with several collaborators (see e.g. Dusser de Barenne, 1934; Dusser de Barenne and McCulloch, 1938) established corticothalamic control. Recently Hagbarth and Kerr (1953, 1954) have succeeded in devising experiments which have carried the approach to these problems to the spinal cord level and thus represent a significant advance. They stimulated the dorsal root L7 in cats with rectangular shocks and recorded from the dorsal columns or from part of the stimulated dorsal root. In the dorsal columns one obtains in response to each shock a spikelike action potential which is followed by a more prolonged relayed discharge, as described by Hursh (1940). The relayed response has a peripheral counterpart in the so-called dorsal root reflex (Barron and Matthews, 1935; Toennies, 1938; Barron, 1940). Both the dorsal column relayed response and the root reflex could be depressed by stimulating regions such as the bulbar and midbrain reticular formation, the ventro-medial part of the anterior vermis, the precentral motor cortex, the primary sensory cortex and the so-called secondary somatic sensory area. This is illustrated in Fig. 46(A). Stimulus frequencies of around 100 per second were used. As clearly shown by the figure, the primary spikelike wave remains uninfluenced. The cord’s slow so-called intermediary potential, described by Hughes and Gasser (1934), was also depressed by stimulation in this manner (Fig. 46, B).

The examples presented should suffice to emphasize that questions concerning feedback mechanisms and direct neural control of the sensory input from stations in the brain are now clamoring for attention. The best known of these mechanisms, the centrifugal control of the muscle spindles, will be dealt with in detail in Chapters 6 and 7. The present examples have been added to indicate the scope of these problems and the necessity of considering them in the light of what has been set forth above about spontaneous activity and the arousal reaction. There are, of course, several other aspects to the general problem of centrifugal control (see Chapter 7), but we do not yet possess enough evidence for dealing with them, except in the case of the muscle spindles.

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Chapter 4

Present State of Dominator-Modulator Theory. Photochemical Parallels

1. First principles. Scotopic and photopic dominators

The retina may contain one or several photosensitive substances with absorption maxima in different wave lengths. Since only that light which is absorbed can be effective in initiating a stimulus, the absorption spectra of these photosensitive substances are close approximations to the spectral sensitivities of the mechanisms concerned. It has been shown that the receptive fields are complex. Taking man as an example, there are not less than 4 million cones, nearly 7 million according to some estimates, and 125,000,000 rods as against only 800,000–1,000,000 optic nerve fibers (figures from Polyak, 1941). Evidently a very minor number of receptors can afford to keep a private path and in view of the way sensory messages are organized elsewhere (Chapter 2) the problem of color reception must be solved by central interpretation of information over a complex frequency code which also expresses interaction (see Chapter 8). Even if one knew every photosensitive substance in a retina, the question of how they are represented in the messages transmitted by the frequency code would remain a problem in its own right.

However, color reception is approached, whether in terms of sensory brightness, receptor potential, or spike frequency, the principle always is the same, and it is easily understood from a schematic presentation. The following is somewhat inaccurate, but I shall add a photochemical derivation below. Let the effect of light (sensory brightness, size of potential, spike frequency) at any wave length be $L_\lambda$. This will be proportional to the amount of energy $E_\lambda$ and the specific sensitivity $S_\lambda$ for this particular wave length. $S_\lambda$ is the retinal sensitivity factor. With $L_\lambda = E_\lambda \cdot S_\lambda$ our problem is to obtain a measure of $S_\lambda$. It is clear that $S_\lambda = L_\lambda / E_\lambda$. If one proceeds to make $L_\lambda$ constant (constant bright-
ness, or receptor potential in mV, constant spike frequency, constant threshold or threshold fusion frequency of flicker), the sensitivity in every wave length is directly measured by $1/E_\lambda$. The curves to be described below have been obtained by recording energy reciprocals for a constant effect in the wave lengths tested.

Many photochemical studies have been carried out on substances extracted from the eye. The absorption spectra of solutions of these substances are obtained from spectrophotometric measurements. If $I$ is the intensity of light incident on the optical cell containing the solution and $I_\lambda$ is the light transmitted, the absorption coefficient (for wave-length $\lambda$) is proportional to the density $D_\lambda = \log I_\lambda/I_\nu$. The amount absorbed is $I_\lambda = I_\lambda - I_\nu$ or the difference between light incident and light transmitted. From the above definition of density ($D_\lambda$) it follows that $I_\lambda$, the amount absorbed, also may be given as $I_\lambda (1 - 10^{-D_\lambda})$. “For small values of $D_\lambda$, such as occur in retinas, this expression approximates $I_\lambda \cdot D_\lambda$. In the determination of spectral sensitivities the values of $I_\lambda$ are recorded which elicit a response of constant magnitude. Constancy of response requires constancy of $I_\lambda \cdot D_\lambda$, the light absorbed, no matter how complex the relations between them may be. For any invariant value of $I_\lambda D_\lambda$ throughout the spectrum, $I_\lambda$ will be an inverse measure of $D_\lambda$ and hence $1/I_\lambda$ will reproduce the absorption spectrum of the visual pigment.” (Dartnall, 1953a, p. 30).

In view of these considerations it was a great event in the history of psychophysics when the frog's visual purple, discovered by Boll (1876, 1877), was for the first time found by König (collected papers, 1903) to possess an absorption curve which fairly closely corresponded to the brightness distribution of the dark-adapted or scotopic human eye. This work, which was soon confirmed by his pupils, Köttgen and Abelsdorff (1896), has since been several times repeated with the improved methods introduced by Lythgoe (1937) and Saito (1938). Fig. 47 illustrates measurements of frog and human visual purple by Crescitelli and Dartnall (1953a), compared with a scotopic brightness distribution averaged by Crawford (1949) from values obtained with fifty observers. Ludvig and McCarthy’s (1938) corrections for absorption in preretinal media have been applied to Crawford’s values. It can be seen that while frog visual purple has its maximum at 5020 Å, the human visual pigment has it at 4970 Å. From their results Crescitelli and Dartnall calculated that the retinal density of human visual purple in situ was as low as 0.016 (at its

* This paper was presented in the Berlin Academy of Sciences by Von Helmholtz in June, 1894.
mediate link is accessible to measurement. The cat’s visual purple is probably identical with that of the human eye rather than with that of the frog.

Several methods are available for obtaining average scotopic sensitivity distributions from this animal. (1) The most difficult method was the first to be used (see Granit, 1943a, 1947). It measures optic nerve frequencies of individual elements with the threshold frequency as the constant index and averages the results obtained with several single fibers. This gave good agreement with the visual purple curve.

(2) Behavioristic tests may be applied to trained animals. This method was used by Gunter (1952), who found agreement with the average scotopic distribution curve of man, as determined by Stiles and Smith (1944), as well as with my results (after correction for selective absorption in preretinal media according to measurements on the bovine eye by Roggenbauer and Wetthauer, 1927). (3) The electroretinogram also is an average. This function was studied by Wirth (1953), who found good agreement with the other measurements. The average spectral sensitivity of the dark-adapted eye may also be measured by recording with the aid of electrical resonance a constant electroretinographic response in terms of flicker at a fixed rate or flicker fusion. The principle of this method (Granit and Wirth, 1953) is to adjust a resonance meter (a tuned amplifier) by varying the energy in each wave length in the spectrum to give a fixed reading to a flickering electroretinogram (fusion, if used, being fixed at zero reading). The flickering electroretinogram is amplified in the usual way (see Chapter 5) and the amplifier is connected to the resonance meter. The result is shown in Fig. 48 and is compared with the human scotopic sensitivity distribution (the so-called scotopic luminosity curve) of Stiles and Smith (1944). There is perhaps a slight shift toward the short wave lengths with this method, emphasized in some animals at certain frequencies of flicker.

So far, then, all is according to expectation, and the cat responds electroretinographically and acts (by behavioristic tests) as if it had succeeded in averaging perceptually the information from the retina when the latter is activated by visual purple.

However, in Granit and Wirth’s, in Wirth’s, and probably also in Gunter’s experiments intensities considerably above those needed to activate visual purple were used. Either this animal must possess visual purple alone or has means of disregarding other types of information. In order to investigate this question it is necessary (1) to study the frequency reports from individual retinal elements at the threshold with the greatest possible accuracy, as well as (2) to find out whether other photosensitive substances contribute to the discharge from such elements.

With some care individual retinal elements can be kept under the microelectrode for several hours, and it is thus possible to measure with sufficient accuracy their threshold distribution of photosensitivity in the dark. Donner and Granit (1949) did this and found a considerable number of curves which did not agree with visual purple absorption. Two examples are shown in Figs. 49 and 50. The maxima were in the right place and broad-band curves were obtained, but the curves show very definitely that substances other than visual purple have influenced them. Fig. 51 illustrates that slight light adaptation sufficed to bring about specific distortions. There was no more light adaptation than is consistent with “scotopic” behavior on the part of

![Fig. 48: Human scotopic sensitivity curve of Stiles and Smith (1944). Filled circles are averages from experiments on four dark-adapted cats, the values being determined by measuring flicker resonance electrically, as described in text. (After Granit and Wirth, J. Physiol., 122, 386. 1953.)](image-url)
the animal (cf. below, sec. 6). It is necessary, in fact, to use a great deal more light adaptation to bring about further shifts of the curve. The conclusion is that in acting as if the information had been based wholly on visual purple absorption, the animal itself had done the averaging that the experimenter with the aid of elementary mathematics could produce from a sufficient number of individual curves referring to single fibers. In Chapter 8 I shall give further instances of how perceived brightness is averaged. I shall also discuss experiments in which the sensory evaluation of the peripheral message has been completely transformed by various procedures to the extent of leaving long-lasting after effects when the observer returned to normal conditions of observation. I refer to this evidence here merely in order to raise the point—rarely mentioned in visual psychophysics—that the largely unknown laws of central integration cannot be neglected in psychophysical experimentation. It is, for instance, hardly possible to expect that the effects obtained with individual retinal elements represent psychophysical functions based on large averages without considering what averaging implies.

**Fig. 49.** Absorption in Dartnall's (1953a) pigment 497 (solid line) compared with Donner and Granit's (1949) scotopic dominators from cat (open circles).

**Fig. 50.** Same as Fig. 49.

**Fig. 51.** Same as Fig. 49. The black dots show the change of the original curve (open circles) after moderate light adaptation.
From both psychophysics and classical electrophysiological work on animals it is well known that vision, after light adaptation, is taken over by cones and that their over-all spectral distribution of sensitivity is different from that of the rods in the dark, based on visual purple. Neglecting for the moment differences due to absorption in the pre-retinal media, we may observe that the curve shifts bodily in light adaptation to around 5600 Å (see e.g. Granit, 1947). This is the Purkinje shift, named after its original discoverer. There are thus two fundamental curves, differing by about 600 Å. These are the scotopic (dark-adapted) and photopic (light-adapted) distributions of spectral sensitivity.

Now, are there any cones in the cat's eye? "Fabulous though the cat's ability may be for 'seeing in the dark', she has a very respectable number of cones—about a third as many as we ourselves" (Walls, 1942, p. 215). Piper (1905) failed to find a Purkinje shift in this animal by electroretinography, but the microelectrode is a more sensitive device and I found the shift in some 36% of the spikes studied in the photopic state, having previously found it regularly in eyes from various other animals possessing a relatively greater number of cones (Granit, 1945b, 1947, for summaries). Fig. 52 shows a relatively pure scotopic curve obtained with a single element. Fig. 53 shows photopic curves from four averaged sets of measurements. The hump at 6,000 Å is of some interest because similar phenomena are also found in man (see e.g. Sloan, 1928; Wright, 1946; Thomson, 1949; Hsia and Graham, 1952; Armington, 1952). These two curves were called the scotopic and photopic dominators and recurred in all animals studied in which the visual mechanism in the dark was based on the type of visual purple known as rhodopsin, provided that the animals had a sufficient number of cones. Photopic dominators could not be found in eyes of guinea pigs and rats. This need not mean more than that the cones are so few in these animals that there is little...
chance of detecting them. The two curves of Figs. 52 and 53 illustrate the Purkinje shift from scotopic (Fig. 52) to photopic (Fig. 53) vision, practically identical in cat and man. Thus, the dominators may be called the carriers of the Purkinje shift.

Rushton (1952) has recently developed a method of measuring visual purple in animal eyes directly by measuring the different amounts of light reflected in dark and light adaptation from the same parts of the retina. In applying a similar method to the cat’s eye, Weale (1953b) has found the absorption curves of two substances, one slowly regenerating and in good agreement with the absorption of visual purple, another rapidly regenerating and suggesting the photopic dominator. Exceedingly bright light was used for bleaching the visual purple. From the regeneration or re-accumulation data Weale has since (personal communication) plotted the two curves of Fig. 54.

Owing to the convergence of several receptors on a single optic nerve fiber, this fiber may respond as a scotopic dominator in the dark-adapted eye and as a photopic dominator after light adaptation. In the experiments on the cat’s eye large fibers were used, and so it may well be asked whether these run to the striate area in the occipital cortex. The minimal latency of response in the visual cortex for optic nerve stimulation is well known to be of the order of 1.6–2.0 msec. (G. Bishop and O’Leary, 1940; Bartley and Bishop, 1940; Marshall, Talbot, and Ades, 1943; Chang and Kaada, 1950), a fact easily confirmed, and so the message must have been conducted in the largest and fastest fibers available (average conduction velocity 34 m/sec., maximum 70 m/sec., according to P. O. Bishop et al., 1953). This raises an interesting problem. Since scotopic and photopic dominators are represented in the same fiber, in proportions depending upon stimulus strength and state of adaptation, these fibers must deal with the general brightness distribution, as shown also by the fact that such elements are the only ones known to reproduce scotopic and photopic brightness. Independently of whether they act as scotopic or photopic dominators, they serve as a basis for achromatic vision and can hardly
represent wave length discrimination (color) except by frequency modulation (see Donner, 1950, and Chapter 8, p. 289).

My technique at the time proved too coarse for the pigeon’s eye, which contains a million optic nerve fibers as against 150,000 in the cat (Bruesh and Arey, 1942). Nevertheless, the average spectral sensitivity of the optic nerve fibers in this eye, in which the cones are in the majority, could be studied in light adaptation. The averaged curve should give the averages of the dominator types of response, and so, indeed, it was found to do, but—curiously enough for an eye based on the rhodopsin system—with its spectrum shifted to 5800 Å. This further shift from 5600 Å was ascribed to absorption by the well-known colored oil globules (Granit, 1942c). Recently Donner (1953) has studied the pigeon’s eye with finer microelectrodes and has succeeded in isolating its photopic dominator response, illustrated in Fig. 55. As will be shown below, there is evidence for ascribing the shift from 5600 to 5800 Å in the pigeon to colored oil globules. In the eyes of certain fishes and tortoises the two dominator curves are found to be shifted toward the red end of the spectrum (see below).

In the work on animals with microelectrodes on the retina there also occurred narrow bands, the so-called modulators, centered in three spectral regions, for which some photochemical equivalents recently have been found. But this is perhaps easier to understand if I first deal with some general questions referring to methods of extraction, broad and narrow absorption bands, and photochemical nomenclature.

2. The photochemical approach. Nomenclature

Visual purple is the term that Kühne’s (1879) great work made classical. He also called this substance rhodopsin. Elsewhere I have given a full account of the historical development of our knowledge in this field (Granit, 1947). Fig. 47 has already shown that the frog visual purple has its maximum at 5020 Å, the human at 4970 Å. Bliss (1948) described visual purple in the squid with a maximum at 4950 Å, placed by Wald (1953) at 4900 Å. The maximum of cattle rhodopsin was given by Krause and Sidwell (1938) at 4950 Å, by Collins and Morton (1950a) at 5,000 Å. The maximum of rat rhodopsin they placed at 4980 Å. This is probably the human and rat visual purple of Crescentelli and Dartnall (1953a) with maximum at 4970 Å (Fig. 47). These visual purples or rhodopsins about which—despite minor discrepancies—there seems to be general agreement, thus vary at least between 4900 and 5020 Å. Kühne and Sewall (1879–80), confirmed by Köttgen and Abelsdorff (1896), described another type of visual purple in fish with maximum in 5400 Å, according to the latter authors. This they called visual violet,* now better purified and defined. As will be shown below, there are also variations in its maximum to be considered.

Two of the leading research groups, that of Wald and his collaborators at Harvard and Dartnall and his colleagues at the Institute of Ophthalmology in London, are agreed in their desire to drop the old nomenclature based on color of the pigments which, of course, in the long run is unsuitable for the simple reason that the photochemically active (i.e. absorbed) light is not the one transmitted and seen. “Visual purple,” however, is too well established by tradition to be eradicable by decree. Wald (see e.g. his summary, 1953) uses the terms rhodopsin and porphyropsin for visual purple and visual violet respectively, prefixed by the name of the animal from which it is extracted; while Dartnall (1952a, 1953a) characterizes all pigments by their absorption maxima in μ, e.g. frog pigment 502 (for frog visual purple with maximum in 5020 in Ångström units). Considering that there are visual purples, or rhodopsins in Wald’s terminology, with maximum varying between 4900 and 5020 Å, I think it clarifying to name them also by their absorption maxima. Behind this disagreement in terminology is also more profound disagreement as to the number and spectral location of the broad absorption bands concerned.

In this discussion the final decision does not rest with the photochemists alone. Considering how well the averaged dominators, when known, reproduce the broad absorption bands, it is painstaking experimentation along electrophysiological lines which ultimately will have to settle the question of whether an absorption band of an extracted substance is likely to be physiologically significant or not. If a substance is easily extracted chemically but cannot be demonstrated electrophysiologically, it is likely to be an artifact or to contain impurities. Many substances absorb light but few are photosensitive. In this field we can well afford to wait and see.

A common feature of present chemical work with the retina is that, following Lythgoe (1937) and Saito (1938), the earlier use of detergents on the detached retina itself has been supplanted by separation of the outer rod segments in a suspension to which the detergent (digitonin, bile salts) later is added. Thus, purer solutions are ob-

* Wald (1953) erroneously ascribes the invention of the term “visual violet” to me. I have used it for historical reasons as a tribute to the discoverers of this substance.
tained. Within the London group Arden (1953) rightly has raised the question of whether the method might not be selective and favor substances with broad absorption bands at the expense of pigments with narrow ones. For this reason, as will be shown below, he has introduced direct measurement of absorption in the suspensions of receptors.

Without entering into further detail in a discussion which cannot deal with photochemistry except as it touches electrophysiology, let me briefly summarize the position. In addition to the photopigments mentioned—490 (or 495), 497, 502—Dartnall (1952a) describes a pigment 467 found in the retina of the tench, a pigment 510 Dartnall (1952b) in the bleak (Alburnus lucidus), and a pigment 519 in the clawed toad (Xenopus laevis) (Dartnall, personal communication). Crescilleti and Dartnall (1953b) have found a pigment 523 in the carp (Cyprinus carpio). Wald, Brown, and Smith (1953) have synthesized a cone pigment cyanopsin (see below), which reproduces my photopic dominator in the cone eye of the tortoise (and the light-adapted tench, Granit, 1941b,d), thus at 6200 Å. Wald (1937) and Bliss (1946) have extracted a cone pigment corresponding to the other photopic dominator, that of man, mammals, frog, etc. (Fig. 53) with maximum around 5600 Å. A similar pigment has since been synthesized (see below) by Wald, Brown, and Smith (1952). Synthesis of visual pigments is the most important advance of recent research with biochemical methods (see below).

Hubbard and Wald (1952) disagree with Dartnall about the pigment 467, which they regard as an artifact. Further disagreement concerns the position of fish visual violet, Wald's porphyropsin. Collins and Morton (1950a) place it at 5250 Å, Kampa (1953) at 5200 Å, Wald (1953) at 5220 Å, and Dartnall (1952a) at 5330 Å except in the carp, where it is found at 5230 Å. The major argument in Hubbard and Wald's criticism of Dartnall's pigment 467 is that it is a product of isomerization, which is an early step in regeneration. If so, why is it absent in pike extracts? Spectral shifts in regeneration is an idea traceable to an early result of Lythgoe's, according to which regeneration from the bleached state does not reproduce the original photopigment. This work was interrupted by Lythgoe's premature death, but Collins and Morton (1950b) reinvestigated the problem and found, indeed, that bleached rhodopsin regenerated into a new substance, called isorhodopsin, with its spectrum slightly shifted toward the short wavelengths. Hubbard and Wald found the new maximum to be at 4870 Å, Collins and Morton at 4920 Å. Dartnall's technique (described in detail, Dartnall, 1952a) is based on difference spectra, a method which he has elaborated with great care, and his opinion (Dartnall, 1953, personal communication) is that the homogeneity of Wald's porphyropsin has not been established.

It has been emphasized by Dartnall (1953a) that all these spectra of the broad type are remarkably similar, merely being displaced along the abscissa, if plotted in terms of frequency instead of wave length. He has therefore calculated a nomogram from which it is possible to plot any absorption curve of the broad type provided its maximum be known.

Investigation of narrow-band visual pigments is just beginning. As stated above, it is premature to assume from the facts emerging from one kind of technique—such as extraction by detergents—that no photochemically active substances are found in the retina other than the broad-band absorption curves. Destruction of the cell membrane may well favor broad bands at the expense of the retina other than the broad-band absorption curves. Destruction of the cell membrane may well favor broad bands at the expense of the retina other than the broad-band absorption curves. Destruction of the cell membrane may well favor broad bands at the expense of the retina other than the broad-band absorption curves. Destruction of the cell membrane may well favor broad bands at the expense of the retina other than the broad-band absorption curves. Destruction of the cell membrane may well favor broad bands at the expense of the retina other than the broad-band absorption curves.
of which suggests a hump in this region found in Denton and Pirenne's (1954) behavioristic data for the spectral sensitivity of this animal.

**VISUAL BLUE-GREEN**

Fig. 56. Evidence for a pigment (in tench retinas) normally destroyed by extraction in red light. Curve 1: extract of tench retinae made in dim blue-green light. Curve 2: the same, made in dim red light (curve 2 scaled to agree with curve 1 at 530 m\(\mu\)). Curve 3: Difference between curve 1 and 2. (By courtesy of H. J. A. Dartnall, Institute of Ophthalmology, London.)

It should be emphasized that two main photochemical systems are known in the retina (for a historical review see Granit, 1941d, 1947; Wald, 1953), one based on Wald's retinene, which is retinaldehyde, or vitamin A\(_1\) aldehyde (Morton and Goodwin, 1944; Ball et al., 1948), the other based on Wald's retinene, which is retinaldehyde, or vitamin A\(_2\) aldehyde (Morton, Salah, and Stubbs, 1947). I have so far chosen my examples chiefly from the former system (visual purple and photopic dominator of mammals, frog, snake). The latter is found in some fish and in tortoises (visual violet and cone or photopic dominator of these animals). Isomers of retinene have been found and discussed by Wald (1953) and his collaborators. They cannot be taken up in this connection without devoting a great deal more space to biochemical points of view.

After this brief presentation of the photochemical situation, let us proceed to compare the photochemical data with the electrophysiological, inasmuch as the latter refer to the same animals.

3. Some further comparisons with broad-band absorption curves

Dartnall (1953a) has made a comparison between broad-band absorption curves from his nomogram with my data for frog and tench respectively as representatives of the two main types of scotopic dominators. To this end it is necessary to know the concentration of the photosensitive pigment in the retina itself in terms of its optical density, as defined above. Only for the frog is this figure available from Dartnall's work. It was calculated to be 0.25 for visual purple (recently confirmed by Arden, 1954d), thus a much higher concentration than in the human retina (cf. above). Fig. 57, from Dartnall's work, compares averaged scotopic dominators in frog and tench with the nomogram curves for pigments 502 and 533 respectively. With the frog the fit is as good as can be expected; the scotopic dominator of the tench has an expansion in the short wave lengths which may be due to fluorescence or to some substance not known (e.g. Dartnall's pigment 467). However, riboflavin, which is fluorescent, is a characteristic component of fish retinas (H. von Euler and Adler, 1933).

Fig. 58 illustrates Dartnall's (1953a) comparison with the photopic dominators of the same animals, assuming (1) that the cone pigments have maxima in respectively 5600 and 6100 A and (2) that their absorption bands agree with the broad-band nomogram template curves based on scotopic substances. The near fit of the right-hand limbs of the curves is, of course, a consequence of the assumptions made concerning the maxima of these absorption bands. Wald's (see below) cone substances corresponding to the photopic domi-
nators of the two systems actually have their maxima in 5620 and 6200 Å respectively. What seems significant in Figs. 57 and 58 is that the cone or photopic dominators average out to be narrower than the nomogram curve. Dartnall's final explanation of the discrepancy between the dominators and his so-called "template curve" is that the photopic dominators cannot be interpreted in terms of a single visual pigment, and he cites my evidence to the effect that it is possible, by selective adaptation, to split dominators (cf. Granit, 1945c, 1947), as has also been done since by Weale (see below), using the method of reflection from the living eye.

However, Dartnall's template curves, if plotted on a basis of wave length and not against frequency (as in Figs. 57 and 58), expand toward the long wave lengths; yet the two main photopic dominators cover substantially the same spectral area for all animals: cat, frog, snake, tortoise, tench. They merely fall into two groups, one with maximum around 5600 Å (cat, frog, snake) for the system based on vitamin A₁ aldehyde, the other (tortoise, tench) with maximum around 6200 Å, for the system based on vitamin A₂ aldehyde as chromophore. A substance corresponding to the latter type of dominator has recently been synthesized by Wald, Brown, and Smith (1953) from cone protein and retinene₂ (retinaldehyder₂). Their values (black dots) are compared with my curve for the tortoise's pure cone eye, drawn through the open circles, in Fig. 59a. The crossed circles refer to my measurements with the light-adapted tench. The fit is as good as can be expected. This substance has not yet been extracted. However, iodopsin has been both extracted and synthesized from cone
protein and retinene, (cf. above, Wald, Brown, and Smith, 1952). It corresponds to the photopic dominator based on vitamin A₁ aldehyde (man, cat, frog, etc.). Fig. 59b illustrates comparisons between broadband chicken pigments and scotopic and photopic dominators of the pigeon. The photopic dominator curve is shifted to the right in the

![Graph](image)

**Fig. 59a.** Comparison of dominator of tortoise's cone eye and photopic dominator of tench with Wald's cyanopsin (Science, 118, 505. 1953). Open circles with curve drawn through them: dominator of tortoise. Crossed circles: photopic dominator of tench (Granit, Acta physiol. scand., 2, 334. 1941). Black dots: Wald's cyanopsin. (By courtesy of G. Wald, Biological Laboratories, Harvard.)

spectrum by comparison with the photopigments. The probable explanation of this discrepancy—as stated—is the existence of absorbing oil globules in the cones of the pigeon. The template curve of Fig. 58 would be a great deal wider than the ones presented in Fig. 59. Extraction, synthesis, and electrophysiological measurements thus show the photopic cone dominators to be narrower than the scotopic ones. The reason for this discrepancy may be the one suggested—that extracts, synthetic substances, and dominators are complex curves; but it is just as likely that all three curves represent as pure substances as those responsible for scotopic dominators. The latter, of course, agree with Dartnall's template as well as with absorption in the extracts from which the template curve was derived. Wald's (1953) results seem to presuppose that the dominators actually represent pure sub-

![Graph](image)

**Fig. 59b.** Scotopic and photopic sensitivities of the pigeon, compared with the absorption spectra of chicken rhodopsin and iodopsin in digitonin solution. The absorption spectra are from Wald, Brown, and Smith (1954–55). The spectral sensitivities were measured electrophysiologically and are plotted in terms of the reciprocals of the numbers of quanta needed to produce a constant response. The scotopic luminosity data are from Donner (J. Physiol., 122, 524. 1953); the photopic data from the same source (barred circles) and from Granit (open circles; Acta physiol. scand., 4, 118. 1942). (From Wald, Brown, and Smith, J. Gen. Physiol. 1954–55. In press. By courtesy of G. Wald, Biological Laboratories, Harvard.)

stances. If so, there are narrower absorption bands than the visual purples. The photopic dominators thus would be a step in the direction toward narrow-band photopigments responsible for modulators, though still falling within the category of broad-band spectra. All four dominators—two in each system—have now been synthesized.
4. The modulators

In working with the electoretinogram of the frog's eye Granit and Wrede (1937) and Granit (published in Wright and Granit, 1938) showed that it was impossible to account for all the changes in the response to variations of wave length by merely two substances, one for the rods and one for the cones. Both in the blue and the red regions of the spectrum sensitivity changes occurred which were independent of the two main types of rod and cone response separated by the Purkinje shift. The general electoretinographic approach has been developed in a new way by Forbes and Burleigh (1952), who have tried to discover whether it is possible to shift instantaneously from one wave length to another without eliciting an electoretinogram. As a preliminary they proved that shifting from white to another white could actually be accomplished without any response whatever from the retina. However, in cone eyes such as those of turtles it was impossible to shift from one wave length to another, whatever their intensity relationship, without producing a fresh electoretinogram. Their photopic sensitivity cannot therefore be based on the properties of one substance only. The same held good for the light-adapted retina of the frog.

Some narrow-band curves were first found in the light-adapted eye of the frog by Granit and Svaetichin (1939), recording with micro-electrodes from single and grouped retinal optic nerve fibers and ganglion cells using microillumination from a spectrum. A very large number of animals (Granit, 1941–45) were then studied in a series of papers most of which were reviewed in 1947 (cf. 1945b). This extensive work gradually led to the conclusion that there were two main types of responses from single elements, dominators and modulators, the former relatively broad, the latter narrow with respect to the spectral area enclosed. The modulators were chiefly found in three regions of predilection widely apart in the spectrum. In my Thomas Young Oration (1945b) I therefore concluded that Young's (1801, 1855) main ideas were "fundamentally correct":

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 in the 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. The electrophysiological work may, indeed, be said to have confirmed the view he gave of the framework of the mechanism of colour reception. Its finished picture looks somewhat different, but the old framework was solid enough and shines through [pp. 462–3].

This view was restated in 1947 (Granit, 1947, p. 317). It was pointed out that the number of modulators within these areas of predilection may well be greater than three and that the fundamental response curves of the trichromatic theory may be mathematical concepts (averages). At an early stage (Granit, 1942a) I raised the question of whether it would be necessary to suggest a polychromatic theory. My reply was: "Statistical averages of the 'modulator' groups actually have three preferential regions, and on this basis it is possible to suggest a trichromatic theory instead of a polychromatic one" (Granit, 1942a, p. 148). I see no reason to depart from this view. Later Hartridge (1950) developed the notion of polychromatism (cf. Motokawa and Ebe, 1953).

It is often stated (cf. Wald, 1953) that all of my records were from a specific type of isolated giant ganglion cell. This is erroneous. To begin with, it was clearly pointed out that I did "not rely merely on experiments with isolated elements. Strict adherence to this criterion may, for instance, lead to the conclusion that blue elements are exceedingly rare whereas often the influence of the blue-sensitive substance can be traced in a less restricted type of response" (Granit, 1942a, p. 139, paper on frog retina). Records of grouped units were presented in this paper and a "blue" modulator plotted from a grouped discharge was shown on p. 144. It is clear that the threshold method which was used favored the most sensitive elements of the group or else that specific color receptors occurred in clusters (Hartridge, 1950). It is also well known today that microelectrode records from frog eyes, unless specifically isolated to contain large spikes only, contain both fiber and ganglion cell responses (Barlow, 1953a,b). As early as 1941 (Granit, 1941a) I pointed out that when microillumination was used, there was often a distance of several millimeters between the microilluminated spot and the place from which the micro-electrode picks up the response. It was only in the later work with the mammalian eye that the technique of recording from large units was systematically explored. With the large spikes dominators were obtained—with very few exceptions—and it was necessary to use indirect methods to split the response into narrower bands. The later work
with indirect methods was summarized in 1950 (Granit, 1950b). I shall not deal with its details here. Other indirect methods have been used by Motokawa, Iwama, and Tukahara (1951) and Tukahara (1951), confirming the modulator concept.

One of my indirect methods (Granit, 1945c) based on the microelectrode technique, consisted in selective adaptation of the dark-adapted cat’s retina with red, blue, and green light. These experiments are of considerable interest today because Weale (personal communication) has recently, with the aid of Rushton’s (1952) method of measuring retinal absorption directly in the living eye by reflection, tried selective adaptation on the same species. It was found impossible to account for the bleaching spectra in the medium and short wave lengths on the basis of visual purple alone. The fast adaptation in the long wave lengths made work at that end very difficult. Weale’s results are shown in Fig. 60, mine in Fig. 61. His narrow-band curve at the blue end of the spectrum is strongly reminiscent of my blue modulator, as isolated in the frog’s eye by the direct technique and in the cat’s eye by indirect methods.

This is work in its beginning, by a new method of approach, and it is still capable of being developed and improved. In itself it is a welcome addition to the extraction techniques based on a detergent which may or may not be selective (cf. Arden, 1953).

![Fig. 60. The method of reflection (as in Fig. 54) applied together with selective adaptation for the analysis of the spectral sensitivity of the cat’s eye. (By courtesy of R. A. Weale, Institute of Ophthalmology, London.)](image-url)

![Fig. 61. Averages of individual modulators as obtained by selective adaptation. Filled circles: red modulators; open circles: green modulators; half-filled circles: blue modulators. Outer contours indicate dispersion. (Granit, J. Neurophysiol., 8, 195. 1945c.)](image-url)

![Fig. 62. Solid line: averaged curve for blue modulator. Four elements. Broken line, here and in Figs. 63 and 64, indicates modulator curves of frog (Granit, 1942b). Equal quantum intensity spectrum. (Donner, J. Physiol., 122, 524. 1953.)](image-url)

Recently, Donner (1953) with his improved microelectrodes has measured the sensitivity distribution of individual elements in the pigeon’s eye, where cone areas are easily found. In addition to the dominator broad-band sensitivity curves (Fig. 55), he found the
modulator narrow-band curves illustrated in Figs. 62, 63, and 64. He has also included frog modulators from my work (Granit, 1942a), from which the response curves of the pigeon differ in being still narrower and shifted slightly toward the red end of the spectrum. He ascribes this shift to colored oil globules. Most interesting is the extreme narrowness of these curves, which illustrate the message as transmitted through the optic nerve upward. The pigeon's is an eye at least as good as and probably better than our own—at any rate very much better provided with cones—and thus it seems that improvement in cone vision, far from expanding the individual color bands over wider and wider spectral areas, actually tends rather to take the opposite course of narrowing them still further.

The cone eye of the snake (Tropidonotus) was used in my experiments (Granit, 1943b), and in this eye, too, it was easy to obtain red and green modulators. For the blue end of the spectrum the energy available in the instrument (Hilger-Tutton monochromator) was probably too low, or else blue modulators are few. Fig. 65 shows pure red modulators and a red coupled with a hump in the green. Green modulators tended to occur connected with the red one. The red modulator with maximum around 6,000 A proved to be the easiest to isolate and was found in a large variety of animals belonging to the retinaldehyde.
system with scotopic dominator around 5,000 Å and photopic dominator around 5600 Å.

In fish eyes (retinaldehyde), with the spectrum shifted toward the long wave lengths, a red modulator was found so far out as to be around 6500 Å (Granit, 1941d). As was pointed out above, human vision is based on the former type of photochemical system (see also Granit, 1947; Wald, 1953; Ball et al., 1946, 1948; Morton et al., 1947, for a discussion of vitamin A1 and A2 aldehyde as the respective chromophoric groups of these two systems).

Recently, Svaetichin (1954a,b) has inserted microelectrodes into the receptor layer of fish and in some preliminary experiments found color discrimination reminiscent of my results with fishes and tortoises. His contention that single cones have been obtained can hardly be said to be based on convincing evidence. Undoubtedly, however, the recording is from relatively restricted areas. Unfortunately, the curves were not recorded in terms of the photochemical function $1/E$. Microelectrodes within the retina have also been used by Tomita et al. (1953) for color work on the frog's retina. Evidence in favor of color discrimination was obtained, but again in terms which at the moment are difficult to evaluate for comparisons with photochemical results.

It should be clearly realized that the concepts “dominators” and “modulators” refer to the kind of information that is delivered by optic nerve fibers to the higher stations in the brain and that the analysis was carried out at the optic nerve level. These generalizations are therefore as such independent of the nature of the mechanism—photochemical alone or photochemical plus neural—which makes the message assume this particular form. It simply has this form and for this reason it is necessary to consider modulators and dominators as a device by means of which nature has chosen to deliver a particular kind of information to the brain.

However, considering that the message, as recorded, actually has traversed the retina, it is extremely interesting to see how relatively well it is reproduced in the case of the scotopic and photopic dominators of two such different systems as that of fish and cat, provided that a number of single fiber responses are averaged. Together with several other lines of evidence (see Chapter 8), this suggests that averaging is an important mode of sensory interpretation. With regard to the photochemical equivalents of the modulators a great deal of work still remains to be done. “When it is certain that the absorption curves of such [i.e. cone] extracts represent reasonably pure substances . . .

then, and not before, is it time to suggest other explanations [i.e. than photochemical ones] of discrepancies between photochemical and electrophysiological results” (Granit, 1947, p. 309). Since this was written, it has become possible to make further comparisons between dominators and photochemical absorption curves (cf. above). The only detailed comparison yet made between a modulator and an absorption curve comes from Arden's (1953) work * on suspensions

* A complete account of Arden's work (1954 a–c) has just been published.
of frog receptors in sucrose. This avoids the use of detergents. In Fig. 66 the line drawn in full is Arden’s curve, the large circles the averages of my three green modulators from the frog’s eye. The dotted line is obtained by assuming that the receptor segment absorbs some light at 4600 Å, but Arden himself is inclined to hold the line drawn in full to be the correct one.

The other aspect of the question, the neural one, theoretically developed by Jahn (1946a), was attacked by myself (Granit, 1949) with the cat’s retina for which, indeed, it was possible to prove that red and green stimuli interact on the same element. This, however, is a demonstration of a possible situation. To conclude immediately (as does Wald, 1953) that all modulators under all circumstances owe their narrowness merely to neural interaction would be premature and, today, does not even seem likely. When more cone substances become available, it should not provide any difficulties, with the much improved microtechniques of today, to return to the problem of neural interaction. For some time it was maintained that there were only two photochemical substances in the eyes of the species discussed above. This view can be entertained no longer. What is required is simply more work.

5. Some theoretical implications

As for the color-theoretical implications of the dominator-modulator concept, I can but reiterate my views, as stated in 1947:

The dominator-modulator theory, as such, is only concerned with a number of facts relating to the reception of and discrimination between wave-lengths, facts which have been accumulated by means of the application of the electrophysiological technique to the eye, as well as with their relation to what we know about the photochemistry and anatomy of the retina. The question as to whether or no any given experimental animal is capable of utilizing its retinal mechanism of wave-length discrimination is, therefore, not of immediate interest. Still less it is claimed that the theory can give any information as to whether, or to what extent, an animal may possess colour vision [Granit, 1947, p. 298].

This does not mean that one should wholly abstain from interpretation of the physiological cues, as has been so successfully done in many cases presented above. Nothing can be gained by refusing to consider evidence obtained with methods other than psychological ones. The task of physiology is to detect cues for behavior based on our “internal measuring instruments” and to do so at all levels where such cues might be had.

From this point of view it seems that the dominators, as stated, can hardly be responsible for anything but the average spectral distribution of scotopic and photopic brightness and that the modulators provide the cues for discrimination of wave-length. This was my standpoint, as presented in 1947, when I mentioned some relevant psychophysical data. It is substantially the same today. The dominators were described as the carriers of the Purkinje shift and there is no reason whatever to depart from this view either. Nor has, to the best of my knowledge, any other physiological evidence regarding the nature of the cues for wave length ever been presented. The recent valuable work by Jung and his collaborators (Jung et al., 1952) with microelectrodes in the optical cortex of the cat has not yet been extended to color reception. It is not intended to discuss physiological optics from the psychophysical point of view.

A very complete and instructive text book has recently been published by Yves le Grand (1952). It is at the moment the best survey of the whole field. Somewhat more popular is a book by Linksz (1952). Color vision from the standpoint of the trichromatic theory has been discussed in considerable detail by Wright (1946), but a great deal has since been added. Thus, for instance, Stiles (1953) at the Madrid conference on physiological optics presented important new results on experimental subdivision of color sensitivity curves in the short wave lengths. Hartridge (1950) has given an account of his polychromatic theory.

6. Mode of action of visual purple

There is probably no aspect of visual physiology in which premature generalizations from apparently simple and incontestable assumptions have proved more deceptive than in this question of the mode of action of visual purple on the rod cell. It used to be held that since light bleached visual purple and regeneration took place in the dark, this was the basis of its photochemical action. It all began with Kühne’s (1877–78) highly seductive optograms. He projected the window of his laboratory on the retina of the frog’s eye and found it reproduced like a photographic image, the optogram, in the bleaching pattern of the photopigment. Then followed the quantitative psychophysical analysis of the increase of light sensitivity of an originally light-adapted
the rat (Tansley, 1931) and the frog (Zwi, 1939) has been followed quantitatively and seemed to be in reasonably good agreement with expectation from the general theory which has been well stated by Lythgoe (1940, p. 26) in a paper devoted to criticism of it:

by photochemical reasoning we can say that, in order to produce a minimal stimulus, a constant amount of visual purple must be broken down, and the more visual purple there is, the less will be the illumination necessary to produce this amount of breakdown. This simple theory can be stated thus: For a threshold stimulus, 

$$ \text{Illumination} \times \text{Concentration of Visual Purple} = A \text{Constant} $$

provided the density of visual purple is small.

Around 1937 I began to suspect that all this needed to be reconsidered. We (Granit, Holmberg, and Zwi, 1938) therefore made direct comparisons between the size of the initial so-called b-potential (Chapter 5) or b-wave of the frog's electroretinogram and the amount of visual purple that could be extracted. The size of an electrical test response to wave length 5,000 Å in a Hilger-Tutton monochromator was first established. Then a filter of density 1.3 was temporarily removed from the beam of the eye, light adapted to one of a number of wave lengths in the equal energy spectrum for 5 minutes (Granit, Terman, and Wrede, 1938). There was a very large drop in the size of the b-wave elicited by the test stimulus when the filter had been reinserted. The amount of reduction depended upon wave length of adaptation. Recovery was followed for 6 minutes. The same experiment was then repeated with a number of animals in which, after 5 minutes exposure to the adapting light, the retina was removed and put in digitonin for extraction of its visual purple. I am giving a set of readings referring to the reduction in the size of the b-wave in different wave-lengths 75 seconds after cessation of bleaching. This additional delay corresponds to some regeneration during the time necessary for removing the retina and placing it in digitonin. It is convenient to give the theoretically expected concentrations of visual purple, as derived by calculation from the drop in the b-wave:

<table>
<thead>
<tr>
<th>Table 3</th>
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<tr>
<td>Reduction in Concentration of Visual Purple 75 Seconds after Cessation of Adaptation, as It Should Be if Calculated from the Reduction in Size of the b-Wave of the Electrical Response</td>
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<tr>
<td>Wave lengths in Å</td>
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<td>Percentage reduction</td>
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the first portion of the curve to the cones, the second (after the kink) to the rods. The second phase of the curve was held to indicate that sensitivity was a simple function of the amount of regenerated visual purple available at each moment in the dark. The same curve may be traced in the mixed eye of the frog by electroretinographic methods (Riggs, 1937), as well as by impulse recording (Granit, 1942a). There can be no doubt about the fact that—in a general way—the first portion of the curve can be ascribed to the cones, the second to the rods. In fact, fast and slow regeneration has since been described by Weale (1953b) in his direct measurements of the light reflected from the retina, mentioned above. Regeneration of visual purple in the eye of

observer in the dark as introduced by Aubert (1865). Kohlrausch (summary, 1931b) was the first to show that dark adaptation in terms of the logarithm of the threshold sensitivity traced the curve of Fig. 67. There is an initial fast portion and a slower extended phase of increase in sensitivity (drop of threshold). Hecht (see summary, 1937) repeated the work and expanded these observations in different ways, agreeing essentially with Kohlrausch about the necessity of ascribing

the threshold log illumination of the test object in microlumens.
These are considerable reductions, and if sensitivity, as expressed by the size of the b-wave (a very good index, as will be shown in Chapter 5), actually is dependent upon the concentration of visual purple, this drop is of an order of magnitude that should make it easy to detect. We recall (Chapter 1) that the b-wave is roughly proportional to log. intensity and, since the sensitivity is proportional to the reciprocal of intensity, the table means that we are dealing with very large drops of sensitivity, of the order of 100-1,000 fold.

The experiment was next repeated in the following way: The one eye of the animal was kept as dark-adapted control, the other one subjected to adaptation exactly as in the electrical tests. Controls showed that with a sufficient number of animals the concentration of visual purple in two dark-adapted left and right eyes did not differ by more than 1%. When the fifteen dark-adapted controls (one eye) were compared with fifteen bleached retinas (the other eye) the values were identical within 1% and the individual samples varied between −4% and +6%. Thus, the adaptation to the weak monochromatic light led to no definitely measurable reduction of the concentration of visual purple despite the large reduction in the b-wave. (Incidentally, it is of considerable interest to note in Table 3 that the short wave lengths were relatively less efficient in reducing the size of the b-wave than were the long wave lengths; see e.g. Granit, 1947).

It proved easy to check these results by placing the visual purple solutions themselves in the spectrum adjusted for adaptation in the same manner as with the frog's eye. Even though the absorption trough (length 20 mm.) containing the solution was kept in the optimal wave length for visual purple absorption (5,000 Å) for 10 minutes, there was only a reduction of maximally 2–3%. This has recently been confirmed by Hagins and Rushton (1953), who used Rushton's direct method of measuring visual purple absorption in the living eye. Light of strength 100,000 times the human threshold had no effect on the rhodopsin density. Rushton (personal communication), in studying visual purple in solution, found a few parts in 1,000 bleached by light, causing a fiftyfold change in threshold.*

Lythgoe (1940) immediately understood and accepted our early results and himself added a number of arguments from psychophysical experiments, in addition to suggesting that the findings should be ac-

* Wald (Science, 1954, vol. 119, pp. 887–892) has since taken up the same problem and calculates that exposure of an eye for 5 sec. to 10 millilamberts (= 100 lux) bleaches at most 1,200 of the 18 million rhodopsin molecules of one rod. This, however, would raise the threshold 8.5 times.
the lower curve, the stimulus area was small and the flash duration brief, it remains to ask why in this case quantum sensitivity, which is the inverse of $N$, has decreased because of light adaptation, despite the virtual absence of bleaching of visual purple.

Rushton and Cohen conclude that the change in quantum sensitivity is greatly influenced by events in the nervous network of the retina (of the kind with which we have become familiar in Chapter 2). Thus their results showed that quantum sensitivity has decreased in light adaptation and increased in dark adaptation, perhaps owing to retinal interaction. Chapter 5 will give further instances of interaction studied by electrophysiological methods (see also Granit, 1947, chapters 11 and 13). It is also possible that centrifugal action with consequent variations of retinal sensitivity (Chapter 3, sec. 6) might be dependent upon area and state of adaptation.

As long as modest light adaptation is used, it is unlikely that the bleaching of visual purple plays any significant role in determining the course of dark adaptation. If rhodopsin is removed by bleaching in strong light, it is reasonable to expect that the substance must be regenerated in order to be present at all. It is easy enough for any reader of this section to pick up a number of papers and summaries on dark adaptation in which most riddles in this field are presented as solved in terms of the old notion of visual purple concentration, and so it is perhaps of some interest to continue to point out difficulties and obscure points (cf. Jahn, 1946b), all of which must be understood before it can be said that we know how the rods are excited by their photopigment.

There is, for instance, a serious discrepancy between on the one hand the fact that most of the outer limb of the rod can be destroyed without significant effect on the electroretinogram (Noell, 1953) and on the other hand the necessity for a high concentration of visual purple in order to obtain maximal electrical responses (Granit, Münsterhjelm, and Zewi, 1939). It is also well known that after adaptation to strong light the recovery of log. sensitivity increases parallel, roughly, with the increase of visual purple (see e.g. Tansley, 1931; Karpe and Tansley, 1947; Johnson and Riggs, 1951; Best, 1953a) and that it also requires much the same time as the regeneration of the photopigment. But sensitivity is defined by the inverse value of energy and not by the logarithm of the threshold. There are probably also conelike rods (Granit, 1947) that may contain a relatively stable variety of rhodopsin.

Bleaching and regeneration play no role in the eye of the horseshoe crab Limulus (Hartline and McDonald, 1947); yet in several respects the behavior of this eye when it is left to recover in the dark after light adaptation is strikingly similar to that of the rods in cat and man. These similarities have been pointed out by Hartline and McDonald.

Turning to visual purple in solution in order to learn something about the photochemical effect itself, one may note that the observation that first pointed out the road to a deeper understanding was Lythgoe's (1937) discovery of transient orange. He found that if the solutions were kept cold, light transformed visual purple into an orange colored substance that disappeared when the test tube was warmed. This is the photochemical process; later changes are thermal. Lythgoe and Quilliam (1938) then proceeded to establish the absorption curve of transient orange (cf. Dartnall, Goodeve, and Lythgoe, 1938) while Broda and Goodeve (1941) introduced the technique of studying visual purple in glycerol-water solutions at several degrees below zero. Thus they succeeded in isolating better than before the photochemical effect, which is independent of temperature, from the thermal reactions transforming the original photopigment transient orange. This line of work has been continued by Wald and his collaborators (see e.g. Wald, 1953), who are in agreement with the British workers that finding in solution a very small shift toward the short wave lengths is the only effect induced by light, actually a shift of the
order of merely 50 Å. Wald, however, uses a different terminology and has split the later thermal reactions into several components.

For the present purpose the important point is that the actual photochemical change (in the retina as well) may consist of the minor shift of the absorption spectrum toward the short wave lengths. This is not likely to be measurable in the living eye. However, its relation to bleaching and regeneration can and must be analyzed so as to bridge the gap between photochemistry and the slow chemical processes of bleaching and regeneration which now, to a superficial view, seem so meaningless for the visual processes after having been in the foreground for almost a hundred years. At the moment we will have to assume that bleaching of visual purple serves merely to remove it from harm’s reach when the cones take over the act of vision. This brings us back to the questions concerning light sensitivity and visual purple concentrations, discussed above. The late A. F. Bliss (1948) found the reddish photopigment in the eye of cephalopods, which he called cephalopopsin, to be an unbleachable rhodopsin and yet very definitely to be the substance mediating the photochemical response to light. In this animal, which has a homogeneous receptor population, there seems to be no need for having one kind of photopigment removed when another takes over. Its photopigment has since been studied by St. George, Goldstone, and Wald (1952).

As to the process of excitation itself, Dartnall (1948b) suggested that activation of a visual purple chromophore by a light quantum may be “succeeded by a chemical process resulting in an electron transfer down the conjugated chain to the protein base and thence, in vivo, to the retinal end organ to which, in all probability, the visual purple molecules are attached.” Wald and Brown (1952) ascribe to the —SH group a role in eliciting the electrical generator potential. At the moment this, however, is a consequence more of their method of analysis than of their evidence. It is of some interest in this connection to recall the lamellar structure of the rods, as found by Schmidt (1938) and studied by Sjöstrand (1949, 1953a,b) with the electron microscope. If the outer limb of the rods consists of superimposed discs the way Sjöstrand pictures them, then considering Noell’s results mentioned above (and in Chapter 5, p. 184), it seems appropriate to ask how many discs are necessary for excitation—and to answer, possibly only the innermost ones. This brings us back to the original suggestion by Granit, Holmberg, and Zewi (1938) that under such circumstances the excess visual purple actually may be regarded as a “store.”

Chapter 5

The Electroretinogram

1. Introduction

An electrophysiology of the retina was recognized at a time when only the muscle and nerve action potentials were known and for the history of this subject I can refer to my book of 1947. It is of some interest to recall that the retinal electrical response to light was discovered independently in Sweden (Upsala) by Frithiof Holmgren (1865-66, 1870-71) and in Scotland (Edinburgh) by Dewar and M’Kendrick (1873a, b), because they converged toward the same result from very different assumptions. The Scottish authors imagined that the newly discovered photoelectric action of light might be the means of activation of the eye and Holmgren, following Du Bois Reymond (1849), wanted to study what was regarded as a natural cross-section of the optic nerve, where it might be possible to observe the resting potential as influenced by an impulse without killing the end of the nerve. He was surprised to find in the fish eyes which were used a deflection of his galvanometer to onset and cessation of illumination. These he first misinterpreted, believing them to be the nerve action potentials he was looking for. Later on (1870-71) Holmgren studied the distribution of the resting potential around the eye and from these results concluded that the electrical responses to onset and cessation of illumination had arisen in the retina itself.

Owing largely to the monumental histological work of Ramón y Cajal (1933), it soon became generally understood what a complex organ the vertebrate retina really is, but it was not until the electronic era of sensory research that this knowledge became part of any relevant physiological stock of ideas. This new era of research was heralded by the pioneer contributions of Adrian and R. Matthews (1927a, b, 1928) on the optic nerve response of the Conger eel. A summary of the achievements up to 1945 was given in my Sensory mechanisms of the retina (1947), and a later summary dealing with the organization of the retinal elements was published in 1950.