Principles and Practice of Clinical Electrophysiology of Vision

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PART XI

Psychophysical Testing

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Psychophysical Testing

Kenneth R. Alexander

INTRODUCTION: PSYCHOPHYSICAL TECHNIQUES THAT ARE RELEVANT TO ELECTROPHYSIOLOGICAL TESTING

Electrophysiological procedures are useful in assessing the functional properties of subpopulations of cells within the visual pathway. For example, the a-wave of the electroretinogram (ERG) has served as an index of photoreceptoral function. With appropriate techniques such as the focal ERG,[1, 114, 119] multifocal ERG,[125] flash visual evoked potential (VEP),[115] and pattern VEP,[11] it is possible to record the electrical response properties of relatively localized regions of the visual field. Nevertheless, the ability to localize the generators of electrophysiological responses spatially within the visual field remains limited to a resolution of a few degrees of visual angle, except possibly for the potential evoked by extremely fine patterns.

Conversely, psychophysical procedures allow an examination of the response properties of comparatively small regions of the visual field. In this sense, psychophysical procedures are complementary to clinical electrophysiology. A potential drawback to psychophysical measurements, however, is that they represent the response properties of the entire visual pathway as well as the influence of cognitive factors and motor skills. Nevertheless, psychophysical procedures, particularly in combination with electrophysiology and fundus reflectometry, have been used to perform a "layer-by-layer" analysis of visual function in order to gain insights into the locus and nature of defects within the visual pathway in disorders of the visual system.[46, 66, 108] The "linking hypotheses" or "propositions" required to specify the relationships between sensory states and physiological states have been addressed by Brindley[26] and Teller.[126]

CRITIQUE OF METHODS OF THRESHOLD DETERMINATION

The general aim of psychophysical methods is the measurement of thresholds (or sensitivity, which is the reciprocal of threshold). The term *threshold* refers to a boundary stimulus condition that results in a change from "no sensation" to "sensation." In present usage, the threshold is defined statistically. An underlying assumption is that, due to various sources of intrinsic noise such as quantal fluctuations in light output or spontaneous neural activity, the stimulus condition that defines the sensory threshold varies from trial to trial. Consequently, the threshold values that are reported typically represent the average of a number of trials, or a "percent seen." To reduce variability in threshold measurements, practice trials are useful in acquainting the subject with the range of sensory experiences to be expected.

There are two general classes of thresholds. First, *absolute* thresholds represent the minimum stimulation necessary for the detection of the presence of a stimulus under a given set of conditions. An example is the threshold luminance required for detecting a flash of light that is presented to the dark-adapted eye. Second, *difference* (or increment) thresholds measure the minimum stimulation necessary for detecting a change in the visual environment. An example of an increment threshold is where the

threshold luminance for the detection of a light flash is measured as a function of the luminance of the background against which it is presented.

Thresholds are often measured by using classic psychophysical procedures that were developed originally by Fechner.[52] Perhaps the most straightforward technique is the method of adjustment, in which the subject alters the test stimulus until it is just detectable. The threshold is then defined as the average of a series of such measurements. Since the subject has direct control over stimulus manipulation, this method is open to potential artifacts. For example, the subject may adjust the stimulus by some fixed, arbitrary amount on each trial without regard to sensory events. A variation of the method of adjustment is the tracking procedure, in which the subject continuously adjusts the stimulus to maintain it at a threshold level. This procedure is especially useful in measuring sensory events that change over time, such as the recovery of sensitivity during dark adaptation.

A second psychophysical technique is the method of limits. In this procedure, the experimenter initially sets the stimulus either below or above the estimated threshold and then alters the luminance systematically in small steps until the subject signals either that the stimulus is just detectable (ascending method) or that it has just disappeared (descending method). The threshold is defined as the average of a series of such measurements. The method of limits has proved useful in the clinical setting. However, it is vulnerable both to errors of habituation, in which the subject maintains the same response without regard to sensory experience, and to errors of anticipation, in which the subject reports prematurely that there has been a change in the stimulus.

A variant of the method of limits is the staircase technique, in which the luminance that is presented on a given trial depends on the response from the previous trial. If the target was "seen," the stimulus luminance is reduced by one step; if it was "not seen," the luminance is increased by one step. The threshold is defined as the average of a number of such reversals. Several staircases can be interleaved, and the particular staircase that is represented on a given trial is determined randomly in order to prevent the observer from adopting a response strategy such as alternating "yes" and "no" responses.[37] An advantage of the staircase procedure is that the stimulus values are constrained to lie near the threshold in order to maximize the information obtained within a session.

In the method of constant stimuli, a set of test stimuli are presented whose luminance values span the estimated threshold in discrete steps. Each stimulus is presented a fixed number of times in random order. The subject responds "seen" or "not seen" on each trial. The "percent seen" is plotted for each stimulus luminance, resulting in a psychometric function. The threshold is typically defined as the luminance that is "seen" 50% of the time. In the method of constant stimuli, "catch" trials are often used in which no test stimulus is presented. If the subject responds that a flash was seen on such a trial, he/she is admonished to try harder.

Although these classic psychophysical techniques can be useful in a clinical setting, it is apparent that they do not take into account the subject's response bias or criterion. An alternative to these classic procedures is the set of methods derived from signal detection theory (SDT), in which there is no assumption of a sensory threshold. Rather, the emphasis is placed on the decision strategies employed by the subject. The task is the detection of a signal (such as a light flash) against a background of noise. The SDT procedures allow a separation of sensitivity from response criterion.[43]

One of the standard SDT methods is the "yes-no" procedure in which there is a single observation period containing either noise alone or a signal added to noise. The observer responds either "yes," a signal was present, or "no," a signal was not present. For simplicity of analysis, it is often assumed that both the "noise" and "signal-plus-noise" probability density distributions are gaussian. In an analysis of the results, the two most important events are *hits*, in which the observer correctly responds that a signal was present, and *false alarms*, in which the observer reports that a signal was present when it was not. A plot of hit rate vs. false alarm rate provides a receiver operating characteristic (ROC) curve from which a measure of sensitivity (such as d') can be derived. In a yes-no procedure, the observer's criterion may be manipulated by varying the payoffs associated with hits and false alarms and/or by varying the a priori probability of signal presentation. This is generally a time-consuming procedure that has seen limited clinical application.

A second method that has been adopted in some clinical settings is the forced-choice procedure. In this method, the observer is presented with two or more observation intervals. These intervals may be separated spatially (i.e., the test stimulus is presented at one of several possible locations within the visual field) or temporally (i.e., the test stimulus is always presented at the same location but in one of

several well-defined time periods). All of the observation intervals but one contain noise, and the observer is to report the interval that contained the signal. The "percent correct" value is plotted as a function of stimulus magnitude. A typical measure of sensitivity is the stimulus that results in a "percent correct" value halfway between chance and perfect performance (e.g., 75% correct in a two-alternative, forced-choice experiment). The results of a two-interval, forced-choice procedure are related quantitatively to those of a comparable "yes-no" procedure.

Forced-choice procedures are often referred to as "criterion free," but in a sense this is misleading. It should be noted that the term *criterion* has been used in two disparate ways in psychophysical experiments. First, criterion refers to the magnitude of sensory experience that is required by an observer in order to respond that a stimulus was present. By this definition, forced-choice procedures are criterion free since criterion plays no role in the determination of percent correct. It should be noted, however, that forced-choice procedures depend on subject cooperation. As an extreme example, a subject may decide to respond incorrectly, so the percent correct is considerably below chance, or the subject may be inattentive on a certain percentage of trials, which adds noise to the determination of sensitivity.

Second, criterion refers to the aspect of the stimulus upon which a detection decision is made (whether the test stimulus was flickering, whether it appeared to be yellow, etc.). A subject is generally free to use any means possible to maximize the percent correct. For example, if a shutter sound is correlated with stimulus presentation, the auditory cue may be used as a basis for judgment. Or the appearance of the stimulus may change in a way that is correlated with increased probability of detection. For example, in probe-on-flash measurements of rod-system luminance-response functions, the presence of the test stimulus can be detected not only on the basis of a local brightening of the region of the test probe but also on its darkening or on the emergence of an afterimage under certain conditions.[3] In this sense, criterion can play a role in forced-choice experiments. Sensory experiences that are correlated with the presentation of the test stimulus allow correct responses in a forced-choice procedure but complicate the quantitative modeling of underlying visual mechanisms.

One of the useful concepts derived from SDT is the "ideal observer." Given complete information about the properties of the signal and noise as well as the properties of the detection system, it is possible to specify quantitatively the ideal performance of that system. This performance of an ideal observer may then be compared with that of human observers to determine how closely their performance approaches that of the ideal. In this way, it is possible to derive a better understanding of the constraints that are placed on human visual performance by optical and neural factors. A recent example of this approach in modeling the development of the human visual system is provided by Banks and Bennett.[15]

Because the classical psychophysical methods, as well as those of SDT, tend to be time-consuming, adaptive psychometric procedures have been developed, in which the stimulus value on any given trial is based on a measure of the performance on previous trials. The purpose of these adaptive procedures is to increase the accuracy and efficiency of threshold determination. An example is the "transformed" staircase,[83] in which complex decision rules are used to derive specific points on a psychometric function. If a "two-down, one-up" rule is used, such that the stimulus value is decreased only after two consecutive positive responses but is increased after one negative response, the average of the reversal points (typically 6 to 8) corresponds to the 70.7% point on a psychometric function.[83] Other points on this psychometric function can be obtained by changing the decision rule. The combination of this technique with the forced-choice procedure has resulted in the forced-choice staircase, which has proven useful clinically. In this type of staircase, the stimulus value on any given trial is determined by the correctness of the response on the immediately preceding trial. Optimized sequences of stimulus alternatives in a two-interval forced-choice procedure have been proposed to minimize response bias.[49] Additional types of adaptive procedures include PEST,[98] QUEST,[131] and Modified Binary Search (MOBS).[127] In the QUEST procedure, for example, the stimulus value on each trial is based on the most probable estimate of threshold as derived from a bayesian statistical analysis of the results of previous trials. A discussion of some of the merits and drawbacks of these adaptive procedures as applied to automated perimetry is provided by Johnson and Shapiro.[69]

Although psychophysical procedures are used primarily to measure thresholds, much of sensory experience results from suprathreshold stimulation. The measurement of responses to suprathreshold stimuli is easily performed by using electrophysiological procedures (e.g., measurement of the b-wave

luminance-response function). However, assessment of visual responses to suprathreshold stimuli is extremely problematic for psychophysical techniques. One approach to the psychophysical measurement of luminance-response functions is provided by the "probe-on-flash" paradigm.[66] In this procedure, a test probe is presented simultaneously with the onset of a larger, concentric light flash. The underlying assumption is that the function relating detection of the probe to flash luminance is related quantitatively to the luminance-response function of the visual system. A detailed analysis of this paradigm has been developed by Hood and Greenstein[66] and Massof et al.[91]

Other procedures have also been developed that attempt to assess the suprathreshold properties of the human visual system. One method is magnitude estimation,[90] in which a subject is asked to assign numbers to the magnitude of the sensory experience that accompanies the presentation of a suprathreshold stimulus such as a light flash. The technique of magnitude production has also been used whereby the subject manipulates the stimulus to generate sensory events of varying magnitude. The stipulation is that the assigned numbers or stimulus settings reflect the magnitude of sensory experience on a ratio scale (i.e., this light is twice as bright as that one). From such techniques, it is possible to derive scales of the relationship between stimulus magnitude *(S)* and sensory magnitude *(R)*. Experiments have typically reported a power law relationship between these two variables:

$$R = kS^n \qquad (1)$$

in which k is a constant of proportionality and n is an exponent that varies with sensory modality.[90]

Matching techniques have also proved useful in the assessment of suprathreshold visual function. An example is the Rayleigh equation, a color-matching procedure that provides an important diagnostic test of congenital color vision deficiencies.[102] A second example is the contrast matching of sine wave gratings of different spatial frequencies. This approach has been used to evaluate the suprathreshold contrast perception of simple and complex spatial patterns.[51]

Visual Channels

Central to the psychophysical testing of individuals with visual disorders is the concept of visual channels or filters. There is abundant psychophysical evidence that visual function is mediated by separate channels or subsystems within the visual pathway that provide parallel processing of information about form, color, movement, and depth.[81, 82, 85] For example, studies indicate that form information is processed by multiple filters with different spatial and temporal properties,[25, 56, 132] responses to stimuli of different wavelengths appear to be mediated by an achromatic and two chromatic channels,[59, 67, 104, 122] and motion sensitivity is governed by direction-specific mechanisms.[120] In disorders of the visual system, there may be selective alterations in the functional properties of these various visual subsystems.[107] There is suggestive evidence that psychophysically derived channels may have physiological correlates in the magnocellular, parvocellular, and blob pathways of the primate geniculocortical visual system.[85]

Through either the appropriate selection of visual stimuli or through changes in the criterion for threshold judgments, it is possible to bias psychophysical tests toward selective detection by specific channels.[68] For example, increasing the duration and size of a long-wavelength test flash shifts detection from a field-additive, achromatic mechanism to a chromatically coded pathway.[73, 129, 130] As a second example, experiments have shown that sensitivity to sine wave gratings can be mediated by either of two visual mechanisms, one primarily responsible for flicker detection and one for the detection of pattern.[77] Through the experimental manipulation of a subject's response criterion, it is possible to study separately the properties of these two detection mechanisms using the same visual stimulus.[30]

In summary, it is apparent that a considerable number of psychophysical procedures have been devised for the purpose of evaluating visual function, both of normal individuals and of those with visual system disorders. Additional methods that are potentially even more efficient in clinical applications are under development.[74] The psychophysical method of choice in any given situation depends ultimately on trade-offs among the necessity for control of criterion changes, the efficiency of threshold estimation, and the nature of the detection task.

DUPLICITY THEORY

It has been well established that human vision, as well as vertebrate vision in general, is mediated by two classes of photoreceptoral systems: rods and cones.[41] This has been termed the "duplicity the-

ory," although it is more an experimentally validated fact than a theory. The rod system functions optimally under conditions of dim (scotopic) illumination, lacks color vision, and has relatively poor spatial and temporal resolution. The cone system is optimized for relatively high (photopic) light levels, is less sensitive to light than the rod system, but has good spatial and temporal resolution, and mediates color vision. It should be noted that the terms *scotopic* and *photopic* have been used both in reference to the receptor system that mediates vision and to the level of illumination, regardless of receptor type. This potential ambiguity of usage is further complicated by the term *mesopic*, which refers to intermediate light levels. Under mesopic conditions, it is possible that both rod and cone systems can mediate vision, depending on such factors as stimulus wavelength and size.

The human retina contains a single type of rod photoreceptor, with rhodopsin as its visual pigment (other vertebrates such as amphibians may have more than one type of rod photoreceptor).[41] There are three types of cone photoreceptors in the human visual system that differ in the spectral absorption characteristics of their photopigments.[117] The spatial densities of rods and cones differ with eccentricity and meridian.[39, 96] The peak spatial density for rods occurs at approximately 15 degrees of eccentricity; that for middle- and long-wavelength–sensitive cones occurs in the center of the fovea. The peak spatial density of short-wavelength cones occurs at approximately 1 degree, with an absence in the foveal center.[94] The luminosity functions for rod and cone systems differ considerably, which results in a noticeable change in the apparent brightness of spectral lights as vision shifts from one receptor type to the other (the "Purkinje shift").

An important consideration in assessing the response properties of rod and cone systems, both in normal individuals and in those with visual disorders, is that information transfer within the visual pathway is limited both by the properties of photoreceptors and by those of the postreceptoral network into which the receptor signals feed. For example, suction electrode recordings from individual primate photoreceptors have shown that cone receptor responses to a light flash are faster than those of rod receptors, while the rods are somewhat more sensitive to light,[18] so that some of the functional differences between rod and cone systems appear to be related to properties of the photoreceptors themselves (see Chapter 7). However, the great differences between rod- and cone-mediated vision are due to a considerable extent to the synaptic and postsynaptic organization of the visual signals. These postreceptoral processes play a large role in limiting the response properties of rod and cone systems. For example, evidence has been presented for a duplex rod critical flicker frequency (CFF) function, not only in visually normal individuals[34, 35] but also in rod monochromats.[64] These findings suggest that rod photoreceptors are capable of responding at temporal frequencies as high as 28 Hz, and that the limited temporal resolution often attributed to the rod system may be imposed by postreceptoral mechanisms. Moreover, the relatively poor temporal resolution of the short-wavelength cone system[133] must result from postreceptoral factors, since the temporal response properties of the short-wavelength cone photoreceptors do not appear to differ from those of the middle- and long-wavelength sensitive cones.[18]

It has sometimes been assumed that rod and cone systems function independently. However, recent studies have demonstrated that the sensitivity of one system can be modified significantly by the other (see Chapter 60 and Benimoff et al.[19] for reviews). Such rod-cone interactions are often most apparent when stimuli are small and/or temporally modulated. Rod-cone interactions can also be observed in ERG recordings.[9, 116] There appear to be several fundamentally different types of rod-cone interactions with underlying mechanisms that vary with stimulus conditions.[5, 40]

DARK ADAPTOMETRY

Basic Clinical Dark Adaptation

It is well known that, following the eye's exposure to a bright light, visual sensitivity requires a substantial period of time to recover. If the light exposure is sufficiently intense, complete recovery can take as long as 45 to 50 minutes.[103] The typical time course of dark adaptation is illustrated in Figure 56–1. This bleaching recovery curve was measured in the peripheral retina of a normal individual by using a test flash of 500 nm, a wavelength to which both rod and cone systems are sensitive. Thresholds are plotted relative to those measured in the completely dark adapted state prior to exposure to a bleaching light.

The dark adaptation curve in Figure 56–1 follows a characteristic two-branched course, with an inflection or "kink" occurring at approximately 10 minutes. In accordance with duplicity theory, the early branch represents the recovery of cone system sensi-

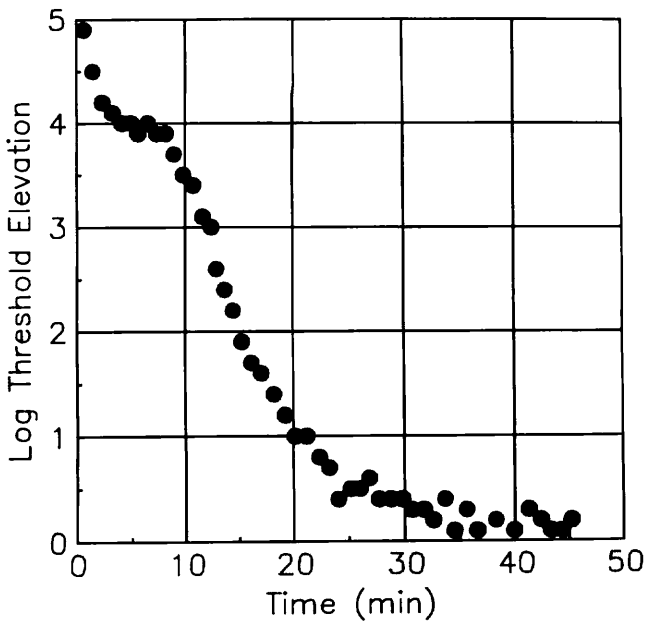

FIG 56–1.
Typical normal dark adaptation curve measured at 20 degrees in the nasal visual field by using a 500-nm, 1.7-degree, 500-ms test flash following a 2-minute exposure to a Ganzfeld bleaching light of 3.6 log cd · m^{-2}. Thresholds are plotted relative to their dark-adapted (prebleach) value. A transition between cone-mediated and rod-mediated detection (rod-cone break) occurs at about 10 minutes. Complete recovery of the rod system requires approximately 45 minutes.

tivity; thresholds measured during the later branch are mediated by the rod system, and the inflection point is termed the rod-cone break. Consequently, as dark adaptation proceeds, a chromatic test flash initially appears colored and later seems colorless as detection shifts to the rod system. The difference between the absolute (colorless) threshold and the threshold for color has been termed the photochromatic interval. It should be noted that the threshold for color does not correspond exactly with the cone detection threshold; the rod system can have a marked influence on color thresholds.[5, 84, 123] This type of rod-cone interaction has been attributed variously to a desaturation of the chromatic cone signal by an achromatic rod signal[84] or to a rod-induced shift in the balance of color-opponent cells.[124]

To a first approximation, the dark adaptation curves of the rod and cone systems may be quantified according to the exponential equation:

$$\log I_t = A + B \exp[-(t - t_R)/\tau)] \qquad (2)$$

in which I_t is the threshold at any given time t during dark adaptation; t_R is either 0 (cone system) or the time of the rod-cone break (rod system); and A, B, and τ are free parameters.[103] This equation provides a quantitative description of dark adaptation that can be helpful in the clinical assessment of abnormalities in the time course of bleaching recovery.[4] Nevertheless, significant deviations from this relationship have been noted for both rod[79, 95] and cone systems.[12, 27, 44]

The recovery of sensitivity following light exposure depends ultimately on the regeneration of bleached photopigment.[100] For example, if the concentration of photopigment within the receptors is reduced through vitamin A deprivation, then the time course of psychophysical dark adaptation is prolonged, and thresholds may never reach normal levels.[71, 101] In addition, there is a general correspondence between the time course of rhodopsin regeneration and the rate of return of rod system sensitivity.[111] Yet, it is clear that psychophysical dark adaptation is not due simply to the recovery of a light absorber. That is, when 90% of rhodopsin has regenerated following an intense bleach, the rod threshold remains elevated by 2 to 4 log units,[79, 95] while the threshold elevation due to a reduced quantum catch would be only approximately 0.1 log unit. It has been proposed that the recovery of rod threshold depends, at least in part, on the removal or inactivation of bleaching intermediates or photoproducts within the photoreceptors, rather than the regeneration of bleached photopigment per se.[79, 99]

To complicate matters, there is considerable evidence that postreceptoral as well as receptoral processes are involved in the recovery of sensitivity during dark adaptation. For example, changes in test flash size can influence the shape of the dark adaptation curve,[10, 23, 111] although test size can have no influence on the rate of photopigment regeneration. The concept of an "adaptation pool" was introduced by Rushton[112] to account for observations that changes in sensitivity appear to result from the pooling of signals from many photoreceptors. Second, dim lights that bleach a trivial amount of photopigment and that have no effect on the receptor potential or on horizontal cell responses in the skate retina nevertheless result in an elevation of b-wave and ganglion cell thresholds that requires several minutes to recover.[57] It has been proposed that threshold elevations observed following weak bleaches and/or early in the course of dark adaptation result from nonreceptoral ("network") mechanisms, where-

as threshold elevations observed later in the course of dark adaptation result from "photochemical" processes occurring within the photoreceptors.[41]

In addition to a recovery of sensitivity, other phenomena accompany the dark adaptation process. After the offset of bleaching, the pupil is initially constricted, and then following a transient series of oscillations, it dilates with a time course similar to the recovery of rod sensitivity.[8] Following the offset of a bleaching light, an afterimage may be apparent, which then fades over time. The initial afterimage, which typically appears colored, originates from the cone system.[29] If the bleaching exposure is of a high intensity, particularly in aphakic individuals, erythropsia may result in which the visual environment appears to be tinged with red.[61] A prolonged, colorless afterimage that originates from the rod system[86] is also often visible. It has been suggested that the rod afterimage may be related to the noisy residual excitation of photoreceptors that has been observed following the cessation of an adapting light.[18]

The apparent correlation between the disappearance of the rod afterimage and the recovery of rod sensitivity has given rise to the concept of the "equivalent background."[17] According to this hypothesis, the aftereffect of bleaching ("dark light") is identical to the desensitizing effect produced by a steady background of "real light." It has been proposed that bleached photoreceptors produce a continuing noise signal in darkness that impairs the detectability of a test flash.[16] This proposal stands in contrast to the photochemical hypothesis, which postulates that the desensitizing effect of bleaching results from the concentration of bleaching photoproducts in the photoreceptor outer segments. A detailed discussion of the differences between these two hypotheses is presented by Geisler.[50] It has been demonstrated that the effects of real and dark light are not always identical,[16, 50] which suggests that the equivalent background hypothesis cannot fully explain the process of bleaching recovery.

In the psychophysical measurement of dark adaptation, the parameters of the test flash have a marked effect on the nature of the recovery curve. One of the primary factors is the test stimulus wavelength, as illustrated in Figure 56–2. This figure presents normal dark adaptation curves obtained with middle-wavelength (open circles) and long-wavelength (filled circles) test flashes. It is apparent that the test flash wavelength influences the time of the transition from cone-mediated to rod-mediated detection (rod-cone break). With a middle-wavelength

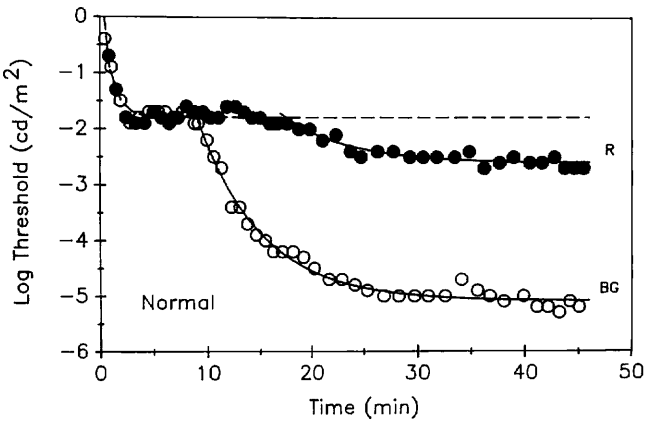

FIG 56–2.
Dark adaptation curves for a normal observer with middle-wavelength *(open circles; BG)* and long-wavelength *(filled circles; R)* test stimuli, with bleaching and test conditions comparable to those of Figure 56–1. The *solid line* through the *open circles* represents the best fit of Equation 2 to the rod-mediated portion. This curve has been shifted vertically to fit the filled circles. The *dashed curve* represents the fit of Equation 2 to the cone-mediated thresholds. Since data are plotted in photopic units, thresholds for the two chromatic stimuli are identical during the cone plateau. The curves subsequently diverge, and the threshold difference indicates that both represent rod-mediated thresholds. The rod-cone break occurs later in time for the R test flash.

test flash, the transition occurs at approximately 10 minutes under these conditions. For a long-wavelength test flash, there is an extended cone plateau, and the rod-cone break occurs considerably later in the course of bleaching recovery. The change in the time of the rod-cone break is predictable from the relative sensitivity of the rod system to the two wavelengths of test flash. This is illustrated by the solid line through the filled circles in Figure 56–2, which is shifted vertically by the differential sensitivity of the rod system to the long-wavelength and middle-wavelength test flashes. Although it is often assumed that long-wavelength test flashes are cone mediated in the retinal periphery, this is not necessarily the case. Large, long-wavelength test stimuli can be detected by rods in the peripheral retina at the end of dark adaptation, as shown in Figure 56–2.

Although not illustrated in Figure 56–2, the characteristics of cone system dark adaptation are also influenced by the wavelength of the test flash. If a short-wavelength test flash is used to measure dark adaptation following long-wavelength bleaching the cone-mediated portion of the curve typically has two

branches. The first branch represents detection by the short-wavelength cone system; the second branch is mediated by the middle-wavelength cone system.[12] Even when dark adaptation is measured with a test stimulus that is detected solely by the long-wavelength cone system, recovery does not necessarily proceed along a single exponential time course. Temporary plateaus and losses of sensitivity are observed and have been attributed to the influence of postreceptoral mechanisms.[27, 44]

The retinal locus of the test flash also has an important influence on the nature of the dark adaptation curve.[62] A small test flash that is presented to the fovea typically results in a dark adaptation curve that is cone mediated throughout bleaching recovery. As illustrated in Figure 56–2, a test flash that is presented to the parafovea can be detected by either the cone or rod system, depending on test flash and bleaching parameters and the time during recovery at which the threshold is measured. Although it is often assumed that detection occurs either through the cone or rod system independently, evidence for rod-cone interactions during dark adaptation has been presented. For example, the foveal cone threshold has been observed to fall slightly during the later part of dark adaptation, an effect that has been attributed to the influence of the rod system.[42] Moreover, during the later part of the cone plateau in the peripheral retina, threshold variability may increase, and the cone-mediated threshold may rise slightly, an effect that has also been ascribed to the influence of the rod system.[134]

Bleaching parameters can have a marked effect on the time course of dark adaptation. One consideration is bleaching wavelength. Short wavelengths are more effective than long wavelengths in desensitizing the rod system. Therefore, short-wavelength bleaches result in a longer cone plateau with a more distinct rod-cone break. Long-wavelength bleaching affects primarily the cone system, so the rod-cone break occurs relatively early in bleaching recovery or may be absent altogether, with thresholds rod mediated throughout dark adaptation.

The duration and intensity of the bleaching light also have an important effect on dark adaptation. The relationship between p, the fraction of unbleached pigment, and t, the bleaching time measured in seconds, has been described by the following relationship:

$$-\frac{dp}{dt} = \frac{pI}{Q} - \frac{(1 - p)}{t_0} \qquad (3)$$

where I is the retinal illuminance in trolands (either photopic or scotopic, as appropriate), Q is the energy of the pulsed stimulus (in td · sec) required to bleach p from 1 to $1/e$ (photosensitivity), and t_0 is the time constant of regeneration in seconds.[6, 65] For the rod system, $Q = 1.57 \cdot 10^7$ scotopic td · sec and $t_0 = 519$ seconds; for the cone system, $Q = 5.0 \cdot 10^6$ photopic td · sec and $t_0 = 130$ seconds.[135] However, significant departures from this first-order kinetic equation have been observed.[24, 36, 109, 121]

For relatively brief bleaching (e.g., less than 45 seconds for the rod system), there is a reciprocal relationship between light energy and duration[113] such that p depends on It_0 in td · sec:

$$\log (\log 1/p) = \log (It_0) - \log Q. \qquad (4)$$

For longer bleaching in which significant regeneration has occurred, the relationship can be described as

$$p = I_0/(I + I_0) \qquad (5)$$

where $I_0 = Q/t_0$.[6] An extremely brief (microsecond to millisecond range), high-intensity flash does not have the same bleaching effect as a longer-duration light delivering the same total number of quanta. This phenomenon has been termed "Rushton's paradox."[103] It has been proposed that this effect results from photoreversal, in which additional quantal absorption can reisomerize bleaching intermediates. Therefore, with extremely brief flashes, it is not possible to bleach the photopigment completely, regardless of the degree of quantal flux. The extent to which such reisomerization can occur in humans depends on a number of factors, including bleaching wavelength, and there is some question as to the exact magnitude of the photoreversal phenomenon.[103, 109]

If the bleaching light is relatively weak, there is a rapid recovery of sensitivity following light offset that has been termed "early dark adaptation"[14] or "Crawford masking"[38] and is presumed to represent neural activity ("network adaptation"). Depending on the adapting level and the photoreceptor system involved, the recovery of sensitivity can require only a few milliseconds or as much as a few minutes. Under such conditions, the threshold elevation at the offset of the adapting field is substantially greater than would be expected from the extent of photopigment bleaching.[113]

It is typically the case that sensitivity begins to re-

cover immediately following the offset of an adapting light. Nevertheless, under certain conditions, thresholds may become transiently elevated rather than reduced during the initial period of dark adaptation. An example is transient tritanopia, in which the cone system threshold for a short-wavelength test flash is elevated transiently following the offset of a yellow adapting light.[13, 104] Comparable results may be observed under other conditions of chromatic adaptation.[105] It has been proposed that transient tritanopia represents the action of a "restoring force" that temporarily elevates the threshold by driving a postreceptoral opponent mechanism to a polarized state.[104] Since transient tritanopia can be observed in the b-wave of the primate ERG, the site of the chromatic interaction appears to be at or distal to the generators of the b-wave.[128]

Although the recovery of sensitivity during dark adaptation is thought to depend predominantly on events that occur within the retina of the bleached eye, binocular interactions have been reported. For example, the time course of dark adaptation for a test flash presented to one eye is affected by the presence of a small, dim light presented to the nontested eye during bleaching adaptation.[80, 88] Moreover, rod thresholds during bleaching recovery can be lowered by pressure blinding the dark-adapted, nontested eye.[88] In addition, the rod absolute threshold in the test eye can be reduced by intense long-wavelength adaptation of the contralateral eye.[106] To account for these findings, it has been proposed that a dark-adapted, nontested eye generates noise that interferes with detection.[88, 106]

For the clinical measurement of dark adaptation, the most widely used, commercially available instrument is the Goldmann-Weekers Dark Adaptometer (Haag-Streit). It should be noted that a calibration error has been observed in some models of this instrument.[87] Perimeters that allow precise control of test stimulus properties, such as the Tübingen perimeter (Oculus), can also be used to measure dark adaptation.[4] Methods for the semiautomation of dark adaptation testing have been reported.[58, 78] A test of dark adaptation that is easily implemented is the macular photostress recovery test, which has been advocated as a method for distinguishing between vision loss due to macular disease and loss resulting from disorders of the optic nerve,[53] although the underlying physiological processes are uncertain. In this procedure, the eye is first exposed to illumination from a penlight, and then the patient is asked to read test letters on an acuity line that is just larger than his best acuity. The time required for the patient to recover the ability to read at least three Snellen letters on this line is used as an index of dark adaptation.

A number of different eye diseases may be accompanied by abnormalities in dark adaptation (reviewed by Krill[76] and Hart[61]). In the clinical evaluation of dark adaptation abnormalities, it is important to distinguish between elevations of threshold and delays in the time course of bleaching recovery per se. For example, some diseases that affect the photoreceptors and/or RPE, such as progressive cone dystrophy[21, 110] and chloroquine toxicity,[33] can result in threshold elevations without an accompanying abnormality in the time course of bleaching recovery. Other disorders of the outer retina may be accompanied by delayed bleaching recovery, including retinitis pigmentosa,[4, 48] age-related maculopathy,[28, 45, 53] acute posterior multifocal placoid pigment epitheliopathy,[60, 72] fundus flavimaculatus,[75, 118] and uveal disease.[7] Moreover, there can be considerable interpatient variability in the degree of dark adaptation abnormality within a given disorder.[4, 72] Some visual disorders that primarily affect the inner retina, such as diabetes mellitus and glaucoma, can also result in an abnormal time course of dark adaptation.[54, 63, 97] In addition, systemic conditions such as vitamin A deficiency,[71, 101] hypoxia,[47, 92] hypoglycemia,[93] and alcohol ingestion[2] can result in dark adaptation abnormalities.

In the clinical assessment of dark adaptation, it is helpful to identify the photoreceptor system that mediates detection in order to determine whether an abnormality is specific to the rod or cone system. Therefore, it is necessary to measure dark adaptation with at least two wavelengths of test flash, to which the rod and cone systems have markedly different sensitivities. For example, Figure 56–3 shows dark adaptation curves measured at 20 degrees in the nasal visual field of an individual with congenital stationary night blindness (see Alexander et al.[5] for further patient characteristics). During the first few minutes of dark adaptation, the superimposition of the data points for the two wavelengths of the test flash indicates that thresholds are cone mediated for this patient during this period. Thresholds for the long-wavelength test flash (filled circles) then remain constant throughout the remainder of bleaching recovery. However, at the normal time of the rod-cone break (approximately 10 minutes as shown by the dashed line), thresholds for the middle-wavelength test flash (open circles) show a slight

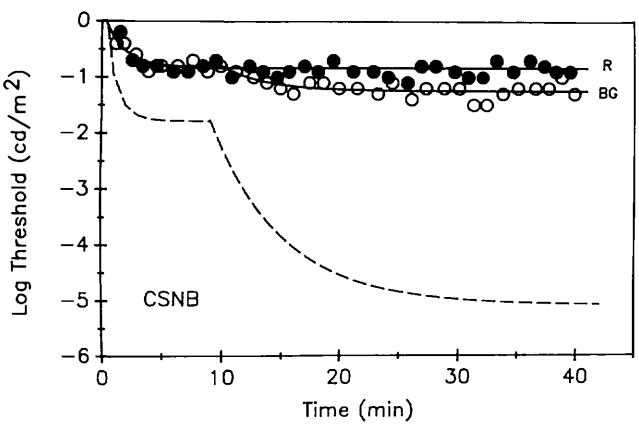

FIG 56–3.
Dark adaptation curves for an individual with congenital stationary night blindness that were measured under conditions comparable to those described in Figure 56–2. The use of chromatic test flashes distinguishes between rod- and cone-mediated thresholds. Thresholds for the R test flash are cone mediated throughout dark adaptation and are elevated above those of a normal observer (*dashed line*, replotted from Fig 56–2). Thresholds for the BG test flash are rod mediated after approximately 10 minutes. Despite the extreme elevation of rod-mediated thresholds, the rod-cone break occurs at the normal time.

decline for this patient. The small but consistent difference between thresholds for the two wavelengths of the test flash during the later portion of dark adaptation indicates that thresholds for the middle-wavelength flash are rod mediated at the end of bleaching recovery, although elevated by approximately 4 log units above normal. Without such a comparison, it might have been concluded erroneously (see Krill[76]) that thresholds obtained with the middle-wavelength test flash represented a delayed recovery of cone sensitivity in this patient with congenital stationary night blindness.

The pathophysiological mechanisms that underlie abnormalities of dark adaptation are likely to be different in various visual disorders, a point that is illustrated exquisitely by studies of patients with fundus albipunctatus and Oguchi's disease.[31, 32, 89] In both diseases, the dark-adapted sensitivity of the rod system is within normal limits once complete rod recovery has occurred. However, this recovery process requires an extraordinarily long period of time. In fundus albipunctatus, the extremely prolonged recovery of rod sensitivity that is observed psychophysically is accompanied by a delayed regeneration of rhodopsin as measured densitometrically.[108] Therefore, the abnormality of dark adaptation observed in this disorder appears to occur at a very distal stage of the visual process.

These findings are in striking contrast to those obtained from patients with Oguchi's disease.[31] In this relatively rare condition, the regeneration of photopigments occurs with a normal time course. However, exposure to lights that bleach an insignificant amount of photopigment results in an extremely prolonged loss of rod sensitivity. It has been proposed that these results, coupled with ERG b-wave abnormalities, implicate a defective neural process within the retina in Oguchi's disease rather than an abnormality in photopigment regeneration.[31]

The administration of vitamin A can be effective in ameliorating dark adaptation abnormalities in individuals with vitamin A deficiency due to systemic conditions such as biliary cirrhosis or Crohn's disease.[71] However, effective treatments for dark adaptation abnormalities in various hereditary retinal diseases are, for the most part, unavailable. Exceptions include abetalipoproteinaemia (Bassen-Kornzweig syndrome), a systemic disorder accompanied by a form of retinitis pigmentosa that results from an absence of lipoproteins containing apoprotein beta,[20] and gyrate atrophy, a chorioretinal degeneration associated with an inability to degrade ornithine due to an enzyme deficiency.[70] In the former, large dosages of vitamin A have been reported to improve dark-adapted thresholds in persons with the early stage of this disorder,[55] and vitamins A and E in combination have been shown to arrest retinal deterioration as measured electrophysiologically.[22] In gyrate atrophy, the dietary restriction of proteins and of arginine, a precursor of ornithine, is being studied to evaluate the apparent effectiveness of this treatment in improving visual function in patients with this disorder.[20] A more comprehensive understanding of the pathophysiology of dark adaptation abnormalities and the development of possible treatment regimens for patients with other visual disorders await further explication of the complex photochemical and neural events underlying the dark adaptation process.

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