CHAPTER 3

Retinal Physiology and Psychophysics

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Highlights

- Electrophysiologic testing provides objective measures of visual system function, which are interpreted in conjunction with structural imaging data; normal structure should not be assumed to mean normal function.
- Multifocal electroretinography (ERG) can produce a topographic ERG map of central retinal cone system function, which can help the clinician diagnose macular dysfunction and assess the extent of central retinal involvement in generalized retinal disease.
- The electro-oculogram assesses the health and function of the retinal pigment epithelium.
- Though nonspecific, visual evoked potentials can objectively demonstrate normal function in the presence of symptoms that suggest otherwise.
- Psychophysical tests can be highly sensitive, but they are subjective and do not provide information about specific levels of the visual system.

Electrophysiologic Testing

Most electrophysiologic tests use evoked potential techniques in which a controlled stimulus is used to evoke an electrophysiologic response. Different techniques can be used to assess the function of the majority of the visual system, extending from the retinal pigment epithelium (RPE) to the primary visual cortex (Table 3-1).

Electrophysiologic testing provides objective measures of visual system function, which are interpreted in conjunction with structural imaging data; normal structure should not be assumed to mean normal function. In order to accurately interpret the data obtained from electrophysiologic testing, the clinician needs to know the origin of the signals generated during testing. The test findings can then be correlated to the patient's underlying pathophysiology. In addition to diagnostic uses, electrophysiologic data are used in objective monitoring, either of disease progression or the efficacy of treatment,

Table 3-1 Electrophysiologic Testing

Electrophysiologic Test	Level of Visual System and Characteristic Tested
Full-field electroretinogram (ffERG)	Generalized retinal function under light- and dark-adapted conditions
Dark-adapted 0.01 (weak flash)	On-bipolar cells (inner nuclear layer) of rod system; the only test that selectively monitors rod system function
Dark-adapted 3.0 (standard flash)	Mixed rod-cone response (rod dominant)
Dark-adapted 10.0/30.0 (strong flash)	Mixed rod-cone response
Oscillatory potentials	Primarily amacrine cell signaling
Light-adapted 3.0 flash	Cones and bipolar cells
Light-adapted 3.0 30-Hz flicker	Generalized cone system function
Multifocal ERG (mfERG)	Measure of cone system function over central 40°–50° of the visual field
Pattern ERG (PERG)	Macular retinal ganglion cell function
Electro-oculogram (EOG)	Generalized retinal pigment epithelium function
Visual evoked potential (VEP)	Function of the entire visual pathway from the retina to area V1 of the visual cortex

and/or as both an outcome measure and an index of safety in the evaluation of novel therapeutic interventions.

A thorough patient history and careful ophthalmic examination help the clinician determine the most appropriate tests to employ; those tests should then be performed using standardized protocols. The International Society for Clinical Electrophysiology of Vision (ISCEV) publishes minimum standards for performing routine tests, thus enabling meaningful interlaboratory comparison and literature searches.

Brigell M, Bach M, Barber C, Moskowitz A, Robson J; Calibration Standard Committee of the International Society for Clinical Electrophysiology of Vision. Guidelines for calibration of stimulus and recording parameters used in clinical electrophysiology of vision. *Doc Ophthalmol*. 2003;107(2):185–193.

Standards, guidelines and extended protocols. International Society for Clinical Electrophysiology of Vision. Accessed January 17, 2022. https://iscev.wildapricot.org/standards

Electroretinography

The clinical electroretinogram (ERG) provides an objective measure of the electrical activity of the retina, usually evoked by a brief flash of light. ERGs are recorded with electrodes that contact the cornea or bulbar conjunctiva or with skin electrodes attached to the lower eyelids. Several types of corneal electrodes can be used, including contact lens, fiber, jet, and gold foil electrodes (Video 3-1). The 3 main types of electroretinography—full-field (Ganzfeld), multifocal, and pattern—are discussed in the following sections.

VIDEO 3-1 Performing electroretinography.
Courtesy of Shriji Patel, MD, MBA.

Full-Field (Ganzfeld) Electroretinography

In full-field electroretinography, a Ganzfeld bowl uniformly illuminates the entire retina with a full-field luminance stimulus; the Ganzfeld also provides a uniform background for photopic adaptation and photopic ERG recording. Regular calibration of flash strength is required for clinical accuracy. Figure 3-1 shows typical full-field ERG (ffERG) responses; however, normal values vary with recording techniques, and each laboratory must establish its own normative data (Video 3-2). Even with standardization, variations in the type of electrode and specific equipment used will affect the test results.

VIDEO 3-2 Interpreting an electroretinogram.
Courtesy of Milam A. Brantley, MD, PhD.

The pupils are dilated to maximize retinal illumination. In most laboratories, the patient is dark-adapted while the pupils are dilating, the electrodes are positioned under dim red light, and then stimulation commences by using an interstimulus interval sufficient to allow the retina to recover between flashes (from 2 seconds for low intensities up to 20 seconds for high intensities). Many laboratories record responses to a series of increasing stimulus strengths. The patient is then light-adapted (using standardized background intensity and adaptation time), and photopic testing is performed, in which the stimuli are delivered under rod-suppressing background illumination.

The ISCEV standard ffERG consists of 6 different responses (see Fig 3-1A). The nomenclature used for these is based on the flash strength as measured in candela-seconds per square meter and the adaptive state of the eye (ie, dark-adapted [DA] or light-adapted [LA]); older terms are given in parentheses in the following list. Measurement of the ERG focuses on the size and timing of the major components, as indicated in Figure 3-1.

1. *DA 0.01 (rod-specific):* In this response, a b-wave arises in the on-bipolar cells (BPCs) (inner nuclear layer) of the rod system. A reduction in this response identifies dysfunction within the rod system, but because it arises at an inner retinal level, this response cannot differentiate between dysfunction at the level of the photoreceptor and inner retinal dysfunction. It therefore acts as a measure of rod system sensitivity.
2. *DA 3.0 (mixed rod–cone):* This response consists of an a-wave and a b-wave. The a-wave at this flash strength usually has 2 peaks between approximately 15 and 21 milliseconds, either of which may be prominent. Because only approximately the first 8 milliseconds of the DA a-wave reflects photoreceptor hyperpolarization, the ISCEV standard includes additional brighter flash testing for better diagnostic specificity.
3. *DA 10.0/30.0:* At either of these flash strengths, the a-wave has an easily measurable peak, and most of the a-wave reflects photoreceptor function. Consequently, this response can localize dysfunction to either a photoreceptor or an inner retinal level. Thus, a reduced DA 0.01 response accompanied by marked reduction in the a-wave of the DA 10.0/30.0 response indicates photoreceptor dysfunction. However, if the a-wave amplitude is normal (see Fig 3-1A) or near normal and the b-wave amplitude is lower than that of the a-wave (known as a negative or electronegative ERG waveform), dysfunction occurs post-phototransduction, at an inner retinal level.

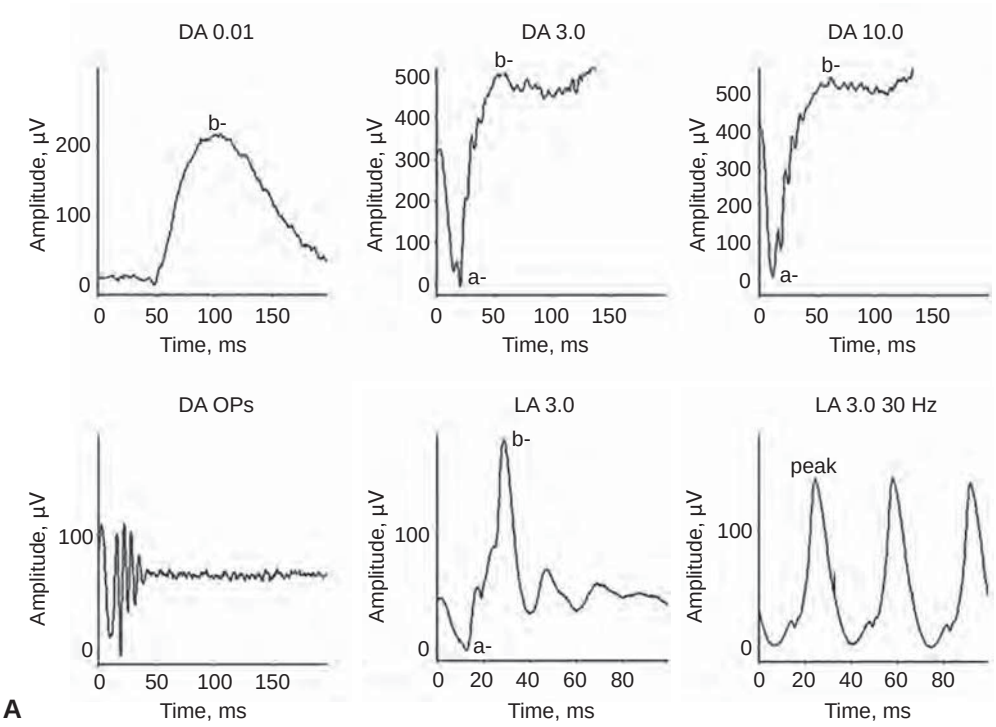

Figure 3-1 **A,** Basic full-field electroretinogram (ffERG) responses as defined by the International Society for Clinical Electrophysiology of Vision. The amplitude and peak times are typical, but normal values must be established for each laboratory using local techniques. a- = a-wave; b- = b-wave; DA = dark-adapted; LA = light-adapted; OPs = oscillatory potentials; numbers following abbreviations denote stimulus intensity (in candela-seconds per square meter). **B,** Standard ffERG setup. *(Part A courtesy of Graham E. Holder, PhD; part B courtesy of Shriji Patel, MD, MBA, and Rocky Munn.)*

4. *Oscillatory potentials:* These small oscillations on the ascending limb of the b-wave probably arise largely in the amacrine cells and can be made more visible by filtering. They are reduced in retinal ischemic states and in most cases of congenital stationary night blindness, but overall, they have limited diagnostic value.
5. *LA 3.0 (photopic single-flash):* This ERG response is obtained by stimulating with a flash superimposed on a rod-suppressing background. The a-wave relates to function in the cone photoreceptors and off-BPCs. The b-wave arises as a synchronized component in on- and off-BPCs. This response thus enables some localization of cone system dysfunction.
6. *LA 3.0 30 Hz (photopic flicker):* The temporal resolution of the rod system is poor, and this response arises in the cone system. It is the more sensitive measure of cone system dysfunction but allows no anatomical specificity. Both timing and amplitude are important parameters; delay in the flicker ERG response is a sensitive measure of generalized retinal cone system dysfunction, whereas reduced amplitude but normal peak time (see Fig 3-1A) usually indicates restricted loss of function.

Several factors influence the size and timing of a normal ERG response, one of which is pupil size; thus, pupil diameter should always be measured at the start of the test. Because ERG amplitude declines with age, age-related controls are necessary. Although newborns have smaller ERG responses with simplified waveforms, the responses mature rapidly, reaching adult values in the first year of life. The ERG is relatively insensitive to refractive error; highly myopic eyes have lower-amplitude ERGs but without the peak-time delay usually associated with inherited retinal degeneration. Similarly, ERG response is generally minimally affected by media opacity such as cataract or vitreous hemorrhage.

As a measure of a biological signal, ERGs have inherent noise. However, a reduction in amplitude of more than 25% over time is usually considered significant—even if the amplitudes remain within the reference range ("normal range"). For peak-time measures, a change greater than 3 milliseconds is regarded as significant for cone-derived response a- or b-waves and brighter-flash DA a-waves; a change greater than 6 milliseconds is significant for DA b-waves.

In general, ERG peak-time shift suggests generalized dysfunction, whereas simple amplitude reduction suggests restricted loss of function such as may occur in a partial retinal detachment (loss of function in the detached area of retina but normal function in the attached retina), branch vascular occlusion, regional uveitic damage, or restricted ("sector") forms of retinitis pigmentosa (RP). Timing is often best assessed using the 30-Hz flicker ERG peak time. Generalized inflammatory disease, such as posterior uveitis, may be associated with delay but preservation of amplitude. Indeed, marked 30-Hz flicker delay with a high amplitude almost always indicates an inflammatory etiology.

Figure 3-2 presents examples of ERG patterns found in association with specific disorders. As the ffERG shows the mass response of the entire retina to flash stimuli, the responses will be normal when dysfunction is confined to the macula. Even though the central macula is cone dense, most retinal cones lie outside the macula; consequently, the macula contributes little to a ffERG. Because abnormal photopic ERG responses indicate cone dysfunction outside the macula, ERG testing can help the clinician distinguish between a macular dystrophy phenotype (normal ffERG response) and a cone or cone–rod dystrophy phenotype (abnormal ERG response), which may have more serious visual implications for the patient. For example, in some patients, *ABCA4* retinopathy (eg, Stargardt disease, fundus

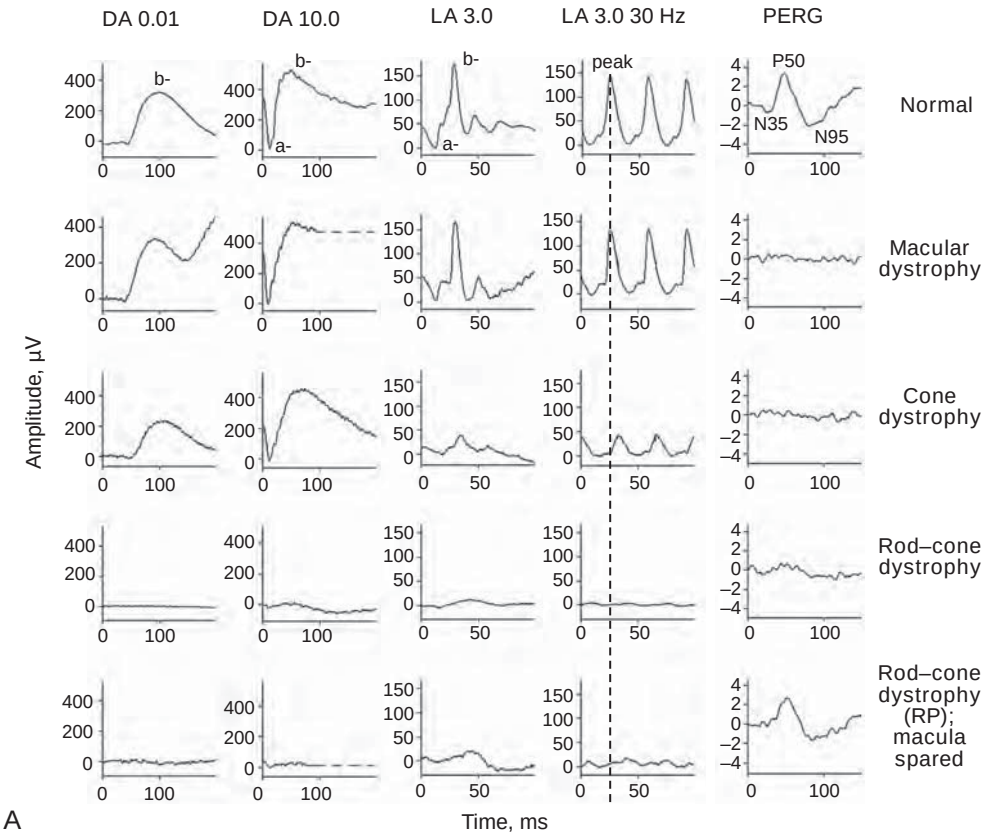

Figure 3-2 ERG findings in various disorders. **A, Normal:** Typical waveforms are shown at the top. The timing of the 30-Hz flicker ERG is shown by the vertical *dashed line*. For all responses, the flash occurs at time 0 ms. **Macular dystrophy:** Full-field ERG (ffERG) responses are all normal, but the pattern ERG (PERG) response is undetectable. **Cone dystrophy:** Dark-adapted (DA) 0.01 (rod-specific) and DA 10.0 ERG responses are normal; light-adapted (LA) 3.0 30-Hz (photopic flicker) and LA 3.0 (single-flash) ERG responses are reduced and delayed; the PERG response is subnormal, indicating macular involvement. **Rod–cone dystrophy:** Retinitis pigmentosa (RP) with macular involvement. All ERG responses are markedly subnormal, with rod ERGs more affected than cone ERGs; severe reduction of the DA 10.0 a-wave, indicating photoreceptor disease; and delayed 30-Hz and LA 3.0 cone ERGs, indicating generalized cone system dysfunction. Abnormal PERG response shows macular involvement. **Rod–cone dystrophy (RP); macula spared:** ffERGs show an abnormal rod–cone response pattern similar to that shown directly above, but a normal PERG response shows macular sparing.

(Continued)

flavimaculatus) can be associated with severe generalized cone and rod system dysfunction. If the ffERGs of these patients are normal at presentation, the dysfunction is confined to the macula and the ERGs have prognostic value: 80% of such patients will still have normal ffERG responses at 10-year follow up.

Fujinami K, Lois N, Davidson AE, et al. A longitudinal study of Stargardt disease: clinical and electrophysiologic assessment, progression, and genotype correlations. *Am J Ophthalmol.* 2013;155(6):1075–1088.

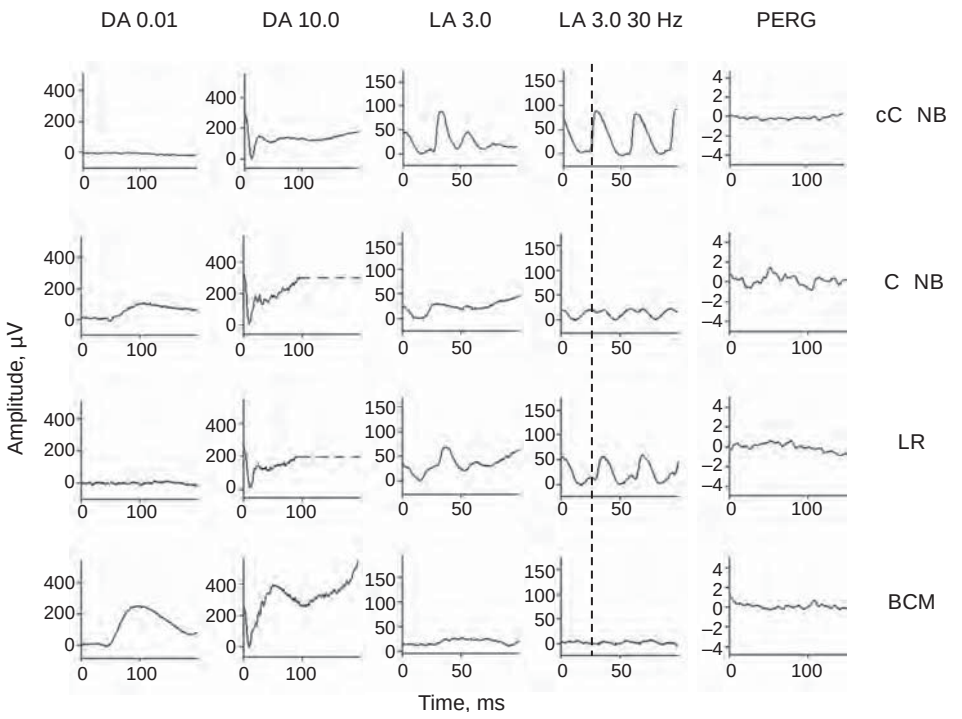

Figure 3-2 *(continued)* **B, cCSNB** ("complete" congenital stationary night blindness): Findings show loss of on-pathway function at a postreceptoral level. DA 0.01 response is undetectable; DA 10.0 response is profoundly electronegative, with the normal a-wave reflecting normal photoreceptor function and the relatively marked b-wave reduction indicating inner retinal disease; 30-Hz flicker ERG shows only minor changes in waveform and mild delay; LA 3.0 ERG shows changes diagnostic of loss of cone on-pathway function but sparing of the off-pathway. The a-wave commences normally but then shows a broadened trough. The b-wave rises sharply, with loss of the photopic oscillatory potentials, and marked reduction in the b-wave:a-wave ratio. The PERG response is markedly subnormal. **iCSNB** ("incomplete" CSNB): DA 0.01 response is subnormal but detectable; DA 10.0 response is markedly electronegative; 30-Hz flicker ERG response is markedly subnormal, showing delay and a characteristic triphasic waveform; LA 3.0 ERG shows a subnormal a-wave and a markedly subnormal b-wave, reflecting involvement of both on- and off-cone pathways; the PERG response is subnormal. **XLRS** (X-linked retinoschisis): DA 0.01 response is severely reduced; DA 10.0 response is profoundly electronegative; 30-Hz flicker ERG shows delay; LA 3.0 ERG shows delay and marked reduction in the b-wave:a-wave ratio; the PERG response is markedly subnormal. **BCM** (blue-cone [S-cone] monochromatism): DA 0.01 and DA 10.0 ERG responses are normal; 30-Hz flicker ERG response is virtually undetectable; LA 3.0 response shows only a small b-wave at approximately 50 ms, consistent with an S-cone origin; PERG response is undetectable. *(Courtesy of Graham E. Holder, PhD.)*

Multifocal Electroretinography

Multifocal electroretinography can produce a topographic ERG map of central retinal cone system function, which can help the clinician diagnose macular dysfunction and assess the extent of central retinal involvement in generalized retinal disease (Fig 3-3). The stimulus consists of multiple hexagons, smaller in the center than the periphery to reflect cone photoreceptor density, each of which flashes in a pseudorandom sequence.

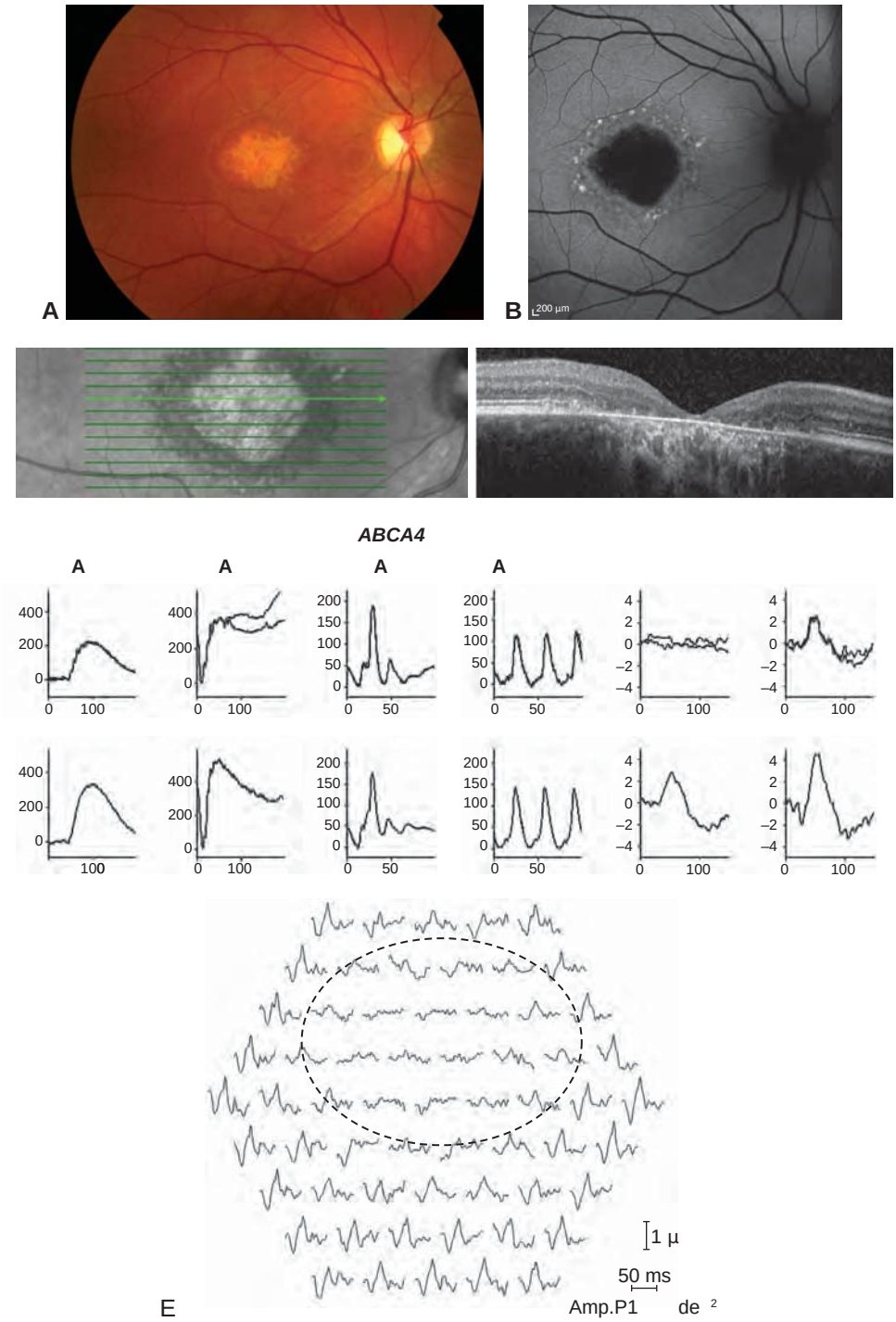

Figure 3-3 Multifocal ERG (mfERG), full-field ERG (ffERG), and pattern ERG (PERG) from a patient with *ABCA4* retinopathy (Stargardt disease; fundus flavimaculatus) show the importance of fixation in mfERG recording and interpretation. **A–C:** Macular atrophy centralized on the fovea. **A,** Fundus photograph. **B,** Fundus autofluorescence image. **C,** Near-infrared and spectral-domain optical coherence tomography (SD-OCT) images. **D,** ffERG responses are normal (see Fig 3-1 for explanation of abbreviations; x-axis = ms; y-axis = µV); PERG response to a 15° field is undetectable; however, PERG response to a 30° field is present but subnormal. **E,** mfERG shows an area of dysfunction that is localized but apparently not around the fovea, which simply reflects the eccentric fixation often present in a patient with a central scotoma. *(Courtesy of Graham E. Holder, PhD.)*

Cross-correlation techniques are used to calculate the small ERGs corresponding to each hexagon. The resulting multifocal ERG (mfERG) waveforms have an initial negative deflection (termed *N1*), followed by a positive peak (termed *P1*) and a second negative deflection (termed *N2*). The N1 deflection derives from the same cells that contribute to the a-wave of the LA ffERG (ie, cone photoreceptors and cone BPCs). The P1 and N2 deflections include contributions from the cells that lead to the LA b-wave and oscillatory potentials.

The overall stimulus field size is usually approximately 40°–50°. For patients with stable and accurate fixation (essential for obtaining technically satisfactory and clinically meaningful results), multifocal electroretinography can objectively determine the spatial distribution of macular dysfunction. The mfERG is less sensitive than the pattern ERG for disorders such as cystoid macular edema, in which primary photoreceptor dysfunction is not the main pathophysiologic feature; these 2 tests can provide complementary information.

Clinicians have increasingly used mfERGs in the diagnosis of hydroxychloroquine toxicity (Fig 3-4). In affected patients, there may be relative sparing of the response to the central foveal hexagon but loss of responses to the ring of surrounding hexagons; a ring analysis may be beneficial. However, it has been demonstrated that Asian patients may show an extramacular pattern of damage, which would not be detected by multifocal electroretinography.

Hoffmann MB, Bach M, Kondo M, et al. ISCEV standard for clinical multifocal electroretinography (mfERG) (2021 update). *Doc Ophthalmol.* 2021;142(1):5–16.

Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF; American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology.* 2016;123(6):1386–1394.

Pattern Electroretinography

The pattern ERG (PERG) captures the retinal response to an isoluminant pattern-reversing checkerboard stimulus presented to the macula; the stimulus is therefore primarily alternating contrast. The image must be in focus on the macula, and electrodes that spare the optics of the eye are used for recording; corneal/contact lens electrodes are not suitable. The responses are small, and signal averaging is needed. However, when technical factors are considered, PERG reliability is similar to that of ffERG. There are 2 main components, P50 and N95, with most patients showing an earlier negative component, N35. N95 arises in the retinal ganglion cells (RGCs) and thus provides a direct measure of central RGC function. The P50 component depends on macular photoreceptor function, even though approximately 70% of it arises in the RGCs; the amplitude of P50 is clinically useful as an objective index of macular function. Because the PERG response is evoked by a stimulus similar to that used in recording the visual evoked potential (VEP; discussed later in this chapter), knowledge of a patient's PERG findings can help the clinician more accurately interpret abnormal VEP findings. The PERG is also useful in diagnosing primary ganglion cell disease such as dominantly inherited optic atrophy or Leber hereditary optic neuropathy.

Holder GE. Pattern electroretinography (PERG) and an integrated approach to visual pathway diagnosis. *Prog Retin Eye Res.* 2001;20(4):531–561.

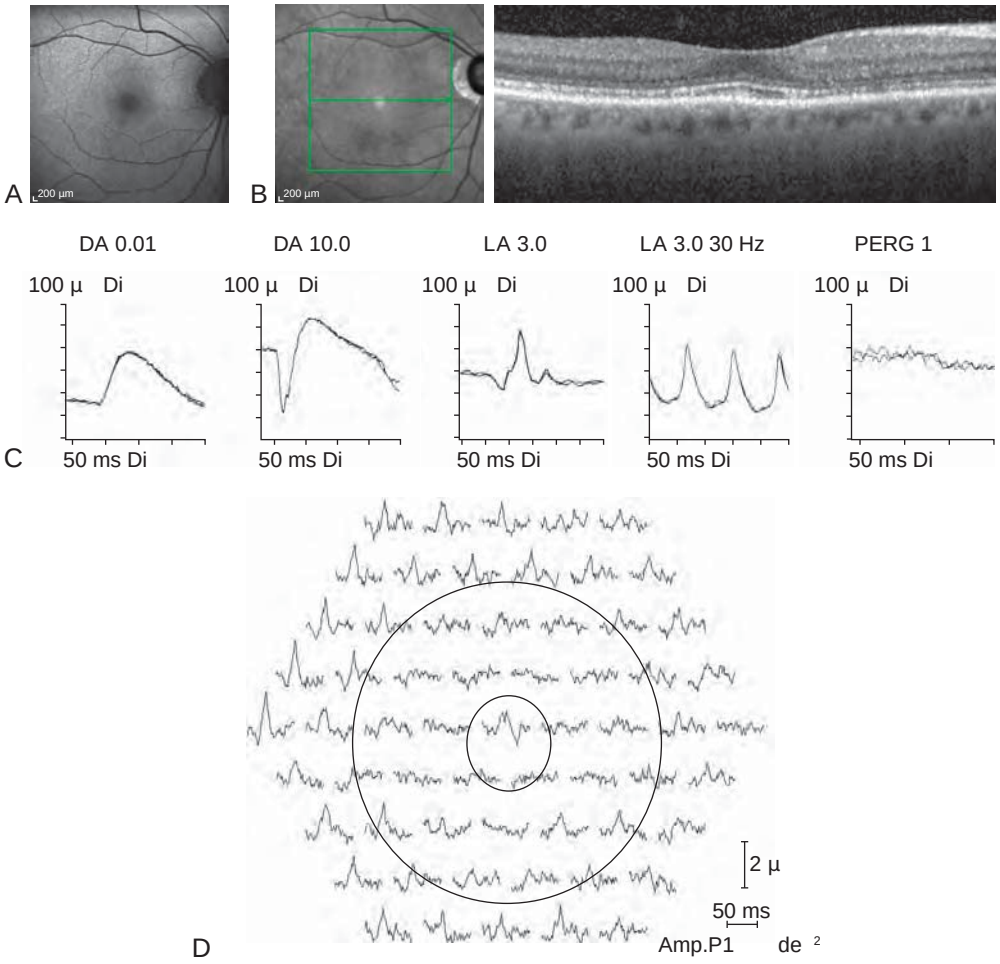

Figure 3-4 mfERG, ffERG, and PERG from a patient with hydroxychloroquine toxicity. **A,** Fundus autofluorescence image. **B,** Near-infrared and SD-OCT images. The changes shown on OCT are less marked, particularly temporal to the fovea, than may have been predicted by the degree of functional vision loss. **C,** ffERG responses are normal (see Fig 3-1 for explanation of abbreviations); PERG response to a 15° field is barely detectable. **D,** The mfERG shows marked abnormality with some sparing of the response to the central foveal hexagon *(inner circle)* but loss of parafoveal responses *(outer circle).* *(Courtesy of Graham E. Holder, PhD.)*

Clinical Considerations

The ERG provides objective data on retinal function and is therefore important in the diagnosis, management, and follow-up of retinal disease. Symptomatic indications include nyctalopia, which requires distinguishing between the potentially blinding rod–cone dystrophies and the relatively benign congenital stationary night blindness (CSNB). The dystrophies are associated with markedly abnormal a-waves in DA bright-flash ERGs; CSNB is usually associated with a normal a-wave and a negative ERG waveform (see Fig 3-2). Other symptomatic indications include photophobia, which indicates generalized cone dysfunction (as

in cone dystrophy), and photopsia or shimmering, which can sometimes signal the development of autoimmune retinopathy, possibly paraneoplastic. The ERG can be used in the assessment and monitoring of inflammatory disorders such as birdshot chorioretinopathy. The ERG facilitates an objective assessment of disease severity, with clinicians using the results in making decisions on when and how to treat; following treatment, the ERG provides a valuable measure of treatment effectiveness that is more sensitive than conventional clinical parameters. In addition, the ERG can be used to monitor for early drug-related retinal toxicity, as can occur with systemically administered chemotherapy.

ERGs must always be interpreted in a clinical context. Results are diagnostic (pathognomonic) for only 3 relatively rare inherited disorders: bradyopsia (mutation in *RGS9* or *R9AP*), enhanced S-cone syndrome *(NR2E3),* and "cone dystrophy with supernormal rod ERG" *(KCNV2).*

The ERG can be useful in assessing patients with vascular disease. In patients with central retinal artery occlusion, the ERG is characteristically negative (b-wave amplitude is smaller than the a-wave amplitude), reflecting the dual blood supply to the retina; the photoreceptors are supplied via the choroidal circulation, but the central retinal artery supplies the inner nuclear layer. Thus, the b-wave amplitude is reduced but the a-wave is relatively preserved. In eyes with central retinal vein occlusion, a negative ERG or delay in the 30-Hz flicker response suggests significant ischemia.

The ERG can also be helpful in determining the carrier state of individuals with X-linked disease. For example, carriers of X-linked RP usually have abnormal ERG findings that reflect lyonization, even with a healthy-appearing fundus. However, in choroideremia, carriers usually exhibit a normal ERG response despite an abnormal fundus appearance (also resulting from lyonization).

Electroretinography is suitable for use in children of all ages, providing objective functional data for patients who may not be able to describe their symptoms. Interpretation of pediatric ERGs involves special consideration, as adult ERG values are not reached until 6–9 months of age and general anesthesia, which may be necessary depending on the child's age, can affect the sensitivity of the assessment.

Johnson MA, Marcus S, Elman MJ, McPhee TJ. Neovascularization in central retinal vein occlusion: electroretinographic findings. *Arch Ophthalmol.* 1988;106(3):348–352.

Vincent A, Robson AG, Holder GE. Pathognomonic (diagnostic) ERGs. A review and update. *Retina.* 2013;33(1):5–12.

Electro-oculography

Electro-oculography assesses the health of the RPE and its interaction with the photoreceptors by measuring the corneo-retinal standing potential during dark adaptation and light adaptation. The standing potential, which reflects the voltage differential across the RPE, is positive at the cornea. Estimates of trans-RPE potential range from 1 to 10 mV.

For the electro-oculographic (EOG) test, the patient makes fixed 30° lateral eye movements for approximately 10 seconds each minute during 15 minutes of dark adaptation, and again during a 12-minute period of light adaptation (Fig 3-5). The amplitude of the signal

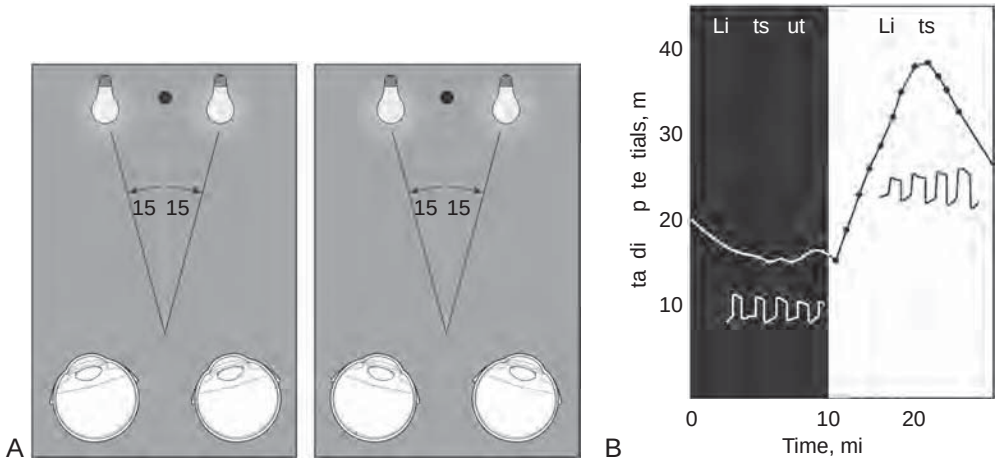

Figure 3-5 The clinical electro-oculogram (EOG). **A,** After electrodes are fixed to an area near the medial and lateral canthi, the patient is asked to alternate their gaze on 2 fixation targets (dimly lit lights), which are separated by a distance that results in a 30° horizontal eye movement. As each eye moves, the voltage between skin electrodes varies in proportion to the size of the standing potential of the eye (the voltage differential across the retinal pigment epithelium). **B,** Plot of the amplitude of the oscillations. As the eyes turn toward the cornea-positive electrodes, an increased potential is measured; thus, the slow back-and-forth motions result in the relatively square-looking voltage curve. During testing, the standing potential diminishes to a minimum in the dark (the *dark trough*) and then rises to a maximum after the light is turned on (the *light peak*). In clinical practice, the EOG result is usually reported as the ratio of the amplitude of the light peak to that of the dark trough expressed as a percentage, the *Arden index* or *ratio.* *(Illustrations by Mark Miller.)*

recorded between electrodes positioned near the medial and lateral canthi reaches a minimum after approximately 12 minutes of dark adaptation—the dark trough—and a maximum at approximately 8 minutes of light adaptation—the light peak. The ratio of the amplitude of the light peak to that of the dark trough is expressed as a percentage (the *Arden index* or *ratio*). A normal light rise will be greater than 170% and requires fully functioning photoreceptors in contact with a normally functioning RPE. The light peak reflects progressive depolarization of the RPE basal membrane via mechanisms that are not fully understood; however, the protein bestrophin is implicated in the final opening of chloride channels.

Any disorder of rod photoreceptor function will affect an EOG, and the light rise is typically severely reduced in an EOG of any widespread photoreceptor degeneration, including RP. However, the EOG is principally used in clinical practice in the diagnosis of acute zonal occult outer retinopathy (AZOOR) and diseases due to mutations in bestrophin 1 *(BEST1)* (see Chapter 12). In patients with Best disease, a dominantly inherited disorder caused by mutations in *BEST1,* a severely reduced or absent EOG light rise is accompanied by a normal ffERG response. Severe loss of the EOG light rise is also seen in patients with autosomal recessive bestrophinopathy (ARB). ARB is a progressive retinal dystrophy and, unlike Best disease, requires biallelic mutation. Affected patients have ffERG responses that are abnormal but not sufficiently so to explain the degree of EOG response abnormality. Also, unlike Best disease carriers, ARB carriers do not show an EOG response abnormality. In patients with adult vitelliform macular dystrophy, the EOG findings may be mildly subnormal but are not reduced as much as they are in Best disease (Fig 3-6).

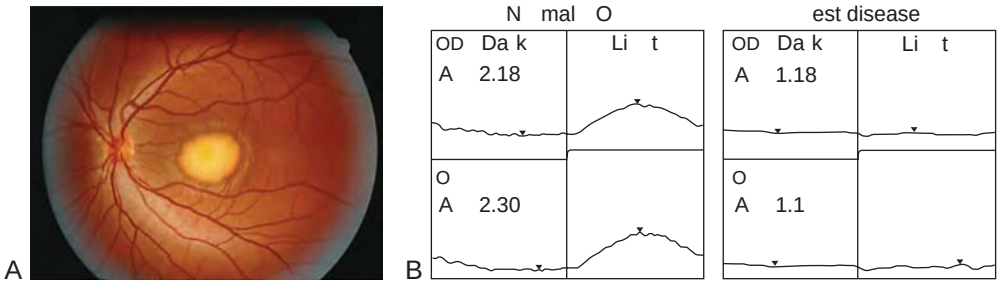

Figure 3-6 Best disease. **A,** Fundus photograph shows an egg yolk–like vitelliform macular lesion. **B,** The EOG demonstrates a reduced light peak to dark trough (Arden) ratio compared with a normal EOG. AR = Arden ratio. *(From Gundogan FC, Yolcu U. Clinical ocular electrophysiology. In: Davey P, ed.* Ophthalmology: Current Clinical and Research Updates. *IntechOpen; 2014. doi:10.5772/57609)*

Arden GB, Constable PA. The electro-oculogram. *Prog Retin Eye Res.* 2006;25(2):207–248.

Burgess R, Millar ID, Leroy BP, et al. Biallelic mutation of *BEST1* causes a distinct retinopathy in humans. *Am J Hum Genet.* 2008;82(1):19–31.

Visual Evoked Potentials

Visual evoked potential (VEP; also called *visual evoked cortical potential [VECP]* or *response [VER]*) testing measures electrical signals produced in the brain in response to stimulation of the retina by either light flashes *(flash VEP)* or patterned stimuli, usually a pattern-reversing black-and-white checkerboard displayed on a monitor (*pattern-reversal VEP* or *pattern onset-offset VEP*). The signals are recorded via electrodes placed on the occipital scalp. The VEP is extracted from the larger background electroencephalogram by averaging the responses to multiple reversals or flashes. Pattern-reversal VEPs have a similar waveform across a population and a remarkably consistent timing; amplitudes show greater variability. Flash VEPs are far more variable across a population but can be useful when clinicians compare eyes or hemispheric responses in the same patient; hemispheric comparison requires multiple recording channels. A normal pattern-reversal VEP (Fig 3-7) contains a major positive component at approximately 100 milliseconds, P100. Measurement is usually taken of P100 amplitude and peak time (sometimes called *latency*).

In adults, VEPs are often used to demonstrate optic nerve conduction delay, particularly in patients with suspected multiple sclerosis; patients with demyelinating optic neuritis almost invariably show VEP delay even when vision recovers (see Fig 3-7). However, there can be subclinical delay in patients without any history or signs of optic neuropathy. In most optic nerve diseases, VEP delay is present, but a VEP abnormality can be confined to amplitude (interocular asymmetry), for example, as in patients with nonarteritic anterior ischemic optic neuropathy. It is important to note that a delayed VEP is not diagnostic of optic nerve disease. Macular dysfunction can cause similarly abnormal findings, and assessment of macular function with multifocal or pattern electroretinography enables improved VEP interpretation. In patients with medically unexplained vision loss, VEPs are crucial when the vision loss is suspected to be nonorganic. Though nonspecific, VEPs can objectively demonstrate normal function in the presence of symptoms that suggest otherwise.

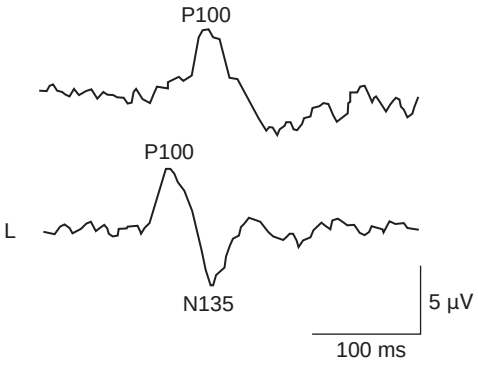

Figure 3-7 Pattern-reversal visual evoked potential from a patient with a 4-month history of right eye (RE) optic neuritis and recovery of right visual acuity to 20/20. Left eye (LE) response is normal; RE P100 component shows profound delay with preservation of amplitude and waveform. *(Courtesy of Graham E. Holder, PhD.)*

VEPs are indispensable in examining children, particularly those who are preverbal, who have apparent vision loss or who present in infancy with roving eye movements or unexplained nystagmus.

Pattern-appearance stimulation—in which the stimulus appears from a uniformly gray background and then disappears, maintaining isoluminance throughout—can also be used to elicit VEPs. VEPs elicited in this manner are particularly useful in demonstrating the intracranial misrouting associated with ocular or oculocutaneous albinism (multiple recording channels are required) because they are less affected by nystagmus than are reversal VEPs. For babies and infants who cannot maintain adequate fixation on a pattern stimulus, flash stimulation is effective. If the check size and contrast levels are varied, pattern-appearance VEPs can also be used to objectively assess visual system resolution, providing a surrogate measure of visual acuity.

Microperimetry

Microperimetry is a visual field test that simultaneously integrates computer threshold perimetry with real-time retinal imaging. Microperimeters measure a patient's response to light stimuli at individual retinal points and then superimpose that data on an image captured by scanning laser ophthalmoscopy or fundus photography. This test can be used to accurately and reliably identify points of impaired retinal light sensitivity as well as assist in localization of functional defects. Retinal tracking allows real-time detection of retinal movement and correction for changes in fixation. This correction is particularly useful in assessing residual visual functioning in patients with significant vision loss due to macular disease. See also BCSC Section 3, *Clinical Optics and Vision Rehabilitation*.

Markowitz SN, Reyes SV. Microperimetry and clinical practice: an evidence-based review. *Can J Ophthalmol.* 2013;48(5):350–357.

Psychophysical Testing

Although electrophysiologic testing objectively assesses the functioning of cell layers and cell types in the visual pathway, it does not always provide localized responses and may

not be sensitive to small areas of localized dysfunction. Psychophysical tests can be highly sensitive, but they are subjective and do not provide information about specific levels of the visual system; perception represents an integration of information provided by different parts of the visual pathway. Psychophysical tests relevant to retinal disease include testing of

- visual acuity
- visual field
- color vision
- contrast sensitivity
- dark adaptation

Color vision, contrast sensitivity, and dark adaptation testing are discussed in this chapter. See BCSC Section 3, *Clinical Optics and Vision Rehabilitation,* for discussion of visual acuity and contrast sensitivity; Section 5, *Neuro-Ophthalmology,* for further discussion of contrast sensitivity; and Section 10, *Glaucoma,* for discussion of visual field testing.

Dingcai C. Color vision and night vision. In: Ryan SJ, Schachat AP, Wilkinson CP, Hinton DR, Sadda SR, Wiedemann P, eds. *Retina.* 5th ed. Elsevier/Saunders; 2013:285–299.

Color Vision

A healthy human retina has 3 cone types, each containing a different outer segment visual pigment: short-wavelength sensitive (S cone; formerly, *blue*), medium-wavelength sensitive (M cone; formerly, *green*), and long-wavelength sensitive (L cone; formerly, *red*). The integrative cells in the retina and higher visual centers are organized primarily to recognize *contrasts* between light or colors, and the receptive fields of color-sensitive cells typically have regions that compare the intensity of red versus green or blue versus yellow.

The classification and the testing of dysfunctional color vision are based on this contrast-recognition physiology. Red-green color deficiency, which is common in males through X-linked inheritance (5%–8% incidence), is traditionally separated into protan and deutan types, referring to absent or defective long-wavelength–sensitive or medium-wavelength–sensitive pigment, respectively. These distinctions have value in terms of patients' perception, even though individuals with normal color vision often have a duplication of pigment genes, and individuals with color vision deficiency may not have single or simple gene defects. Blue-yellow color deficiency is rarely inherited and can be an important early marker for acquired disease. Inherited color vision defects are described in Chapter 12.

Testing of color vision

The most accurate instrument for classifying congenital red-green color defects is the *anomaloscope,* but it is not widely used. In this test, the patient views a split screen and is asked to match the yellow appearance of one half by mixing varying proportions of red and green light in the other half. Individuals with red-green color deficiency use abnormal proportions of red and green to make the match.

The most common tests of color vision use colored tablets or diagrams. These tests must be performed in appropriate lighting, usually illumination that mimics sunlight.

Pseudoisochromatic plates, such as the *Ishihara* plates (which assess color discrimination along protan [red] and deutan [green] axes only) and *Hardy-Rand-Rittler* plates (which also assess the tritan [blue] axis), present colored numbers or figures against a background of colored dots (Fig 3-8). The colors of both figure and background are selected from hues that are difficult for a person with abnormal color vision to distinguish. Individuals with defective color vision see either no pattern at all or an alternative pattern based on brightness rather than hue. These tests are quick to perform and sensitive for screening for color vision abnormalities, but they are not effective in classifying the deficiency.

Panel tests, including the Farnsworth-Munsell 100 and the Farnsworth Panel D-15 hue tests, are more accurate in classifying color deficiency. The *Farnsworth-Munsell 100-hue test* is very sensitive because the difference in hues between adjacent tablets approximates the minimum that a typical observer can distinguish (1–4 nm). The spectrum is divided into 4 parts of 25 colored tablets each, and the patient is asked to discriminate between subtle shades of similar colors. Testing is tiring and time-consuming but is more sensitive in identifying difficulties with hue discrimination and color confusion.

Consisting of only 15 colored tablets, the *Farnsworth Panel D-15 test* (Fig 3-9) is quicker than the Farnsworth-Munsell 100 and more convenient for routine clinical use. The hues are more saturated, and they cover the spectrum so that patients will confuse colors for which they have deficient perception (such as red and green). The patient is asked to arrange the tablets in sequence, and errors can be quickly plotted to define the color deficiency. The D-15 test may miss mildly affected individuals, but it is still deemed useful because of its speed. The relative insensitivity may also be an asset in judging the practical significance of mild degrees of color deficiency. For example, individuals who fail the Ishihara plates but pass the D-15 test will probably not have color discrimination problems under most circumstances and in most occupations. Desaturated versions of the D-15 test, such as the L'Anthony D-15, which recognize more subtle degrees of color deficiency, are perhaps more clinically useful.

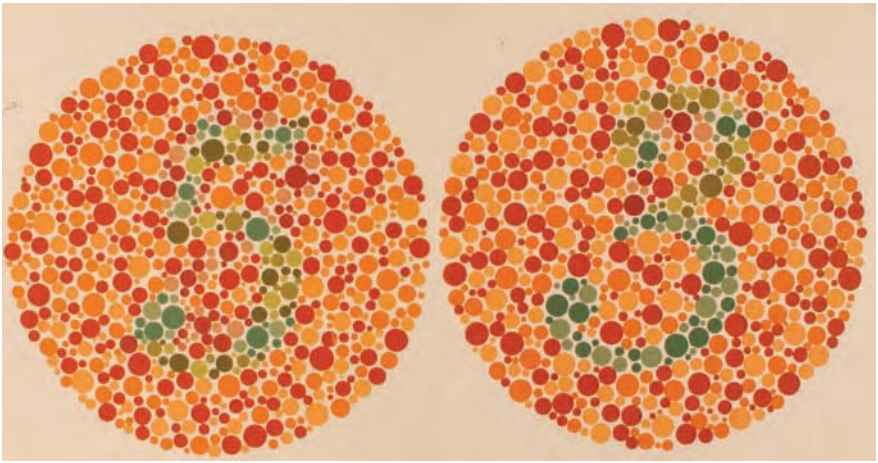

Figure 3-8 Pseudoisochromatic plates. *(Courtesy of Carl Regillo, MD.)*

Figure 3-9 Farnsworth Panel D-15 test. *(© 2021 American Academy of Ophthalmology.)*

Individuals with major congenital color deficiencies typically show a distinct protan or deutan pattern on the D-15 scoring graph, whereas those with acquired optic nerve or retinal disease show an irregular pattern of errors. Tritan axis errors (blue-yellow confusion), which usually signify acquired disease, are readily detected using the D-15 test. Enlarged versions (PV-16 tests) are available for testing patients with reduced visual acuity.

Neitz M, Green DG, Neitz J. Visual acuity, color vision, and adaptation. In: Albert DM, Miller JW, Azar DT, Blodi BA, eds. *Albert & Jakobiec's Principles and Practice of Ophthalmology.* 3rd ed. Saunders; 2008:chap 123.

Contrast Sensitivity

Contrast sensitivity (CS) is a very important concept to understand. The loss of CS often results in visual difficulties and dysfunction out of proportion to the patient's measured visual acuity. For example, patients with nonexudative macular degeneration or diabetic macular edema may have good measured visual acuity of 20/30 or better but have diminished CS that makes it difficult for them to perform routine visual tasks such as reading the newspaper or navigating stairways. Because a conventional Snellen visual acuity is based on high-contrast, achromatic, square-wave stimuli, it does not measure the patient's ability to perceive the subtleties of light. However, the visual system codes much of what is seen on the basis of contrast rather than spatial resolution, with subtleties of light and dark providing most of the richness of visual perception. For example, when dusk, fog, or smoke reduces contrast, it becomes very difficult for anyone to resolve ordinary objects. Similarly, when a patient becomes unable to perceive contrast under ordinary environmental conditions because of retinal disease or media opacity, visual function is adversely impacted.

Testing of contrast sensitivity

Several clinical tests of CS are available. Most relate CS to *spatial frequency,* which refers to the size of the light–dark cycles. Individuals are typically most sensitive to contrast for

objects that have a spatial frequency between 2 and 5 cycles per degree, but this sensitivity can change in patients with ophthalmic disease. Some tests use letters or optotypes of varying dimness and size to provide a more clinical context.

The *Pelli-Robson test* measures CS using a single, large letter size (20/60 optotype), with the contrast of the 3-letter groups decreasing from top to bottom of the chart and left to right within each line (Fig 3-10). Patients read the letters, starting with the highest contrast, and continue until they are unable to read 2 or 3 letters in a single group. The subject is assigned a score based on the contrast of the last group in which 2 or 3 letters were correctly read. The Pelli-Robson score is a logarithmic measure of the subject's CS. Thus, a score of 2 means that the subject could read at least 2 of the 3 letters with a contrast of 1% (CS = 100%, or $\log_{10} 2$). That is, a score of 2.0 indicates normal CS of 100%. A Pelli-Robson CS score less than 1.5 is consistent with visual impairment, and a score less than 1.0 represents visual disability.

See BCSC Section 3, *Clinical Optics and Vision Rehabilitation,* and Section 5, *Neuro-Ophthalmology,* for additional discussion of CS testing.

Owsley C. Contrast sensitivity. *Ophthalmol Clin North Am.* 2003;16(2):171–177.

Rubin GS. Visual acuity and contrast sensitivity. In: Ryan SJ, Schachat AP, Wilkinson CP, Hinton DR, Sadda SR, Wiedemann P, eds. *Retina.* 5th ed. Elsevier/Saunders; 2013:300–306.

Figure 3-10 The top 5 of 8 lines of a standard Pelli-Robson contrast sensitivity chart. The top left 3-letter block has a log contrast value of 0.05; there is a log contrast change of 0.15 with each 3-letter block. In the full 8-line chart, the lowest contrast letters have a log value of 2.3; 2.0 represents normal contrast sensitivity. *(Used with permission from Pelli DG, Robson JG, Wilkins AJ. The design of a new letter chart for measuring contrast sensitivity.* Clin Vision Sci. *1988;2(3):187–199.)*

Dark Adaptometry

The sensitivity of the human eye extends over a range of 10–11 $\log_{10}$ units. Cones and rods adapt to different levels of background light through neural mechanisms and through the bleaching and regeneration of visual pigments. Clinical dark adaptometry primarily measures the absolute thresholds of cone and rod sensitivity.

Dark adaptation can be measured and quantified with the *Goldmann-Weekers (G-W) adaptometer;* however, it is neither widely available nor used. Although newer instruments have been introduced, they have yet to gain widespread acceptance, and most of the research literature is devoted to the G-W instrument.

Dark adaptometry is useful in assessing patients with nyctalopia. Although it is a subjective test, dark adaptometry can complement the ERG; as a *focal test* (relevant when interpreting results from patients with local rather than generalized retinal dysfunction), it can be a more sensitive indicator of pathology than the ERG, especially early in the disease process.