it is—or was then in the process of—becoming. I would insist that the new paradigm I have tried to describe is taking hold, particularly among the younger members of the profession. On balance, however, there is little doubt that most of the work in the field is still descriptively, rather than causally, oriented.

In relatively few studies is the central problem of explaining change directly considered in terms of either the relevant data sought or the conceptual apparatus used. In spite of the widespread acceptance in theory of regional-ecological models that should depend on rigorous statistical sampling, the predominant focus of research for most investigators remains the arbitrarily chosen slice of a particular ancient site that is excavated. Specialists in the natural environment are still too often employed as technicians "expected to provide ready answers to poorly formulated questions" (*9*), rather than engaged in a genuinely collaborative study. Problems and objectives too often are formulated only as armchair generalizations, rather than as sharply focused hypotheses to which definitive answers must be sought in regional or local sequences. Meanwhile, separated by a wide gulf from the former, the conduct of much research at the local level remains practically innocent of relevance to any theoretical problem whatever.

Holistic presuppositions about societies in general also have not been sufficiently clarified and tested. As a result, there may well be an excessive emphasis in archeological interpretation on stability rather than instability as the salient human condition. To phrase this differently, an oddly antiquated, almost Victorian emphasis continues on institutions and behavior that performed integrative functions—art styles, rituals, elites—at the expense of conflict, marginality and dissonance as sources of creativity and change. Possibly for the same reason, most reconstructions of archeological sequences still consist of a succession of qualitatively distinct, smoothly functioning phases or stages rather than of the continuous interplay of forces marked at intervals by new transformational forms. Finally, most of us remain excessively timid, reluctant to tackle the grand problems of comparison, generalization, and synthesis, even though the certainty of being found in frequent error if we did so ought to be heavily outweighed by the opportunity to deepen, sharpen, and ultimately justify our inquiries. But, before I allow these criticisms of the present state of archeology to seem overwhelming, perhaps I should ask whether at least some of them do not have analogs in the natural sciences as well.

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The Development of Retinal Neurophysiology

Ragnar Granit

For some 20 years my main experimentation has not been within the field of retinal electrophysiology; my interests have shifted to problems of motor control—chiefly muscular sense organs and quantitative properties of firing motoneurons. For this reason my lecture will be as retrospective as the Award and deal with the rebirth of retinal studies that was inspired by the increasing accessibility of electronic equipment from the mid-1920's onward. Before this era, vision was chiefly studied by psychophysical methods; these had led to well-established correlations between perceptions of such things as color and luminosity and physically defined entities within the centimeter-gram-second system of units. But in 1926 Adrian and Zotterman (*1*), using the afferent nerve of a stretch receptor in a frog muscle, had shown that it was possible by amplification to record the impulses in single nerve fibers, and in 1927 and 1928 Adrian and Rachel Matthews (*2, 3*) published their important experiments with the mass discharge in the long optic nerve of the *Conger* eel. Evidently the electrophysiological approach was the one now destined to pave the way for deeper understanding of how this, our noblest sense organ, had organized its interpretation of the world of light, form, and color.

Frithiof Holmgren (1831–97) (*4*) at Uppsala, who in 1865 discovered the electrical response of the retina to light, the electroretinogram of today, had realized that many problems of vision could be analyzed by what he called his "method of objectivating the impressions on the retina," but amplification with the aid of the vacuum tube gave this general idea quite a different dimension; it was—Lord Adrian said—as if we had got a new, very powerful microscope to work with.

The basic idea of my own approach was formed during my study of Ramón y Cajal's (*5*) classical description of the retina as a "true nervous centre," as clarified by his silver-stain preparations and likewise suggested by its embryological development from the brain. It seemed to me likely that psychophysical data might, with some profit to the field, be translatable into neurological equiva-

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Professor Granit won the 1967 Nobel Prize for medicine or physiology, along with H. K. Hartline and George Wald. This is the text of his lecture before the Royal Caroline Institute on 12 December 1967. He is professor emeritus in the neurophysiological department of the Medical Nobel Institute, the Royal Caroline Institute, Stockholm 60, Sweden. The article is published here with the permission of the Nobel Foundation and will also be included in the complete volume of *Les Prix Nobel en 1967*, as well as in the series *Nobel Lectures* (in English) published by the Elsevier Publishing Company, Amsterdam and New York.

lents; so in 1928 I went to the laboratory of Sir Charles Sherrington at Oxford in order to learn something about nervous centers. A few years ago it gave me great pleasure to write an appraisal (*6*) of this eminent physiologist and the concepts he bequeathed to posterity. Sherrington and Adrian shared the Nobel Prize for medicine in 1932.

At the Johnson Foundation for Medical Physics, University of Pennsylvania, I made an attempt to put this general program into practice by a psychophysical technique; to this end I chose the fusion frequency of a flickering light that is proportional to the logarithm of stimulus intensity (Ferry-Porter law). This was done because I wanted an absolute measure of whether an excitatory state rose or fell, instead of the relative one by the customary psychophysical technique comparing two half-fields. It was thus assumed that, at least to a first approximation, the intensity of retinal excitation would be measured by the fusion frequency. Very much later (1952) Christina Enroth (*7*), in a thesis from the Nobel Institute, showed that the fusion frequency of the impulses from single retinal ganglion cells was in fact proportional to their impulse frequency. However, at the time (1929–31) by use of this hypothesis it proved possible to demonstrate facilitation between small flickering light spots separated by a weakly illuminated background (*8*), and to show that the fusion frequency within limits was proportional to the area illuminated. These effects corresponded to the excitability changes measured by Adrian and Matthews (*3*) in similar experiments using the mass discharge from the eel's optic nerve as indicator. With adjacent fields at different levels of brightness the fusion frequency rose in the brighter and fell in the darker field (*9*), a fact interpreted as demonstrating a mechanism of contrast:

> The theoretical significance of the observation seems to be that the inhibitory system is excited relatively more and more as the intensity of the excitatory process in a group of neurones increases. Consequently the inhibitory effect passing from the more stimulated area to the adjacent less stimulated area will be greater than the inhibitory effect passing in the opposite direction (*9*, p. 671).

Today this sounds like a description of Hartline's (*10, 11*) lateral inhibition in the *Limulus* eye, or of recurrent inhibition in the motoneurons, as measured by Granit and Renkin (*12*).

By these findings I was convinced that psychophysics could be translated into neurology, but psychophysics was as strange a subject to neurologists as was neurology to psychophysicists; so the implications of this work fell between two chairs. Only the physiologists were understanding listeners.

Next I decided to take up the electroretinogram and thereafter to remain within physiology. The complex electroretinogram had to be split into components, a piece of work begun at Oxford (*13*), and the analysis established by various means (since greatly improved) served as a starting point for much work up to the present day (*14*). In a thesis from the Nobel Institute in cooperation with the Ophthalmological Clinic of the Caroline Institute, Karpe (*15*) made electroretinography a useful clinical method, nowadays considerably developed and employed all over the world. Frithiof Holmgren, who was always very keen on applied physiology, would have been pleased if he had lived to see this development.

Although the electroretinogram was a mass response from the whole retina, it proved possible with its aid to take a few definite steps forward on the road toward a retinal neurophysiology. A slow cornea-positive component (PI) was found not to cause impulse activity in the optic nerve; another, faster component of similar sign (PII) mimicked the mass discharge with its rise at onset (on-effect) and cessation (off-effect) of illumination. Very definitely it could be shown (*16*) that the electroretinogram altered with light- and dark-adaptation in such a manner that it was impossible to understand the processes involved in adaptation on a purely photochemical basis, the prevailing notion of the day. After some further work I came to the conclusion that the light-adapted eye makes more use of inhibition, which was assumed to be relatively more important for cone projections within the retina.

However, to me at the time (in Helsingfors) the greatest problem of all was how to prove inhibition to be present in the retina itself. Both the design of this organ and the findings with the flicker method, which I have mentioned, suggested that, under some as yet unknown circumstances, impulses in the optic nerve might be stopped by light. The electroretinogram suggested an approach to this question. Since the discharge correlated with a cornea-positive electrical deflexion, might not the opposite cornea-negative deflexion, obtained when a flash was superimposed on the off-effect, indicate inhibition? This effect had been studied by Granit and Riddell (*16*) in great detail. By recording of the mass discharge in the optic nerve together with the electroretinogram, this surmise was verified.

There was the postulated inhibition (*17*). Very few if any later experiments have given me such delight. With my background in the physiology of the central nervous system, acquired in Sherrington's laboratory, I now knew for certain that the details of the visual image were elaborated by the interplay of excitation and inhibition in the nervous centre of the retina itself. Hartline (*11, 18*), by his elegant method of splitting single fibers in the optic nerve, soon found any amount of inhibition, and so did we when, somewhat later (see below), our microelectrode studies of the retina permitted isolation of single fibers. With this technique I later went on to show that the "on" and "off" components of the discharge were mutually exclusive when they were made to clash (*19*), and held this to be a "belated vindication of the essential truth of Hering's contention that there are two fundamental processes of opposite character in the retina" (*20*).

The following quotation, written in 1943, shows how the problem of form-discrimination was formulated at that time: "The accurate appreciation of contour, in particular, must be due to minute fluctuations of the eye balls resulting in on- and off-effects as well as sudden inhibitions of the latter" (*21*, p. 168). The important role of the eye movements (*22*) has since been demonstrated experimentally in several papers. Off-impulses do not require complete cessation of light; diminution of brightness suffices. Thus, because of the minute fluctuations of the eye bulb, the contour between two different levels of brightness acquires a life of its own, created by the interplay of excitation and inhibition at "on" and "off." No more need be said to show why the experimental establishment of retinal inhibition seemed so decisive a step toward a retinal neurophysiology capable of interpreting visual events. It is well known that for several years the leading theme of single-fiber work with the retina has been the effects of the interplay of excitation and inhibition.

So many things appeared tempting for study at the time that it was difficult to choose. Next I fell for the temptation

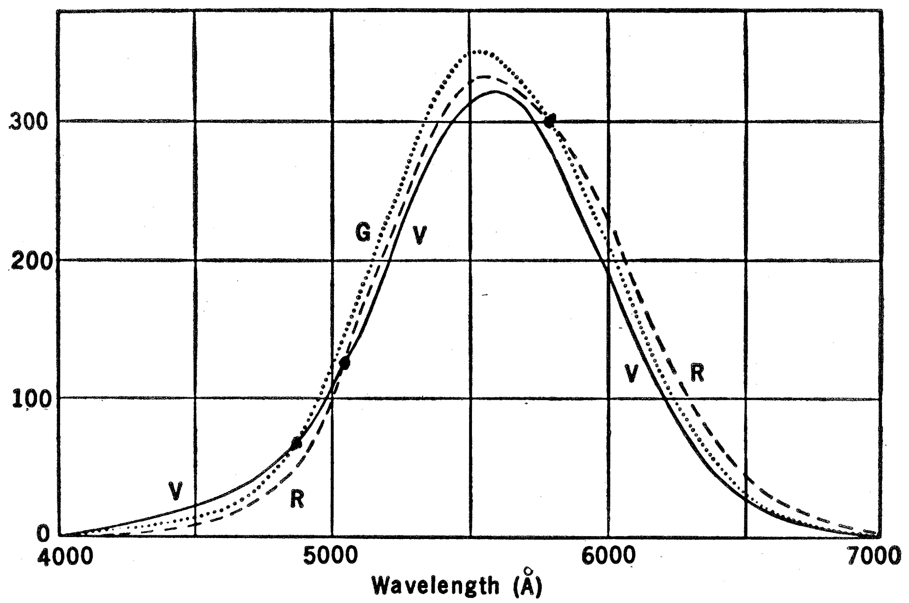


Fig. 1. Spectral distribution of the three primaries *V, G,* and *R,* according to Hecht's hypothesis (*28*). *G,* Green; *R,* red; *V,* violet.

to analyze the relation between the amount of rhodopsin and the sensitivity of the dark-adapted eye. In his valuable thesis from my laboratory at Helsingfors, Zewi (*23*) had shown that the total amount of rhodopsin could be extracted from a pair of frog's eyes, with an average accuracy of 4 percent, when left and right eyes of nine animals were compared. Our basic experiment (*24*) demonstrated that spectral lights of wavelengths between 4700 and 5850 angstroms, which were so weak that they could not bleach a rhodopsin solution tested at 5000 angstroms, nevertheless reduced the electroretinographically measured sensitivity of eyes exposed to them by as much as 74 to 56 percent, depending upon the wavelength chosen. The unexposed eye then served as control. The recent work of Donner and Reuter (*25*) suggests an explanation: they have shown that metarhodopsin II, one of the intermediary products of the bleaching of rhodopsin by Wald (*26*), is likely to trigger a negative feedback depressing the sensitivity of the rods. This effect is probably responsible for the unduly neglected findings of Elenius (*27*) with short-duration light-adaptations of the rabbit's eye.

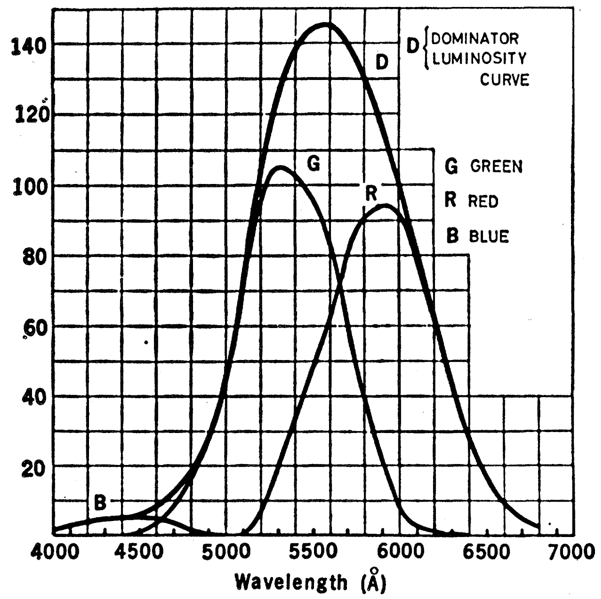
Another temptation was of course the mechanism of wavelength reception; this problem was then merely a branch of color psychophysics, and Hecht (*28*), who had the enviable gift of always being plausible, had developed a trichromatic theory according to which there were, to be sure, three types of cones, but overlapping very closely in spectral distribution of sensitivity (Fig. 1). The element of plausibility came from his thorough mathematical elaboration of the theory to explain a number of well-known, precise psychophysical observations on color. To a neurological approach, however, the idea of wavelength differences between the narrow fringes of the three curves (Fig. 1) appeared to raise such formidable demands on the internal machinery of the retina that it seemed more reasonable to assume Hecht to be wrong. As a matter of fact our earliest experiments with the electroretinogram elicited by spectral lights (*29*) showed in unmistakable terms that there had to be substances in the retina with absorption spectra in different and widely separated bands of wavelength.

At Helsingfors we then changed to microelectrodes—glass tubes with silver cores pulled out in a flame to fine tips—applied directly to the retinas of frogs (*30*). In Stockholm after 1940 these were replaced by platinum wires, insulated with molten glass, because the silver tips had a number of undesirable properties. It should not be overlooked that the first experiments on the frog retina were carried out under microillumination. The spectral lights were reflected internally from a silver-coated glass rod drawn out to a fine tip. When this light spot and the microelectrode were adjusted relative to one another in order that a precise response might be obtained, the distance between the two tips was often so great that only the optic-nerve fibers themselves could be considered as sources of the spikes obtained. Although I have often pointed out this circumstance, our results are generally being presented as though they all referred to the giant ganglion cells studied some years later in the cat retina (*31*).

The main method was to illuminate the retina with spectral lights calibrated with respect to energy and to listen to the threshold responses of spikes, heard from the loudspeaker. The spectral sensitivity is defined as the inverse value of the energy required for the threshold response, and this figure was afterwards corrected for equal quantum intensity in every wavelength. Optimal signal:noise ratio was established partly by adjustment of the microelectrodes and partly by working at the turning point of the characteristic curve of the amplifier.

With this method, isolation of single fibers need not necessarily be perfect. Choice of the threshold response as index implies in itself functional isolation of the most sensitive wavelength to which a response is obtained. The type of response used was photographed, but the threshold was determined acoustically. When an eye is "mixed," that is, it contains both rods and cones in large numbers, one must maintain its state of light-adaptation by special regularly recurring controls. Another advantage of light-adaptation is that threshold responses of even a small group of fibers then are very precise and sharply delimited. However, pure cone eyes (grass snake and tortoise) also were studied.

These experiments, carried out on many species of animals, lasted about 5 years, the last 4 after my move to Stockholm. They showed that there were two main types of message to the higher centers: (i) either the spectral distribution of sensitivity was wide, comprising the whole visible spectrum, with a maximum around 5600 angstroms (Fig. 2) that shifted to about 5000 angstroms after dark-adaptation, or (ii) there were narrow bands, restricted to three main regions (Fig. 3). In the dominantly rod eye of the rat an occasional narrow band, after light-adaptation, was seen at 5000 angstroms and ascribed to rhodopsin; this is not included in Fig. 3. I called the broad bands "dominators" and the narrow bands "modulators." Especial care was devoted to proving that a single well-isolated spike could deliver the photopic 5600-angstrom dominator in light-adaptation as well as the 5000-angstrom scotopic dominator after dark-adaptation. This is the electrophysiological version of the Purkinje shift from



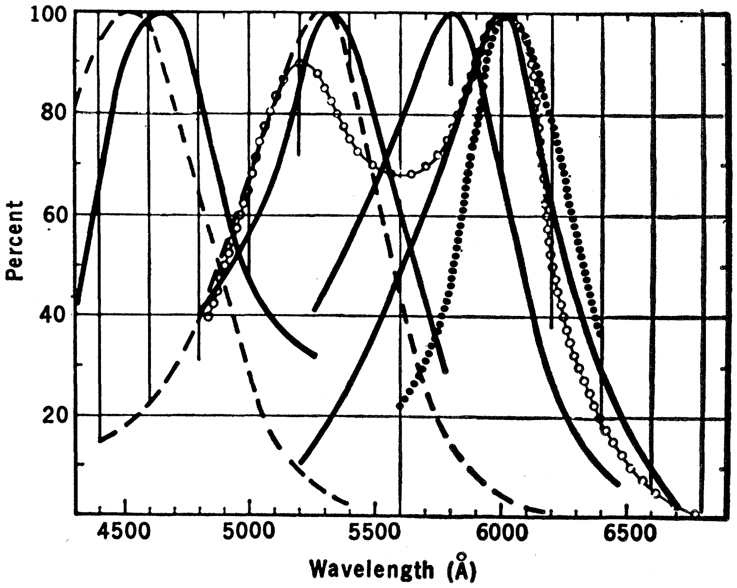


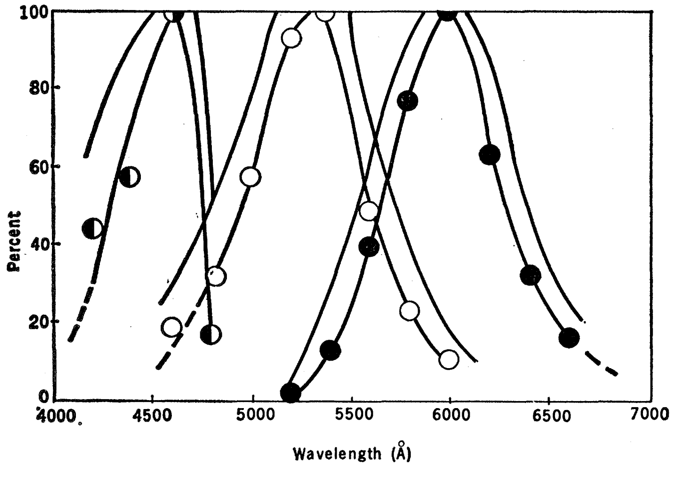
Fig. 2 (left). Synthesis of human photopic luminosity curve (identical with photopic dominator) on the basis of three fundamental sensation curves *B*, *G*, and *R*. Modulators indicated in original (*40*) are omitted. Fig. 3 (right). Distribution of sensitivity of modulators from the eyes of rat (dotted line), guinea pig (broken lines), frog (solid lines), and snake (line bearing circles). The narrow rhodopsin curve at 5000 angstroms in the original figure (*42*) is omitted.

photopic to scotopic vision, of which the dominator was held to be the carrier fiber.

Since the one nerve fiber can deliver both rod and cone messages, these experiments also showed that there is convergence of rods and cones toward the same final common path, as Cajal's silver stains had shown anatomically; they proved one more point that seemed to me most important: Clearly, since a single fiber could carry both rod and cone messages in the form of a dominator band destined for the same upper station, the visual message would have to be the same. Now, since luminosity is the sensory equivalent common to rods and cones—indeed the rods are likely to record very little else—the brain must receive a special message of luminosity as distinct from color specification. Wavelength-discrimination was therefore held to be dependent on the narrow modulator bands. Similar bands were later beautifully isolated by Donner (*32*) in the pigeon's eye with the aid of considerably improved microelectrodes.

There was not at the time enough photochemical work to exclude the possibility that narrow spectral bands might represent absorption spectra of photochemical substances. Therefore I limited my theoretical interpretation (*33*) to stating that wavelength-discrimination was based on the modulator type of response. Later on my own work (*34*) and work by others (*35*) led to the view that the narrowness of the modulator bands was a product of interaction between overlapping broad-band absorption spectra whose form in man soon began to emerge from the valuable ophthalmoscopic work of Rushton (*36*) and Weale (*37*). Modulation thus came to illustrate a principle common in the neural organization of most afferent systems, and signifying a crispening of the information by interaction, probably largely inhibitory in nature.

A great deal of experimental labor was invested in the measurement of dominator curves in various eyes and in proving their composite nature with respect to elements sensitive to different wavelengths (*38*), a theme developed 10 years later by Donner and Rushton



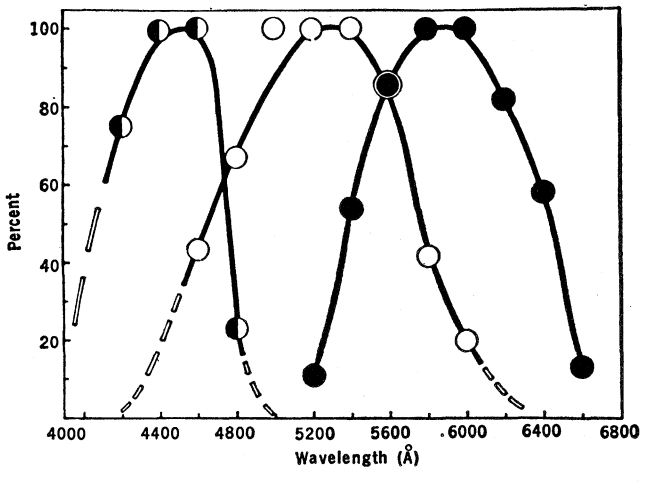


Fig. 4 (left). Averages of individual modulators from cat eye after selective adaption with blue, green, or red filter (*40*). Outer contours indicate dispersion. Fig. 5 (right). Extreme values obtained in the experiments summarized in Fig. 4 (*40*).

(*39*). It is of some interest to observe in retrospect how relatively easy it was to discover by our methods special sensitivity to blue light in the eyes of several mammals, compared with the difficulties later encountered in demonstrating a blue-absorbing substance in human eyes.

The retina of the cat, to which my final work (*40*) in this field was devoted, has a considerable number of cones. It surprised me at first that, in order to demonstrate specific sensitivity to several different regions of the spectrum in the cat's light-adapted eye, it was necessary to have recourse to selective adaptation. The explanation is probably that the cat, compared with pigeon and monkey, has relatively few optic-nerve fibers. The idea of the adaptation experiment was to bleach away a sizeable amount of rhodopsin by red, green, and blue lights. Since rhodopsin is a homogeneous substance, the relative effects of the bleaching lights, whatever their colors, could only be along proportional ordinates as determined by the ordinates of the absorption spectrum of these bleaching lights for rhodopsin. Remaining peaks of differential sensitivity in different spectral regions would then have to be caused by cone substances. On the basis of 4000 observations the three curves of Fig. 4 were obtained; Fig. 5 shows the extreme values. After averaging of these curves to add up to the photopic dominator with maximum around 5600 angstroms, the theoretical curves of Fig. 2 were drawn for the basically similar human eye (its periphery), which do not differ very much from curves later obtained by various means (*26*).

These results were criticized on the ground that the cat does not see colors; such an attack on the existence of a retinal color mechanism was utterly irrelevant and has since proved to have been in error. With the highly developed training methods of the present day it has not proved too difficult to make the cat respond to wavelength differences as distinct from differences of luminosity (*41*).

In my Thomas Young Oration at the Royal Institution in London in 1945 I felt it safe to state that

> The mechanism of colour reception is organized by the peripheral visual apparatus, the number of colour-sensitive elements is relatively limited, and these elements represent widely different regions of the visible spectrum. Those were Young's three fundamental assumptions. He was right even in assuming three main types of colour-receiving apparatus. These are the three preferential regions within which modulators are found (*33*).

I also made some attempts to relate these findings to color psychophysics (*21, 33, 42*), but the somewhat monotonous work of recording spectral sensitivities and the absence of photochemical data gave me a distaste for the whole field; later on the microelectrode approach was taken over and greatly improved by fresh minds. I finished the Thomas Young Oration with the statement that I thought myself right, but

> Further experience may nevertheless necessitate modifications. I can only hope that I shall not have to make these experiences myself, but that somebody else will try his hand at the optic nerve. I also feel just now that it would be interesting to see for a while what photochemistry and colour psychophysics could do for this field before any further labour is invested in electrophysiological work (*33*, pp. 462–3).

In the form of an extensive review completed in 1959, I paid a leave-taking visit to the field in volume 2 of *The Eye* (*35*) and found it occupied by a large number of very competent workers. There was no need to return to it.

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