeared since our publication and confirmed the presence of separate age-stable and age-dependent components and an accelerating change in lens density with age.

Our work in intraobserver variability produced two major outcomes. We emphasized the importance of photopigment optical density in color matching. Furthermore, we introduced the concept that the human lens had age-dependent and age-independent components.

Cone Numerosity

A widely held view of the organization of color vision, traceable to Hering (1920), postulates a postreceptoral stage of representation that combines signals from the L-, M-, and S-cone types by taking their sums or differences. The spectral sensitivity of V(λ) has often been modeled as a linear sum of cone photopigment sensitivities, with the L-cone contribution being roughly twice that of the M-cones (Smith & Pokorny 1975). There is wide variation in HFP spectral sensitivities among color-normal observers (e.g., Coblentz & Emerson 1917), interpreted as variation in the relative number of the L- and M-cones. But could it be due to differences in gain for the two receptor types or some postreceptoral factor? We addressed this question by developing a paradigm to estimate the L-/M-cone ratio from point source detection thresholds. We measured the effect of test wavelength on psychometric function shape for absolute threshold point source detection (Vimal et al. 1989, Wesner et al. 1991). The rationale of the approach was that, at longer wavelengths, the spatial locations of M-cones would form "probability troughs," yielding shallower psychometric functions. The two studies included L/M ratio estimates from five observers. There was good concordance between the ratios from the point source detection and HFP, with estimated L/M ratios ranging from 1.5 to 7.3. Subsequent to our work, there have been several studies using diverse techniques that confirm the 2:1 L/M average ratio and considerable interobserver variability. These techniques included microspectrophotometry of single human cones (Dartnall et al. 1983); analyses of mRNA from donor retinae (Hagstrom et al. 1997, Yamaguchi et al. 1997); and adaptive optics imaging of the spatial arrangement of L-, M- and S-cones in the living human eye (Hofer et al. 2005, Roorda & Williams 1999).

Are there perceptual consequences of variation in the L-/M-cone ratio? Though the wavelength of unique yellow might be expected to vary with the relative numbers of L- and M-cones (Hurvich & Jameson 1964, Otake & Cicerone 2000), systematic studies indicate no correlation between the two (Hailwood & Roaf 1937, Ingling et al. 1990, Mollon & Jordan 1997, Pokorny et al. 1991). In 1977, we developed a hypothesis that could account for the spectral locations of unique yellow in protanomalous, deuteranomalous, and normal trichromats. We suggested that unique yellow is the wavelength that produces the same ratio of quantum catches in the L- and M-cones as does the average illumination of the observer's environment. We further elaborated on this idea for normal color vison (Miyahara et al. 1998, Pokorny & Smith 1987, Pokorny et al. 1991). The hypothesis is consistent with reports that long-lasting shifts in the wavelength identified as unique yellow are seen following exposure to chromatically biased environments (Belmore & Shevell 2008, Eisner & Enoch 1982, Neitz et al. 2002).

COLOR DEFECTS

X-Chromosome-Linked Disorders

The X-chromosome-linked disorders have been recognized since the late 1700s (Judd 1943). Identification of these defects was considered important because the developing transport industry depended on use of colored signal lights. Tests using 2° fields were developed and standardized. Traffic light chromaticity boundaries were established that would be most distinguishable by color-defective observers (Nathan et al. 1964).

We were routinely testing color vision for our own research interests and for Alex Krill. It became obvious that the complex optical equipment used for color matching was difficult to use for patients with reduced visual acuity. A colleague in England, Jack Moreland, was experiencing similar problems. He designed a versatile system for clinical use, the Moreland anomaloscope (Moreland & Young 1974). The definitive tool for red–green color defect is the Rayleigh equation, a match of a 589 nm light to a mixture of 545 nm and 670 nm lights. The Moreland anomaloscope

was an open design. Interference filters controlled the spectral composition of the primaries. The field size could be varied. The design allowed measurement of multiple matches, the Rayleigh equation, and the Moreland equation, a blue–green equation that let us study tritan defects as well as clinical color defects. We persuaded Jack to build one for us and immediately started to use it.

The Moreland anomaloscope allowed us to vary the diameter of the visual stimulus. Protanopes and deuteranopes showed a measurable increase in discrimination ability with a 10° test field. The result was consistent with the dichromats using rod signals as an independent chromatic mechanism (Smith & Pokorny 1977). Since everyday life involves vision determined by the entire visual field, many observers with these defects have fewer problems than conventional color tests indicate.

Anomalous trichromats make Rayleigh matches that are displaced from the normal match but are not full range. They show considerable variability in match width. Their brightness matches agree with the corresponding dichromat. Our early theoretical approach evaluated the visual pigments of anomalous trichromats with narrow match widths and good discrimination ability (Pokorny et al. 1973). We computed the expected Rayleigh match, assuming a König fundamental and an anomalous cone shifted on the wavenumber axis. The pairs of L- and M-photopigments for average deuteranomalous and protanomalous trichromats have wavelength separations of 6–7 nm, while the normal average difference is approximately 27 nm.

We also assessed the visual world of deuteranomalous trichromats using foveal viewing. We performed hue estimation and found a considerable loss of accuracy compared to normals. In hue estimation, color-normal observers use restricted color names (e.g., red, yellow, green, and blue) and assign proportions to the names, showing high agreement. Anomalous individuals show no dominant color. A wavelength that a color-normal observer would reliably identify as primarily yellow might be assigned green, yellow, or red on successive presentations (Smith et al. 1973). We simulated the deuteranomalous receptor excitations in color-normal observers by calculating the sensitivity (i.e., L-/M-cone) ratio. Pigment sensitivity ratios were calculated for theoretical pigments of deuteranomalous trichromats (Pokorny et al. 1973). The change in the ratios for the deuteranomalous photopigments for the 150 nm spectral range, from 530 to 680 nm, compares to a spectral range for normals of 26 nm, which represents wavelengths of 571–597 nm. We viewed the deuteranomalous trichromat as having the foveal red–green discrimination capacity for wavelengths 530–680 nm equivalent to a reduced spectrum for normal trichromats for wavelengths of 571–597 nm. When color-normal observers were briefly presented with monochromatic lights in this reduced range, their color-naming behavior was like that of the deuteranomalous trichromats (Pokorny & Smith 1977). Others have employed this strategy to investigate the color worlds of human dichromats (Brettel et al. 1997) and New World monkeys (Rowe & Jacobs 2004).

Autosomal-Dominant Tritan Defect

In the 1970s at The University of Chicago, we had tested the color vison of a large number of individuals with color vision defects but never saw a case of autosomal dominant tritanopia. This is surprising, since the incidence of congenital tritanopia has been estimated to be between 1/10,000 and 1/65,000. With Alex Krill, we measured the color vision of a large number of patients with dominant inherited optic atrophy (Krill et al. 1970, 1971). This condition is characterized by a pallor of the optic nerve, normal or close to normal visual acuity, and a blue–yellow color vision defect. The incidence of this disease is in the range reported for congenital tritanopia. Color vision findings were indistinguishable from those of tritanopes. We questioned the existence of tritanopia as an independent condition. Loe Went had documented five pedigrees

with autosomal-dominant tritan defect in the Netherlands. We tested 39 observers from these pedigrees, none of whom showed evidence of optic atrophy (Pokorny et al. 1981). The two defects have identical color vision defects, but the dominant optic atrophy does involve the optic nerve and appears to be more common in the United States.

We had taken our Moreland anomaloscope to the Netherlands. On Wednesdays and Fridays, we loaded our car with color testing equipment and the anomaloscope and drove to a town or village to test a given descendant family. One Dutch pedigree had over four generations of affected members living in a wide area of the country. All affected individuals showed abnormal Moreland equations and discrimination loss. Of great interest were our interactions with each family. We were always first offered coffee and cakes. Then we spread out our equipment on the dining room table and started the tests. Finally, we would tell them who had the tritan defect, often to great amusement among young siblings. Subsequently, we learned that the various descendent families became interested in their common color defect and arranged a family reunion.

Achromatopsia

Autosomal recessive achromatopsia is a disorder in which the cones are largely absent. In mammalian retinas, the visual system is not developed at birth. In humans, the cone-rich fovea develops by cone replication and migration in the weeks after birth. In achromatopsia, the fovea never develops, and individuals have low visual acuity and little ability to distinguish colors. Achromatopsia is a rare defect in the United States. Our major study occurred in the Netherlands, where our colleague, ophthalmologist Albert Pinckers, had studied many pedigrees of achromatopsia. He also sent us to an ophthalmologist friend who followed the achromats in a school for the blind. Once again, we found that the use of a large 10° test field revealed residual cone activity in a majority, 22/32, of the observers. This residual activity could be in any cone complement. Among the recessive achromatopias, there is considerable variation among families (Pokorny et al. 1982).

Pseudoprotanomaly

Pseudoprotanomaly has been defined in patients with acquired retinal abnormalities, e.g., patients who have suffered from leakage in the choriocapillaris or developed a scar in the foveal area. The term "pseudo" indicated that the Rayleigh match was shifted red-ward from normal but did not approach congenital protanomaly (Jaeger & Nover 1951, Köllner 1912). We investigated this finding with anomaloscope matching and Stiles-Crawford effect measurements from three patients with central serous choroidopathy. Color matches in the affected eye of each patient were displaced to red and could be explained by the hypothesis that the visual photopigments were in reduced optical density due to receptor disorientation caused by serous elevation of the sensory retina. The measured Stiles-Crawford effects of the affected eyes were abnormal, confirming the hypothesis of receptor disorientation. Measurements were made over a period of months, and as recovery progressed, the cones reoriented to point in the direction of the pupil, and the color matches returned to equivalence with the unaffected eye (Smith et al. 1978a). A comparable pattern of anomaloscope matching and Stiles-Crawford effect measurements was seen for other retinal diseases (Pokorny et al. 1980, Smith et al. 1978b).

We were interested in the clinical application of retinal densitometry and collaborated with Dutch ophthalmologists in the study of retinal disease (Keunen et al. 1989, van Meel et al. 1984). Central serous choroidopathy patients showed slow regeneration during the active phase, but their recovery showed normal regeneration times (van Meel et al. 1984). We assumed that transport of retinaldehyde from the pigment epithelium was hindered by the abnormal fluid buildup.

Our later thoughts on pseudoprotanomaly were developed through our testing of patients with early age-related macular degeneration. These patients initially showed minor visual acuity change. The color-match-area effect was absent. We posited that thickening and degeneration in the pigment epithelium was the source of these problems. The active form of this disease with choroidal vessel invasion culminates in severe loss of visual acuity and pseudoprotanomaly (Smith et al. 1988).

Our major contribution to the study of congenital color defects came from showing additional discrimination engendered by use of large fields. We also attempted to evaluate the perceptual world of the anomalous trichromat. The explanation of pseudoprotanomaly was important in clinical ophthalmology and emphasized the importance of photopigment optical density in color matching.

TEMPORAL PROCESSING

Reaction Time

An early study in temporal processing involved reaction time to chromatic lights with and without luminance increments. Reaction times were measured using an equiluminant change from white to spectral light (Nissen & Pokorny 1977). We found that reaction times to pure chromatic changes were wavelength dependent and slow. If stimuli included even a small luminance increment, then reaction time was faster and independent of wavelength. A second experimental paradigm involved a discriminative reaction time task in which a chromatic or white stimulus of the same luminance was presented on a dimmer achromatic background. Subjects were instructed to respond to chromatic stimuli but withhold a response if the stimulus was white. In this case, the same wavelength dependence was found as for the equiluminant change paradigm (Nissen et al. 1979).

Stimulus Waveform Manipulation

Our multichannel optical designs using tungsten or xenon light sources gave us little control in the temporal domain. Color matching is usually performed under continuous view. For brief presentations, we could use shutters, and for repetitive stimuli, we used rotating discs. Flexible control of temporal stimuli arrived with the development of LEDs in the 1980s. We designed electronics so that the LED could be driven linearly by any temporal waveform (360 pts per cycle) at an average 100 Td retinal illuminance. We initially used LEDs with peak wavelengths of 568 and 630 nm. Short-wavelength LEDs of good photopic luminance were not then available. We subsequently heard that Shuji Nakamura, a Japanese engineer, had developed high-radiance shortwave LEDs, but these were not available commercially. One of our members had a charming Japanese wife. When she needed to visit her mother, she volunteered to visit Nakamura and persuade him to sell her some of his new LEDs. He was quite fascinated by her quest and cheerfully gave her a handful of his blue LEDs. Nakamura subsequently won the 2014 Nobel Prize in Physics for his invention.

We began a series of psychophysical investigations of chromatic temporal processing in trichromats. In heterochromatic flicker photometry, a pair of lights in sinusoidal counterphase modulation often shows residual flicker after adjustment to equiluminance, i.e., after the sensation of flicker has been minimized by adjusting the relative radiance of the lights. De Lange (1958) observed that this residual flicker sensation could be cancelled by adjusting the relative physical phase of the two component lights. He ascribed the phenomenon to a latency difference between the cones. We approached the phase shift phenomenon by measuring modulation thresholds as a

function of the relative physical phase of red and green LEDs (Lindsey et al. 1986). As the relative phase was varied, modulation thresholds traced out a U-shaped function. The physical phase at which the modulation threshold was maximal corresponded to the phase at which subjects saw little or no residual flicker. Phase shifts measured with this technique are revealed by a translation of the U-shaped function along the physical phase axis, which we termed phase asymmetry. At low frequencies, modulation sensitivity is highest to purely chromatic modulation (with the lights modulated in counterphase, i.e., a phase difference near 180°), while at high frequencies, modulation sensitivity is highest to purely achromatic modulation (with the lights in phase, i.e., a phase difference near 0°). The function relating the phase of least sensitivity to temporal frequency rose rapidly from near 0° at 1 Hz, crossing 180° near 20 Hz and reaching 190° at higher frequencies. In further studies, Swanson et al. (1987) showed that these phase differences could not be ascribed to temporal response differences between the L- and M-cones, which would have required unrealistic latency differences of 20–60 ms. Thus the cause of these phase asymmetries must be sought in postreceptoral processing.

Retinal Ganglion Cells

Our studies of the RGCs were initiated by Barry Lee. After isolation of a ganglion cell's activity, pulsed lights were used to characterize cells of the PC- and MC-pathways. The LED stimulator was then positioned to obtain precise alignment of the stimulus on the receptive-field center. Recordings were from ganglion cells from parafoveal retina with retinal eccentricities of 2°–10°. Protocols were programmed for diverse experiments and, once a cell was categorized, were prioritized and run in sequence. One run could take 10–30 minutes. The protocol sequences continued as long as the cell responses were viable. Cell responses were stored and Fourier analyzed, and measures of cell sensitivity were derived. The experiments ran continuously for five to six days. A huge and rich body of data resulted.

The MC-cell response showed the same phase properties that we had earlier measured by psychophysics. To account for the phase asymmetry, we developed a MC-pathway receptive field model with linear summation of M- and L-cones to receptive field centers and surrounds and with an additional cone opponent chromatic input to the surrounds (Smith et al. 1992).

Long-wavelength chromatic adaptation results in a disproportionate reduction in visual sensitivity to rapidly modulated lights at moderate to high retinal illuminances. This anomaly, observed psychophysically (Ives 1912, Pokorny et al. 1993), can be seen in MC-pathway cells (Pokorny et al. 2001).

The PC-cells showed a good high-frequency response. This result differs from psychophysical results that show a poor temporal response to chromatic modulation (Lee et al. 1990).

In a series of experiments, we investigated the temporal response properties of MC- and PC-ganglion cells. MC-pathway cells displayed linear behavior only for low-contrast luminance modulation. PC-cells showed a high degree of temporal linearity. The responses of both cell types to complex waveforms (Kremers et al. 1993) and brief pulses (Lee et al. 1994) can be directly predicted from sinewave responses even at high contrast. This response linearity reflects the lack of a contrast gain control mechanism (Benardete et al. 1992).

Our major contributions to temporal processing include our examination of psychophysical phase asymmetries, which was followed by our collaboration with Barry Lee demonstrating that these effects could be seen in the MC-pathway cells. We also compared temporal response characteristics in both psychophysics and physiological data. We demonstrated that psychophysically measured slow temporal processing of pure chromaticity was not determined at the retinal level.

CHROMATIC AND LUMINANCE MODULATION

Our early psychophysical studies included chromatic discrimination (Pokorny & Smith 1970, Smith et al. 2000, Yeh et al. 1993a), hue estimation of spectral lights (Pokorny & Smith 1977, Smith et al. 1973), and purity discrimination (Yeh et al. 1993b).

Chromatic Discrimination

It became clear that extension of this work into spatial aspects of equiluminant vision would require a TV monitor display system. We purchased a PIXAR graphics display. It was a 3-primary color system but had the advantage that it allowed presentation of complex spatial patterns. An additional advance was that of MacLeod & Boynton (1979), who proposed a cone receptor chromaticity diagram.

The stimulus display was a four-square array, with one square differing from the other three in chromaticity. The observer's task was to identify the odd man out. The array could be presented in an equiluminant white (EEW) or chromatic surround. Two conditions of preadaptation were chosen: In the Pulse condition, the adaptation was just the screen illuminance/chromaticity; in the Pedestal condition, the four-square array was also presented. With a white surround, the thresholds described a V shape with minimum at white. With chromatic surrounds, the minimum moved to the surround chromaticity (Smith et al. 2000). The presence of either spatial or temporal chromatic contrast between the test and adapting field is sufficient to degrade +L-M- (Zele et al. 2006) and S-cone discrimination (Cao et al. 2008c). The data could be described by a model that incorporated early adaptation to illuminance followed by chromatic opponency (Pokorny & Smith 2004). We showed the generality of the model by demonstrating its ability to predict our earlier studies of wavelength discrimination (Pokorny & Smith 1970) and colorimetric purity discrimination (Yeh et al. 1993b).

Maxwell Matches

The linearity of color matching requires that a color-matching function obtained using one set of primaries be a linear transform of a color-matching function obtained using another set of primaries (Grassmann 1853). Failures have been reported in the short-wavelength region of the spectrum when color matches made to a white standard (Maxwell 1855) and matches made near the spectrum locus (maximum saturation color matches) were transformed to a common set of primaries. Crawford (1965) and Wyszecki & Stiles (1982) showed that the two conditions gave discrepant data in the short-to-middle-wavelength region of the spectrum. For test stimuli of wavelengths shorter than the short-wavelength primary, the short-wavelength and long-wavelength color-matching functions were higher for the Maxwell match than for the maximum saturation match, and the middle-wavelength color-matching functions were lower. For test stimuli of middle and long wavelengths, color-matching functions were closely similar for both matches. Qasim Zaidi (1986) used an experimental design that constrained possible sources of the discrepancy. He made maximum saturation matches and achieved a desaturated condition by adding a spatially homogeneous long-wavelength light to the entire matching field. Zaidi's data followed closely the results from Crawford and Wyszecki and negated explanations based on possible computational or prereceptoral artifacts.

We revisited this issue with Jun Xu (Pokorny et al. 2012). Our experimental results pointed to the conjunction of three factors as the cause of the failure. Two factors were related to retinal inhomogeneity, the spatial inhomogeneity of the macular pigment distribution and the spatially dissimilar L-/M- and S-cone distributions. The third factor involved a change in the weightings

of postreceptoral mechanisms mediating S-cone chromatic and L-/M-cone luminance discrimination (Tyndall 1933), due to the S-cones approaching saturation at high contrasts (Mollon & Estévez 1988). Desaturation could reduce these high chromatic signals and bring the neurons back to a more favorable operating region. We concluded that observers more heavily weighed luminance equality between the two half fields for the saturated matching condition and more heavily weighed S-cone equality in the desaturated matches. The analysis was consistent with Maxwell matches being made at a more eccentric location within the stimulus field.

Functional Isolation of MC- and PC-Pathways

The path between psychophysics and physiology proved a "two-way street." We initially worked with Barry Lee to explore the physiological basis of the psychophysically observed phase effect. Following our exposure to retinal cell behavior, we realized that we could design a psychophysical method that measures MC- and PC-pathway contrast discrimination by exploiting contrast gain differences in the MC- and PC-pathways. MC-cells showed (*a*) a rapid increase in spike frequency with increase in stimulus contrast and (*b*) saturation at modest contrast levels. PC-cells (*a*) showed a slower rate of increase in spike frequency with increased contrast and (*b*) continued to respond at high contrasts (Kaplan & Shapley 1986, Lee et al. 1990).

The psychophysical method was a contrast discrimination task using the four-square array developed for chromaticity discrimination (Pokorny & Smith 1997). The array was fixed at the (EEW) white point and varied in retinal illuminance. Two paradigms were designed to provide complementary information. The steady pedestal paradigm reveals MC-pathway gain. In the absence of temporal stimulus transients, the MC-pathway units are more sensitive than those of the PC-pathway cells (Kaplan & Shapley 1986). The pulsed pedestal paradigm reveals PC-pathway gain. When the pedestals are briefly presented, the MC-pathway response briefly saturates, leaving the PC-pathway to mediate discrimination. Contrast thresholds were measured to pulses that were incremented or decremented from the average retinal illuminance.

With the single-unit recordings, an ON-center cell gave a brisk response to positive change in luminance, and an OFF-center cell gave a brisk response to negative change in luminance. The dynamic range in the preferred stimulus direction (e.g., luminance increment for an ON-center cell) allowed a graded response with contrast changes. The dynamic range in the nonpreferred direction was limited because cells ceased firing when confronted with a small change in the nonpreferred contrast direction (Schiller 1992). Thus, when pulsed pedestals were incremented in luminance, we interpreted the threshold as being mediated by the ON-pathway, and when decremented, by the OFF-pathway. The thresholds depended on the contrast of the pedestal array, and the data were well described by a model fit of a saturation equation that has been used to characterize the contrast response of single cells in the PC-pathway (Kaplan & Shapley 1986). Note that the zero-pedestal stimulus was common to both the pulsed and steady pedestal conditions because both reduce to this condition at zero contrast.

An advantage of the method is that MC- and PC-pathway-isolating stimuli were identical at the time of the contrast discrimination judgment, differing only in terms of the eye's adaptation state immediately preceding this judgment. This obviates the influence of preretinal factors, which might confound results if color or spatial frequency tasks were used to separate MC- and PC-pathway function.

In a series of publications, the temporal (Pokorny & Smith 1997) and spatial summation properties (Smith et al. 2001b) of psychophysically isolated MC- and PC-pathway mechanisms were explored. Subsequently, spatial resolution was measured under the pulsed and steady conditions (Leonova et al. 2003), and collaborative clinical studies were carried out using this methodology

(Alexander et al. 2001, 2004a,b; Cao et al. 2011). Others have used this methodology to study visual function in interesting ways both in normal vision and in a variety of visual and systemic diseases (Pokorny 2011).

Studies of Postreceptoral Pathways for Rod Signals and Rod–Cone Interaction

The rod mechanism participates in the visual process over a wide range of light levels. For broadband illuminants, this range extends to about three log units above cone threshold (1–1,000 photopic td). Thus, both rod and cone mechanisms are capable of conveying visual information over much of the dynamic range of everyday vision. There are conflicting reports in the literature concerning rod input to the MC- and PC-pathways. Our recordings with Barry (Lee et al. 1997) at parafoveal (5–10° eccentricity) locations showed strong rod input to MC-pathway units, weaker rod input to PC-pathway units, and no measurable rod input to S − (L + M) units. The light level needed to be one log unit lower to observe rod activity in PC-pathway units than it did for MC-pathway units.

There is a substantial psychophysical literature on rod–cone and cone–rod interactions (Buck 2013, Zele & Cao 2015). In many experimental situations, optimal stimulus manipulations cannot be achieved with the instrumentation and experimental designs that have been available in the past. With Arthur Shapiro, we developed a theoretical treatment of rods in colorimetric systems. The analysis yielded a method to present stimuli to isolate rods, any cone type, or combinations of rods and cones (Shapiro et al. 1996). We employed this methodology (*a*) to evaluate the generality of certain literature findings with more complete stimulus control and (*b*) to study classes of phenomena that previously had not been amenable to experimental evaluation.

The first apparatus that we constructed was an 8-channel Maxwellian view colorimeter with four primaries in both the center and surround fields (Sun et al. 2001a). The stimuli originated from LEDs with spectral sharpening by interference filters. This instrument proved arduous to align and needed periodic readjustment. A second-generation photostimulator had the four LED lights combined by a fiber-optic assembly. The fiber-optic bundles were merged into a single bundle and fed to a spatial homogenizer terminated by a diffuser. A field lens placed large images of the diffusers in the plane of an artificial pupil. The fields appeared highly uniform, and following alignment and calibration, the center and surround fields were indistinguishable (Pokorny et al. 2004).

The development of the theory and instrumentation for separately controlling stimulation of rods and each of the three cone types allowed us to pursue diverse topics, including studies of rod influences on color perception (Cao et al. 2005, 2008a), rod–cone interaction in detection (Sun et al. 2001b), chromatic discrimination (Cao et al. 2008b), suppressive rod–cone interaction (Cao et al. 2006), brightness induction from rods (Sun et al. 2001a), flicker adaptation (Zhuang et al. 2015), rod–cone interactions in the temporal domain (Zele et al. 2008), rod and cone impulse response functions (Cao et al. 2007), and rod mechanism contrast gain (Cao & Pokorny 2010).

Our studies of chromatic and achromatic discrimination have had important consequences for understanding such discriminations and their relation to retinal physiology. Today, our students continue to pursue both normal and clinical research in these areas.

INTRACELLULAR RECORDING

The Horizontal Cells

We worked with Dennis Dacey to record from horizontal cells. The extraordinary feature of the preparation was that the cells could be identified visually for electrode penetration and,

after recording, could be stained for anatomical review. Barry had worked with Dennis on software both for stimulus control and cell response recording, and we built a 3-LED device to present the full array of cone- and postreceptoral pathway–isolating stimuli based on the Smith-Pokorny fundamentals. The results showed that the H1 cell received input from L- and M-cones, and the H2 cell received S-cone input in addition. H1 cells showed adaptation to low light levels but did not reach Weber's Law (Lee et al. 1999). We also measured the temporal frequency response and fit the data with a quasilinear model (Smith et al. 2001a). We then showed that this model could also describe the pulse response.

Melanopsin Studies

Dennis initiated a major research project to develop a classification of primate RGCs (Dacey 1999). In 2003, he started to use a photodynamic retrograde tracer (Dacey et al. 2003). This allowed him to link the anatomy and physiology of the RGCs that project to the lateral geniculate nucleus (and other cortical structures). He found 11 different types of RGCs differentiated by dendritic field size, branching density, and stratification in the inner plexiform layer. Giant cells were a unique subpopulation of some 3,000 RGCs whose dendrites ramified over a wide retinal area and expressed a photopigment, melanopsin. Additionally, Paul Gamlin and Dennis noted that injections in the pretectal olivary nucleus also filled the Giant cell. This work paralleled reports of a melanopsin pathway in rodents (Berson et al. 2002). Our work with Dennis expanded when he asked us to collaborate on characterizing the Giant cells.

We worked with Dennis and Paul to assess the spectral sensitivity and found that the melanopsin photopigment had a λmax of 482 nm. The melanopsin response showed a slow onset and very long-lasting response. The Giant cells also expressed input from rods and cones. The dark-adapted Giant cell responded with a rod response. As light levels increased, the melanopsin response appeared, and the rod response dropped out. Then, at even higher levels, the cone responses added to the melanopsin response. The L- and M-cones had positive inputs, and S-cones had a negative input, independent of the Giant cell stratification in the retina. These cone inputs showed their customary RGC characteristics. At high levels, there was an immediate cone response on which rode the long-lasting melanopsin response. The total spikes were linear with the logarithm of light level.

We then collaborated with Paul Gamlin at the University of Alabama at Birmingham on studies of pupillary responses in macaques and human observers. Primates exhibit sustained pupillary constriction responses in the presence of continuous light and following light offset. These responses parallel the responses of the Giant RGCs. Macaque pupillary behavior after pharmacological blockade of retinal rod–cone pathways displayed the same action spectrum, slow kinetics, and irradiance coding as the sustained, melanopsin-derived ganglion cell responses that we had measured with Dennis. We extended our observations to humans by using the sustained pupil response following light offset to document the contribution of these Giant ganglion cells to human pupillary responses. This study showed that Giant RGCs play a role in the pupillary light reflex and are primarily responsible for the sustained pupil constriction that occurs following light offset (Gamlin et al. 2007).

In summary, the H-cell studies with Dennis were important in establishing an early stage of light adaptation in the retina. The Giant RGC study characterized the anatomy and physiology of these cells in primates (Dacey et al. 2005). Furthermore, the data suggested that the Giant RGCs might serve as input to perceptions of increasing brightness over long periods, e.g., from low levels at night to maximal daylight. This result has been confirmed in humans psychophysically (Zele et al. 2018).

SUMMARY AND CONCLUSIONS

Five interwoven themes guided and directed our careers.

1. We emphasized the importance of integrating data obtained from many types of experiments. We typically collected data on a variety of carefully chosen visual functions: color mixture, visual sensitivity at and above threshold, chromatic discrimination, and spatial and temporal discrimination. Any one experiment might have many explanations; our strategy was to look for a convergence of data or to use one paradigm to rule out a hypothesis generated by a different paradigm.
2. We drew attention to the concept of using a reduced or altered system. Using observers with congenital color vision defects or deficits due to ophthalmic disease, we could both characterize the nature of the defect and make inferences about normal color vision. Our approach emphasized the "two-way street" between normal and abnormal. We stressed the necessity of complete and accurate description of all of the normal and color-defective observers, and of the clinical patients; for example, ruling out congenital color defects was important in clinical patients.
3. In our collaborations with retinal anatomists and neurophysiologists, we compared psychophysical and physiological data for identical protocols measured in primate retinal cells and in human behavioral experiments, a second "two-way street." Most models of psychophysical data relied on the concept of threshold linearity. We compared physiology and psychophysics for threshold paradigms and evaluated the nonlinearities that occurred as the cells were driven into saturating ranges.
4. We emphasized the need for a well-equipped laboratory. We provided specialized instrumentation for a variety of projects, and we could construct or quickly modify instruments for new projects. The instrumentation was available, functional, and reliable. We were helped by extraordinary advances in technology, which gave us LEDS, lasers, and computers. Although laboratory maintenance was labor intensive, we could point to an important serendipity: Our facilities were available for collaborative work with visiting scientists and postdoctoral fellows. It was usual for us to have several major projects active at any one time. In turn, we benefited from the infusion of new ideas.
5. Our theoretical approach was based on the question: To what extent could established physical principles or biological phenomena explain the data on vision and visual perception? Often, we examined the plausibility of various hypotheses that were not subject to direct experimental evaluation.

We have enjoyed our 50 years exploring the visual system. It is gratifying to realize that many of the inferences that we made from psychophysics have been confirmed by more recent anatomical, genetic, biophysical, and physiological results. We have made life-long friends with colleagues, collaborators, postdocs, and graduate students. We were pleased by how many of our graduate students and postdocs chose to pursue a career including a mixture of basic and clinical research. We believe that there are great futures for students who follow Graham's and our precepts.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We acknowledge support from the National Eye Institute for both research and training for many years. We thank our many collaborators and students, some of whom were not mentioned due to space concerns. Julie Bellanca, David Brainard, Ding Cai Cao, Dennis Dacey, Barry Lee, Judith L. Sensibar, Steve Shevell, and Andrew Zele provided helpful comments on drafts of this manuscript. Jules Quinlan and Linda Glennie ran the laboratory for many years and were indispensable. They helped us and the students and filled the place with their intelligence and charm.

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