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Clinical Electrophysiology

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Introduction

Electrophysiological testing of patients with retinal disease began in clinical departments in the late 1940s. Under the influence of the great Swedish pioneers, Holmgren (1) and Granit (2), the electroretinogram was being dissected into component parts, and early intraretinal electrode studies were beginning to tell which cells or cell layers gave rise to the various components. A detailed discussion of the electroretinogram, or ERG as it is commonly abbreviated, is found in the accompanying chapter by Ido Perlman. A little after the introduction of the ERG as a test of the state of the patient's retina, another diagnostic test called the electrooculogram (EOG) was introduced to the clinic (3). The EOG had advantages over the ERG in that electrodes did not touch the surface of the eye. The changes in the standing potential across the eyeball were recorded by skin electrodes during simple eye movements and after exposure to periods of light and dark. Over the years, ERG recording techniques have become progressively more sophisticated, even in the clinical setting. With the advent of perimetry and pattern ERG techniques, more precise mapping of lesioned areas of the retina is now possible. The most recent advance in ERG technology is the multifocal pattern ERG, analysed and mapped by computer averaging techniques. It allows a detailed assessment of the state of the macular area.

Where the previous chapter (The Electroretinogram: ERG) presents the basic science behind the waveforms and components of the massed ERG response, in this chapter the intention is to show purely the clinical use of the various electrophysiological tests. The chapter is based on experience in the ERG clinic of the Moran Eye Center.

The Electroretinogram (ERG)

The global or full-field electroretinogram (ERG) is a mass electrical response of the retina to photic stimulation. The ERG is a test used worldwide to assess the status of the retina in eye diseases in human patients and in laboratory animals used as models of retinal disease.

The basic method of recording the electrical response, known as the global or full-field ERG, is by stimulating the eye with a bright light source, such as a flash produced by a strobe lamp. The intense flash of light elicits a biphasic waveform recordable at the cornea similar to that illustrated in Fig. 1. The two components that are most often measured are the a- and b-waves. The a-wave is the first large negative component, followed by the b-wave, which is corneal positive and usually larger in amplitude.

Two principal measures of the ERG waveform are taken: 1) the amplitude (a) from the baseline to the negative trough of the a-wave, and the amplitude of the b-wave measured from the trough of the a-wave to the following peak of the b-wave; and 2) the time (t) from flash onset to the trough of the a-wave and the time (t) from flash

onset to the peak of the b-wave (Fig. 2). These times, reflecting peak latency, are referred to as "implicit times" in the jargon of electroretinography.

The a-wave, sometimes called the "late receptor potential," reflects the general physiological health of the photoreceptors in the outer retina. In contrast, the b-wave reflects the health of the inner layers of the retina, including the ON bipolar cells and the Muller cells (4). Two other waveforms that are sometimes recorded in the clinic (see the previous chapter) are the c-wave originating in the pigment epithelium (5) and the d-wave indicating activity of the OFF bipolar cells (Fig. 3a). Later, we shall discuss some wavelets that occur on the rising phase of the b-wave known as oscillitatory potentials (OPs). OPs are thought to reflect activity in amacrine cells.

The ERG of a normal full-term infant looks similar to a mature ERG. The ERG attains peak amplitude in adolescence and slowly declines in amplitude throughout life (6). After age 55-60 years, the amplitude of the ERG declines even more. Implicit times slow gradually from adolescence through old age as well. Below are two figures illustrating how the b-wave attenuates in amplitude with age and slows in its implicit time (Fig. 3a and Fig. 3b). There is considerable variation among individuals, but the linear regression line in each figure indicates the trend of aging affects on the ERG.

ERG Recording Electrodes

The ERG can be recorded several ways. The pupil is usually dilated. There are a number of corneal ERG electrodes that are in common use. Some are speculum structures (Fig. 4) that hold the eye open and have a contact lens with a wire ring that "floats" on the cornea supported by a small spring (7). Some versions use carbon, wire, or gold foil to record electrical activity. There are also cotton-wick electrodes (Fig. 4) (8).

There are yet other simpler ERG recording devices (Fig. 5) using gold Mylar tape that can be inserted between the lower lid and sclera/cornea. Most electrodes are monopolar, i.e., are referred to another electrode site most commonly on the forehead. Some are bipolar with the reference electrodes built into a metal surface on a speculum.

Each of these electrodes records large voltage responses directly from the cornea, and each has advantages and disadvantages. We use Burian speculum electrodes when possible. Sizes are available down to a size that fits in the eye of most full-term babies. When the eye is too small for speculum recording electrodes, we use the ERG Jet type most of the time. When the eye is very small, such as in some microphthalmic eyes or cases of trauma to tissue surrounding the eye, we use a carbon-wick or gold Mylar tape.

The ERG can also be recorded using skin electrodes placed just above and below the eye, or below the eye and next to the lateral canthus. Because skin electrodes are not in direct contact with the cornea, there is significant attenuation in amplitude of the ERG, so a number of individual responses to flash stimulation must be averaged by computer. Pictured in Fig. 6 is a comparison of bright white flash ERGs recorded from the same person using three types of recording devices and an averaged ERG from skin electrodes.

If electrodes are to be reused, they must be sterilized with a solution that neutralizes prion-transmitted diseases such as Creutzfeldt-Jakob disease (CJD). We use household bleach, e.g., Chlorox (active ingredient, sodium hypochlorite), diluted to a 10% solution with distilled water. The electrodes need only be submerged in this solution for 1 minute. Do not leave electrodes in this solution more than a few minutes.

Light Stimulation for ERGs

There are also several methods of stimulating the eye. Some laboratories use a strobe lamp that is mobile and can be easily placed in front of a person whether sitting or reclining (Fig. 7). The mobility of a strobe lamp or an array of LEDs is a necessity in some situations, such as at the hospital bedside or in the operating room.

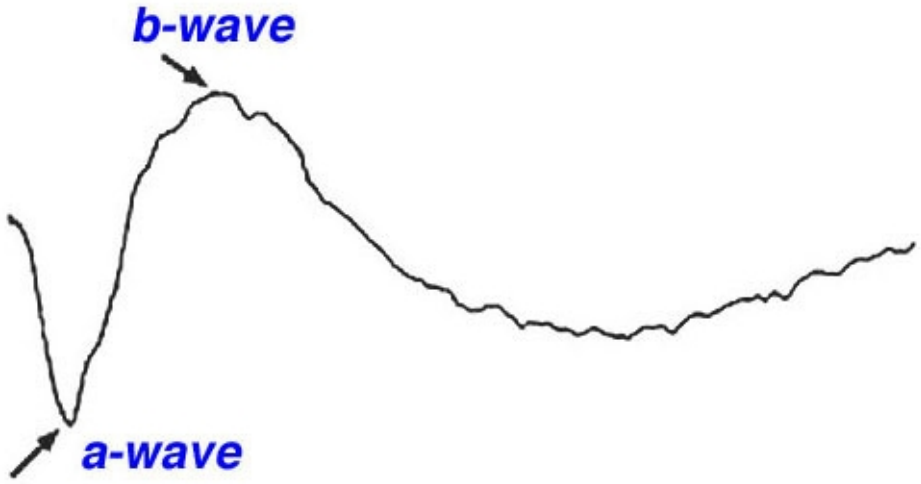

Figure 1. The biphasic waveform of the typical normal patient.

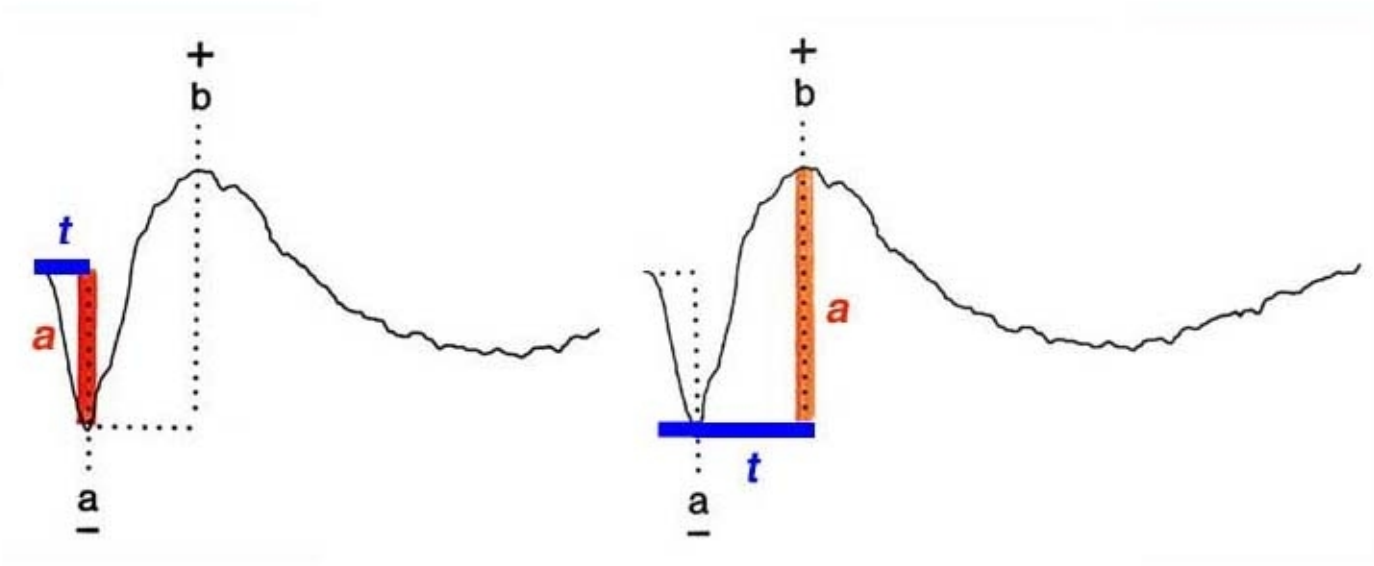

Figure 2. Amplitude and implicit time measurements of the ERG waveform.

For patients over 5 years of age, most laboratories use a Ganzfeld (globe) with a chin rest and fixation points (Fig. 8). The Ganzfeld allows the best control of background illumination and stimulus flash intensity. Either strobe lamp or Ganzfeld methods of flash presentation can be used to record the ERG after a single flash or to average responses to several flashes with the aid of a computer. Clinical decisions can be made from ERGs generated by either methodology.

Testing Infants for ERGs

Infants up to about 2 years of age can usually be tested without sedation by the parent holding them bundled in a blanket. It is difficult to get a child less than 5 years of age to allow a contact lens or speculum recording

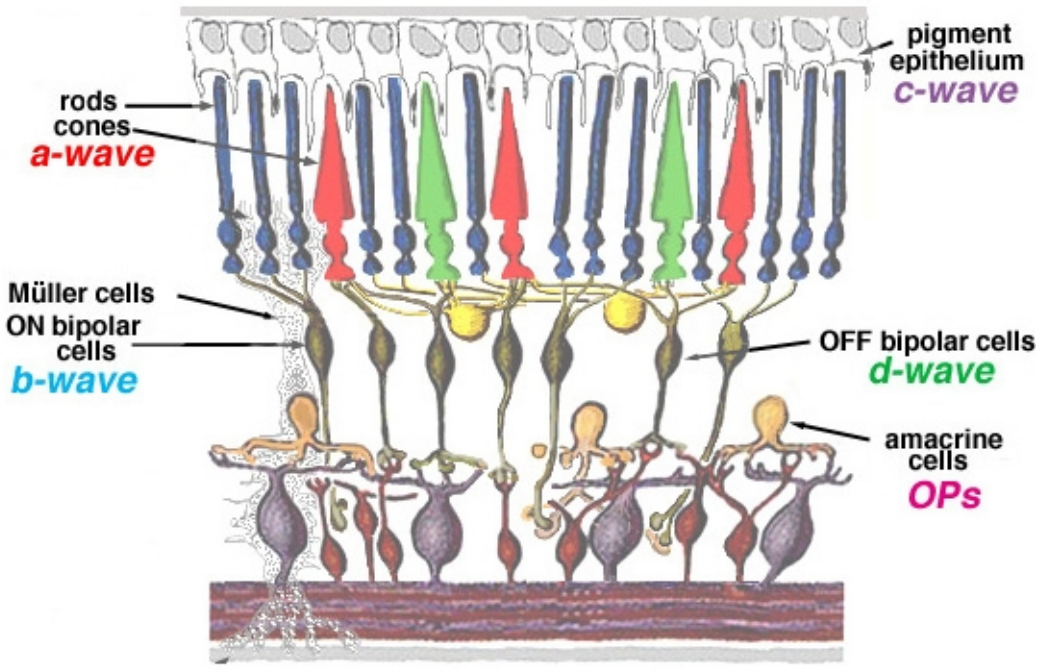

Figure 3a. Schematic of the retina to show where the major components of the ERG originate.

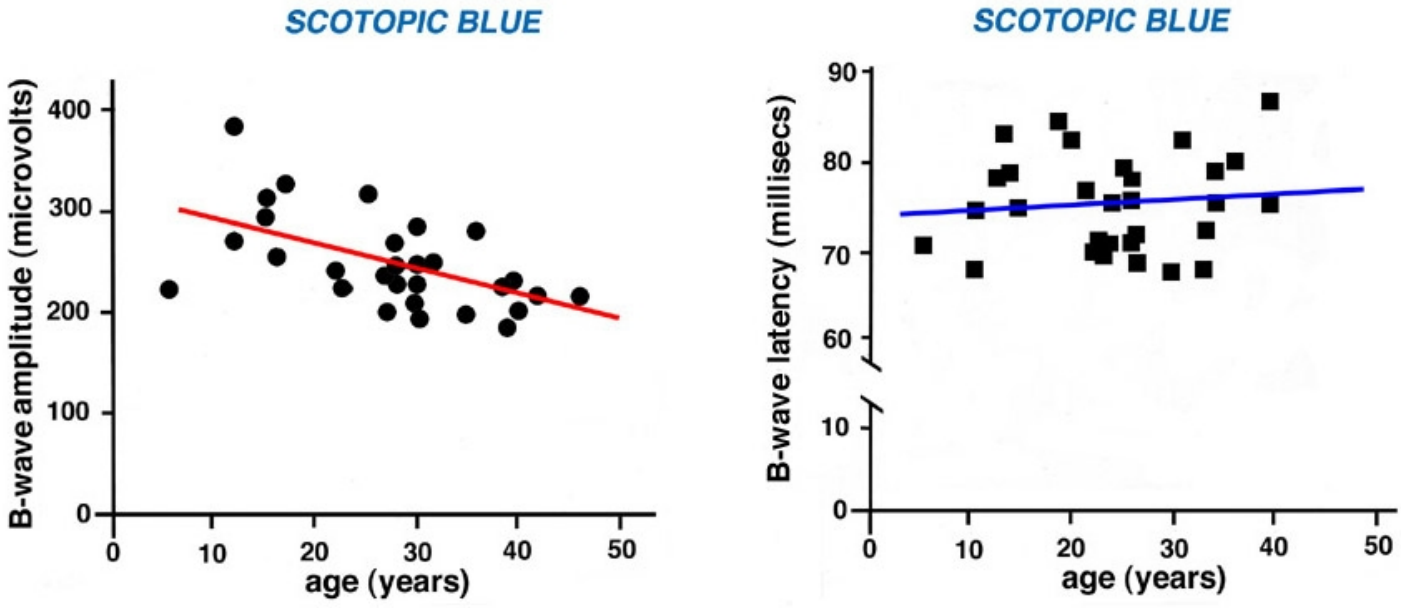

Figure 3b. Scatter plot of b-wave amplitudes and latencies with age with regression lines to show the aging effects.

electrode in the eye, so skin or scleral electrodes can be used, with their limitations. Alternatively, the child is sedated or anesthetized. Many clinics use chloral hydrate or the 3-in-1 "cardiac cocktail" to sedate pediatric patients. Chloral hydrate has several limitations, including that dose restrictions limit the use to patients weighing less than about 15 kg.

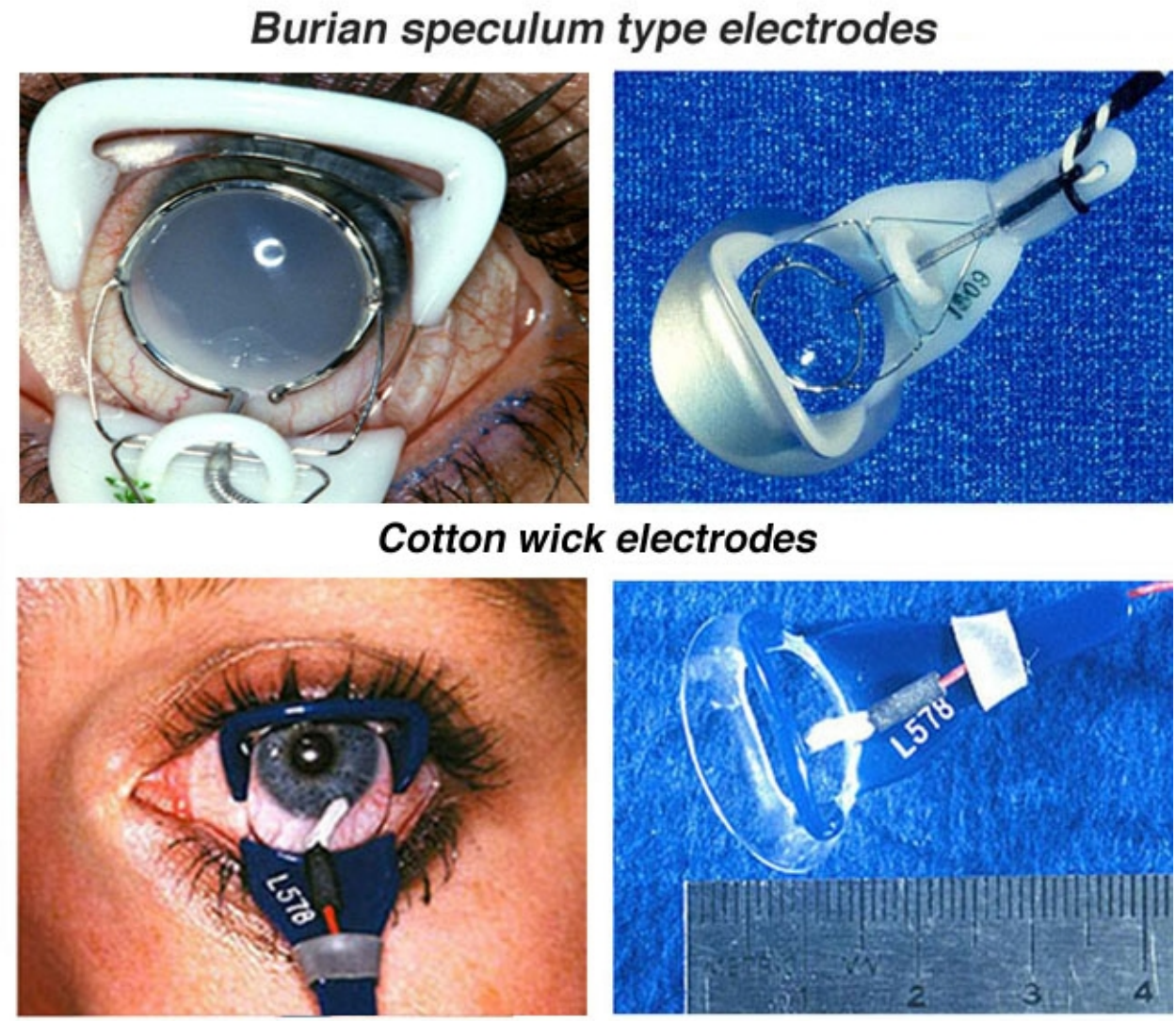

Figure 4. Speculum or Burian-type electrodes used to record the human ERG.

Both of these sedatives have little effect on the ERG. ERG testing is also sometimes performed as part of a more extensive exam under anesthesia (EUA). Few laboratories have Ganzfeld stimulators that can be tilted and placed over the face of a sedated patient, and it is difficult to use such equipment in the operating room. Thus, flash stimuli with sedated patients are usually delivered with a strobe lamp (Fig. 7). In an ERG laboratory, the sedated patient can be dark adapted, and a more or less normal series of stimuli can be used, although the length of effect of the sedative usually necessitates that the method be abbreviated to just three or four stimuli. Dark adaptation, even for a few minutes, followed by single flashes of white or blue will assess scotopic ERG function. Photopic single flashes and 30 Hz flicker can be used to evaluate cone function.

It is usually not possible to completely darken the operating room, so abbreviated testing is accomplished under mesopic and photopic light conditions. Anesthesia affects the ERG, varying with type and depth of anesthesia. Some anesthetics can attenuate b-wave amplitude as much as 50%. Light levels of anesthesia have little affect, and most anesthetics do not usually affect a-waves or implicit times.

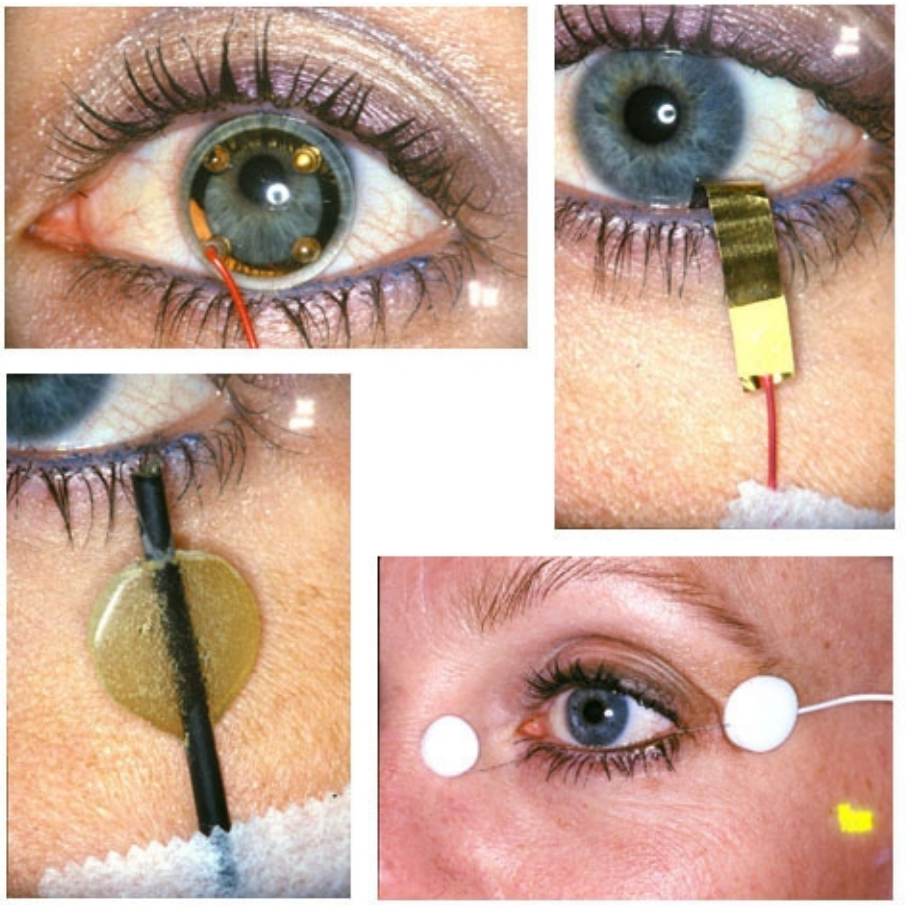

Figure 5. Other simple types of electrodes used to record the human ERG.

Separating Rod and Cone ERGs

Most disorders of the retina are detected by an attenuation of amplitude. Implicit times, of both a- and b-waves, are also affected in some conditions. Implicit times and amplitudes vary, depending upon whether the eye is dark adapted, and brightness and color of the light stimulus. These parameters allow separation of rod and cone activity in any duplex retina.

Rods and cones differ in number, peak color sensitivity, threshold, and recovery. There are about 120 million rods in each retina, and about 6-7 million cones (see the Facts and Figures chapter). Because of sheer numbers, the ERG following a white flash is dominated by the mass response of the rods. By manipulating adaptation level and background illumination, flash intensity, color of the flash, and rate of stimulation, rod and cone activity can be significantly isolated.

Using Color Stimuli

Peak wavelength sensitivity for rods is around 510 nm, and the peak sensitivity of cones as a group is about 560 nm (tennis ball yellow). By using color filters such as the Kodak Blue and Red Wratten series shown in Fig. 9a, you can essentially isolate rod and cone ERGs using dim flash stimuli into photopic (cone) and scotopic (rod) signals as illustrated in Fig. 9b. Dim red analyses both rod and cone function by identifying b_X and b-wave. Rods are about three log units more sensitive than cones. However, cones recover faster than rods.

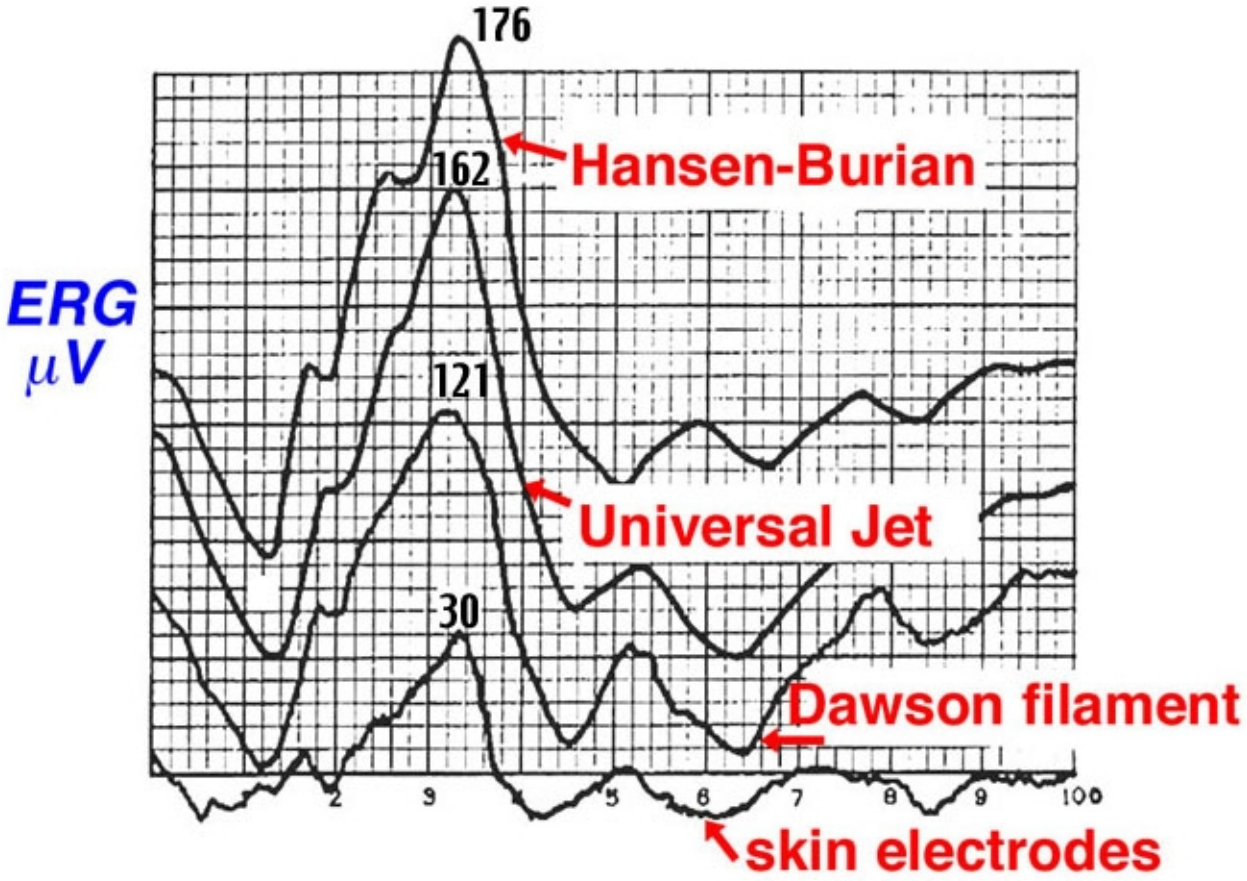

Figure 6. Typical ERGs as recorded with different electrodes.

Using different rates (flicker) of stimulus presentation also allows rod and cone contributions to the ERG to be separated. Even under ideal conditions, rods cannot follow a flickering light up to 20 per second, whereas cones can easily follow a 30-Hz flicker, which is the rate routinely used to test if a retina has good cone physiology (Fig. 9c).

ERG Recording Methods

There are many ways of recording ERGs from patients (9, 10). I recommend reviewing ISCEV standards before recording ERGs (11). Most procedures give similar results but vary mainly in sequence. Some laboratories record the light-adapted state first, and others dark-adapt first. Some laboratories use only white flashes, and others included colored flashes. Many laboratories use a scotopic intensity series as well. Supplemental analysis, such as Perlman's (12) relationship between the ratio of a- and b-wave amplitudes, can be extracted from this intensity series. If only bright white flash stimuli are used, subtle abnormalities will be missed.

The method we use in our clinic is:

1. Dark adapt patient for a set time of 30 minutes.
2. Attach electrodes using dim red illumination. We use an indirect headlamp with several Wratten 26 red filters so that a mobile dark room "safe" light is simulated.
3. Record ERG using single, scotopically balanced, dim blue and red flashes and bright white flashes, as illustrated in the sample ERGs of Fig. 9b. Some laboratories average several responses.

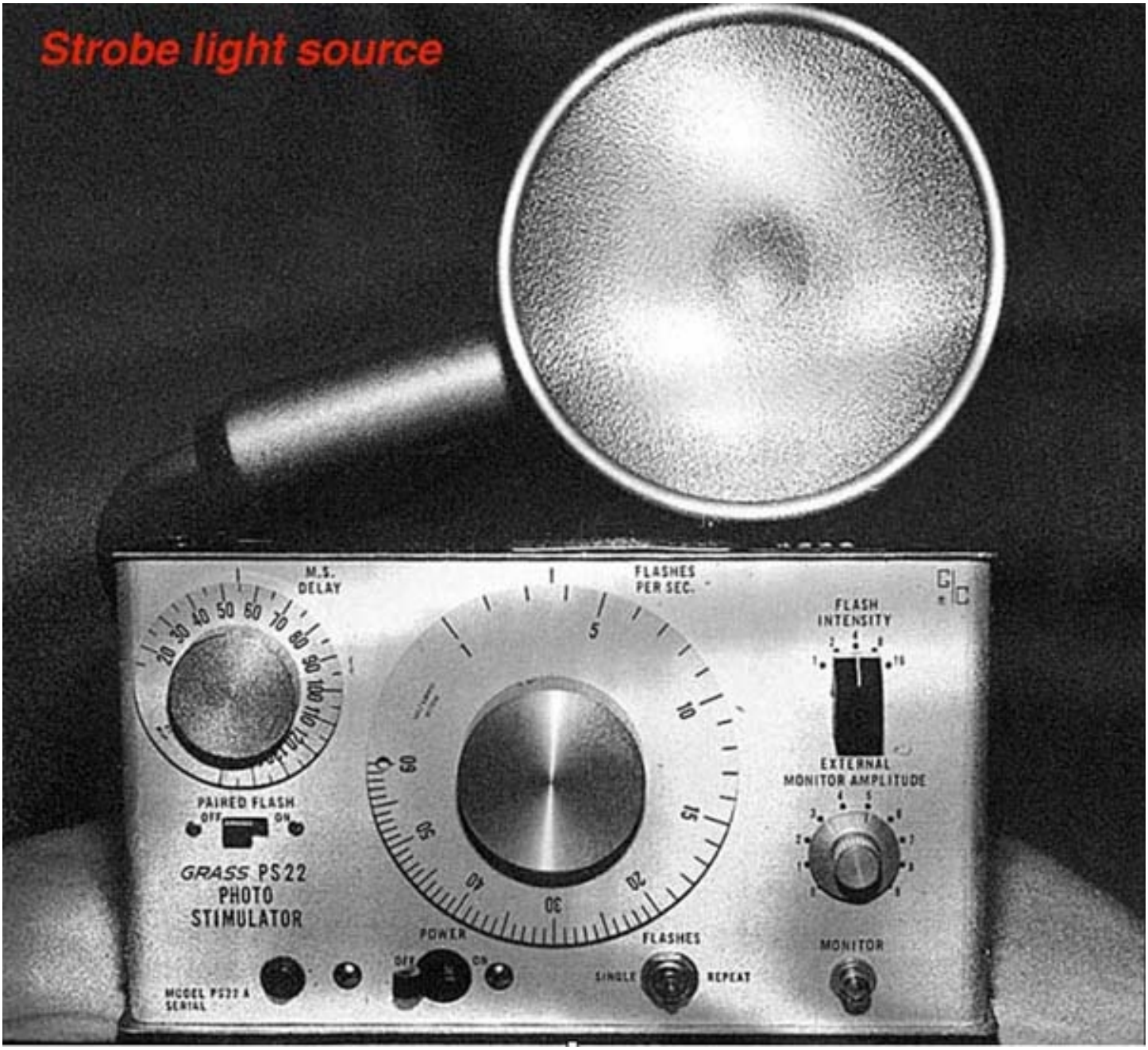

Figure 7. Portable strobe light source.

4. Turn on moderately high background illumination of about 10 ftL for about 10 minutes and record ERGs using 30-Hz flicker and bright white flashes (Fig. 9c). Responses recorded using moderately high background illumination accentuate the cone system by bleaching the rods, and only cones can recover fast enough between flashes to accurately follow a flickering 30-Hz light.

Recording Scotopic ERGs

Thirty minutes or more in the dark produces a state of 98% or more dark adaptation in most individuals. The use of two or more log unit filters to reduce flash intensity and dim blue filters limits the ERG to reflecting rods only. "Scotopically balanced" blue and red filters (Fig. 9b) mean that deep blue and red filters with transmission spectra that do not overlap are matched through trial and error addition of neutral density filters until the ERGs produce b-wave amplitudes of the same size. The purpose of this is to establish a standard so that differences

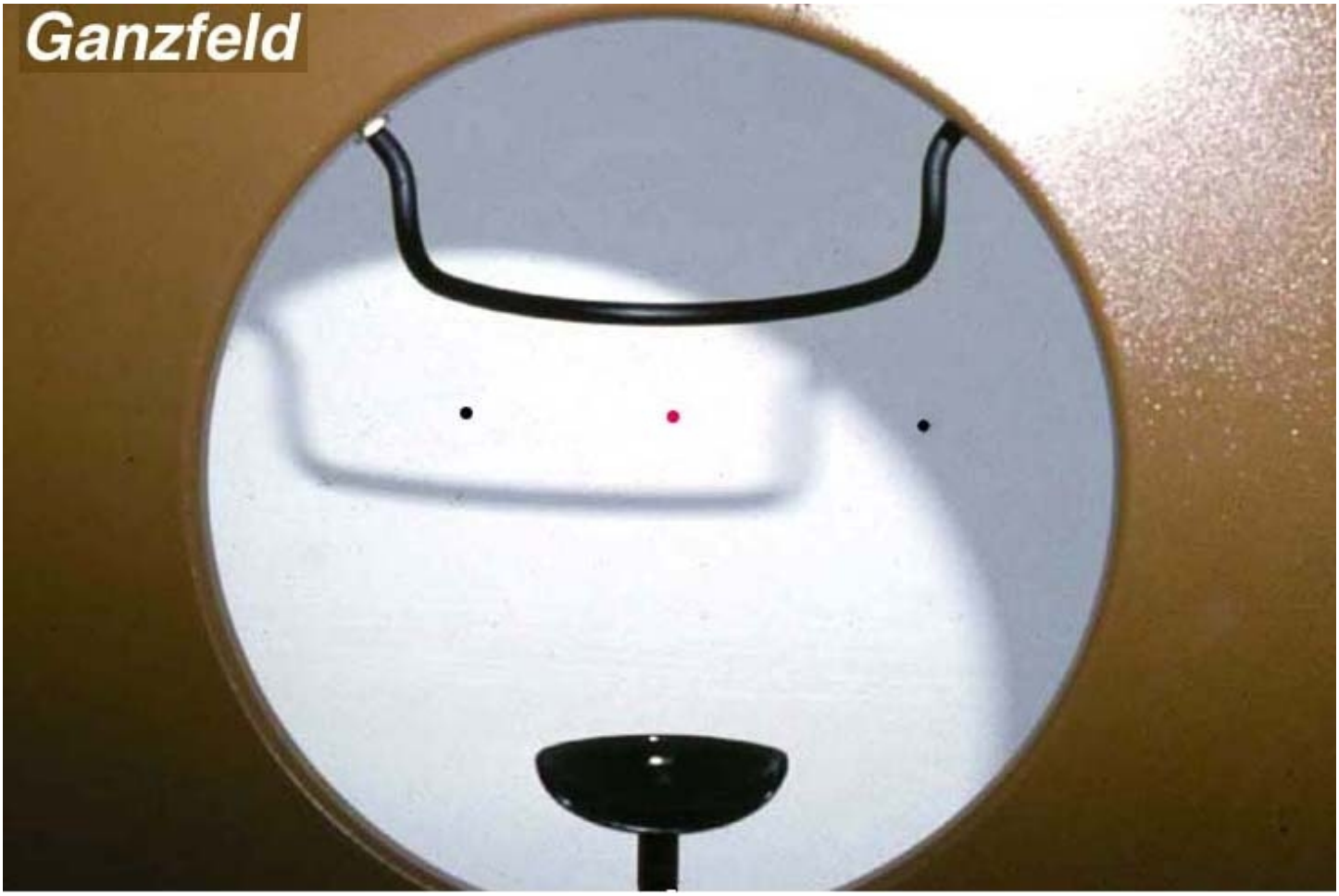

Figure 8. The Ganzfeld stimulation globe.

between rod and cone physiology can be more easily detected. We do this routinely for all patients tested in our clinic. The scotopic dim blue ERG is the most sensitive, not only to rod disorders but also to systemic metabolic aberrations and retinal toxicity.

Oscillatory Potentials (OPs)

Some laboratories also include recording oscillatory potentials (OPs). OPs seen on the ascending limb of most b-waves, in both scotopic and photopic bright flash ERG recordings, were first described by Cobb and Morton (13). By raising the low bandpass from the usual <1 Hz up to around 100 Hz, the slower a- and b-wave components are filtered out, leaving a burst of cone OPs following a bright white flash between about 15 and 40 msec (Fig. 10). Scotopic rod OPs produced by dim blue flash appear later between about 25 and 55 msec. OPs are thought to reflect activity initiated by amacrine cells in the inner retina (14).

This brings up an interesting clinical anecdote that also indicates the vulnerability of the ERGs to changes in retinal chemistry. For over 50 years, the irrigating solution of choice when removing enlarged prostate glands has been glycine. When the procedure takes a long time or the surgeon cuts deeply into the venous beds surrounding the prostate gland, an awake patient under spinal block anesthesia has said, "Why did you turn the lights off?" This can create considerable consternation among personnel in a brightly illuminated operating room. Glycine is an inhibitory transmitter in the retina, particularly associated with amacrine cells. When the glycine reaches retinal circulation, it short circuits the amacrine cell pathways in the retina and turns off the

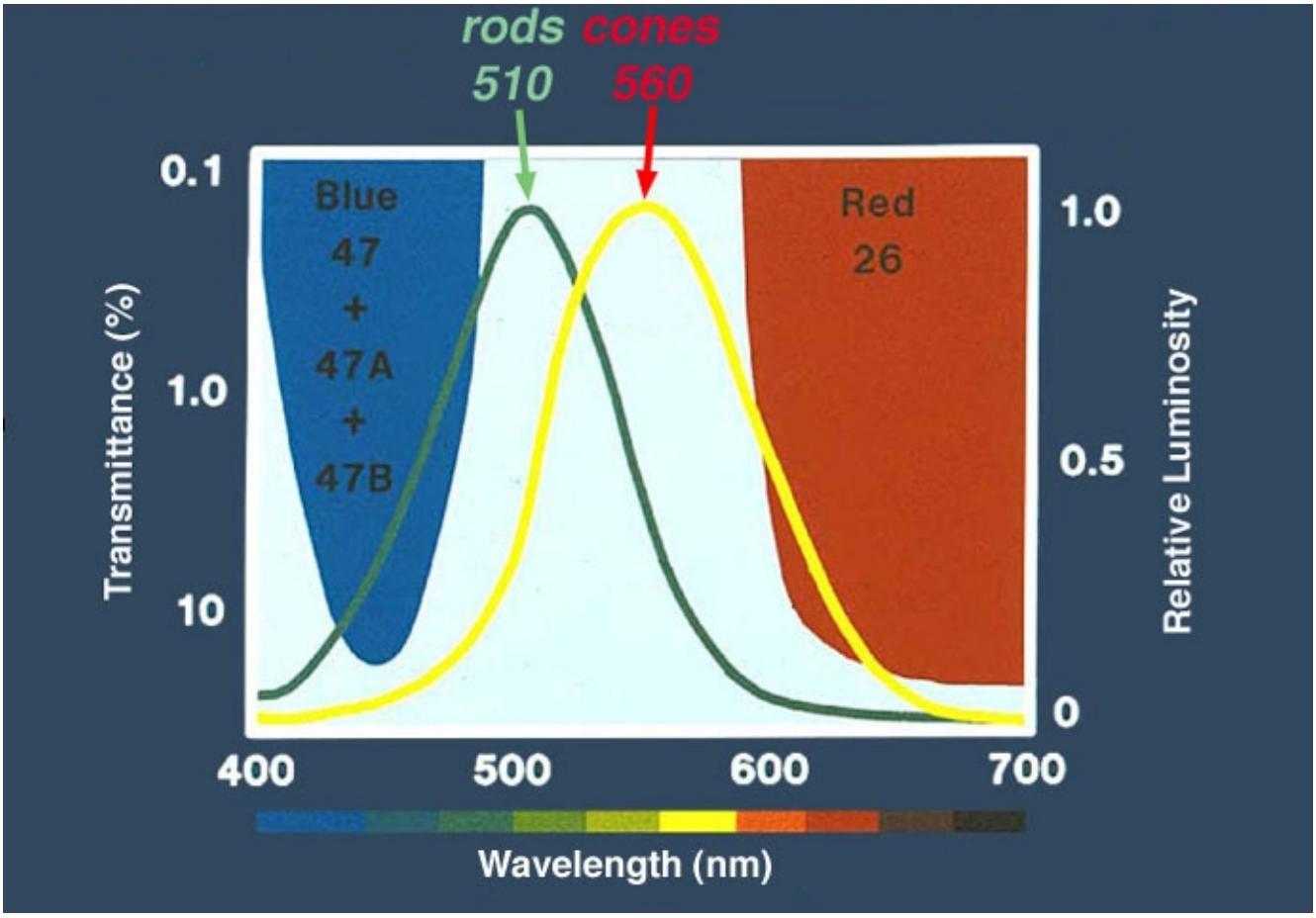

Figure 9a. Filter conditions used to isolate rod and cone components of the ERG using dim scotopic flashes.

source of OPs (15). OPs specifically disappear from the ascending limb of the b-wave. OPs and vision return to the patient over several hours as the glycine is metabolized (Fig. 11).

OPs are significantly attenuated in various retinal degenerations, among them are the following:

- Retinitis pigmentosa
- Central serous retinopathy
- CSNB type 2
- Birdshot choroidopathy
- Retinoschisis
- Carriers of X-linked CSNB
- Diabetic retinopathy
- Hypertensive retinopathy
- CRVO and CRAO
- Takayasu's (pulseless) disease

ERGs in Retinitis pigmentosa-like Diseases

In all forms of retinal pathology, there is considerable variability. There are no absolute rules. Genetic variation in penetrance and expression, in combination with individual differences, affects retinal electrophysiology.

ERGs recorded from a representative normal subject (Fig. 12a) and from a patient with retinitis pigmentosa (RP) (Fig. 12b) using the above methodology are illustrated in Fig. 13. The scotopic blue and red ERG traces are 200

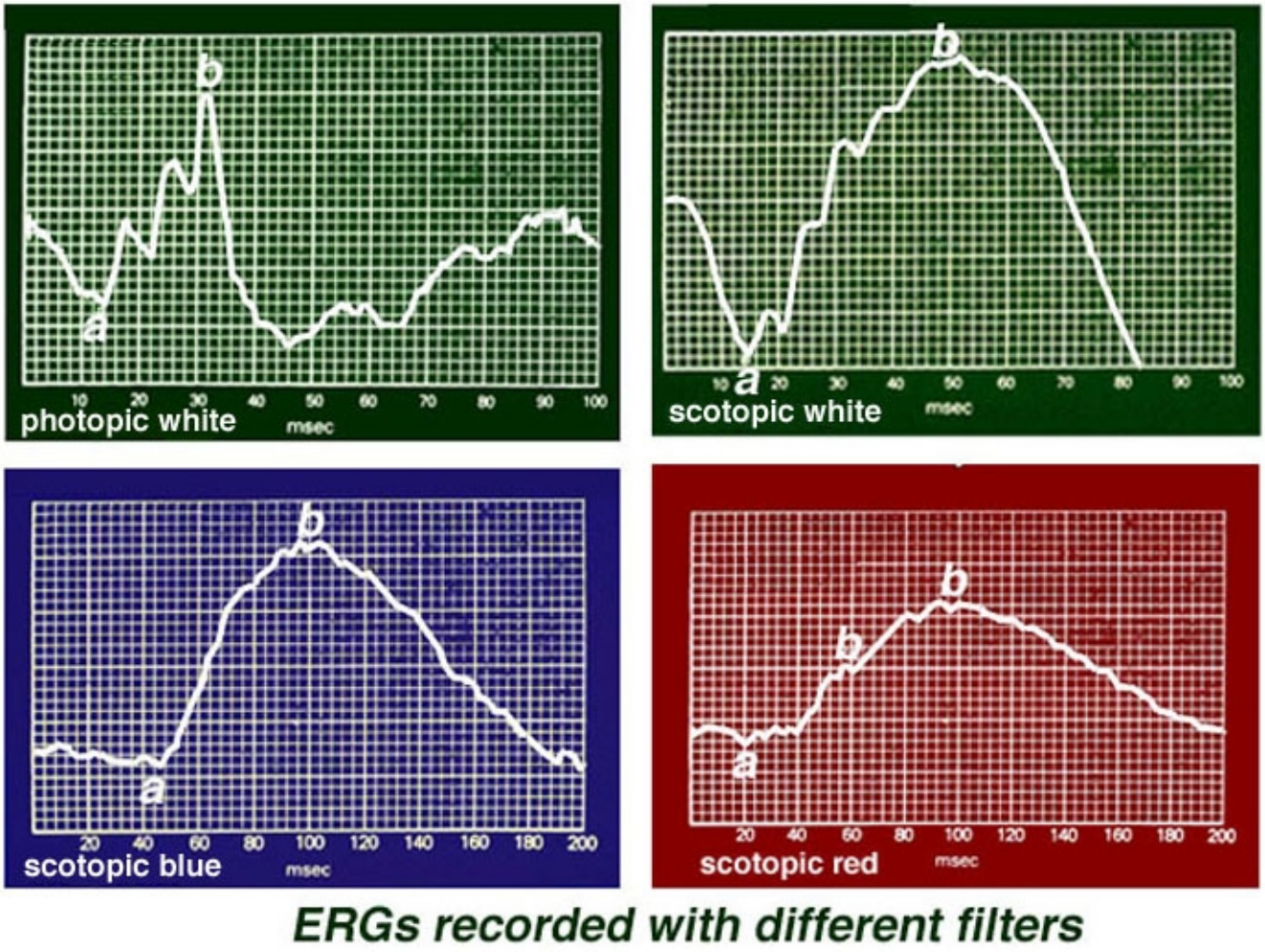

Figure 9b. Typical testing parameters used in our ERG recording set up.

msec, and the other traces are 100 msec. The vertical calibration is 100 microvolts. The low bandpass limit was 0.1 Hz, and the upper bandpass limit was 1 KHz. When dim stimuli are used, such as an intensity series starting with low intensity white or dim scotopic red and blue flashes, it is important that the low bandpass be less than 1 Hz. The slow b-wave initiated by dim stimuli will be attenuated if a low bandpass is not used.

The first two responses are scotopically matched blue and red ERGs. The blue flash was dim enough that no a-wave can be discerned in a normal patient, leaving only the rod-dominated slower b-wave. The red flash is bright enough that oscillations can be observed just after the a-wave. Bright white flash in the dark produces the largest amplitude ERG. The 30-Hz flicker illustrates the response of the rapidly recovering cones, and the photopic response is representative of a normal response, with the more sensitive rods bleached by background illumination. Oscillatory potentials on the ascending b-wave are seen in responses to moderately high intensity white flashes and in response to red, yellow, and green flashes (Fig. 13).

This particular case of RP was selected because the individual was tested early in the onset of RP, as a young adult when she still had remnants of a cone ERG. As in most cases of RP, the rods are affected most severely, as evidenced by the extinguished response to the blue flash. Although it may take some imagination, some of those "squiggles" in the first half of the response to red flashes are remnants of photopic cone physiology. There are also remnants of cone physiology in the responses to bright white flash in the dark, 30-Hz flicker, and photopic white flash. In many individuals with RP, the electrophysiological progression is more severe with all ERGs

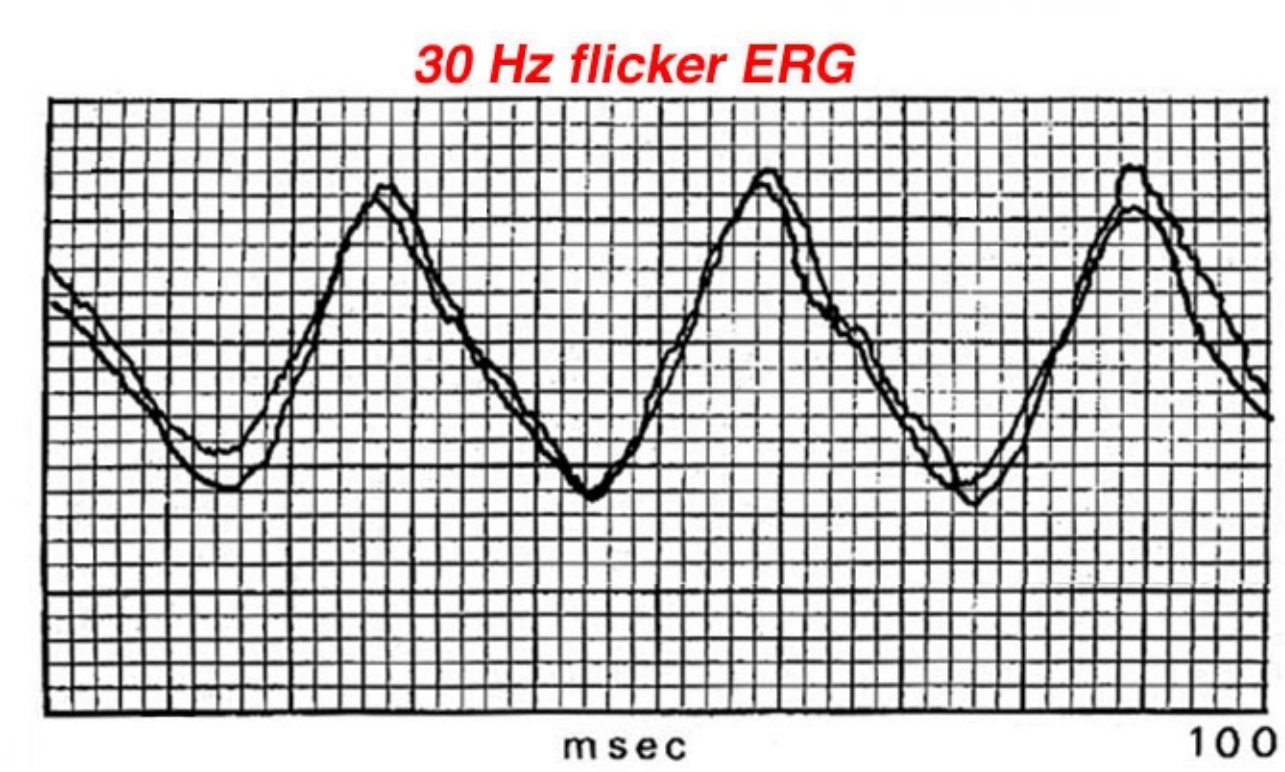

Figure 9c. Typical 30-Hz flicker ERG recorded in our clinic.

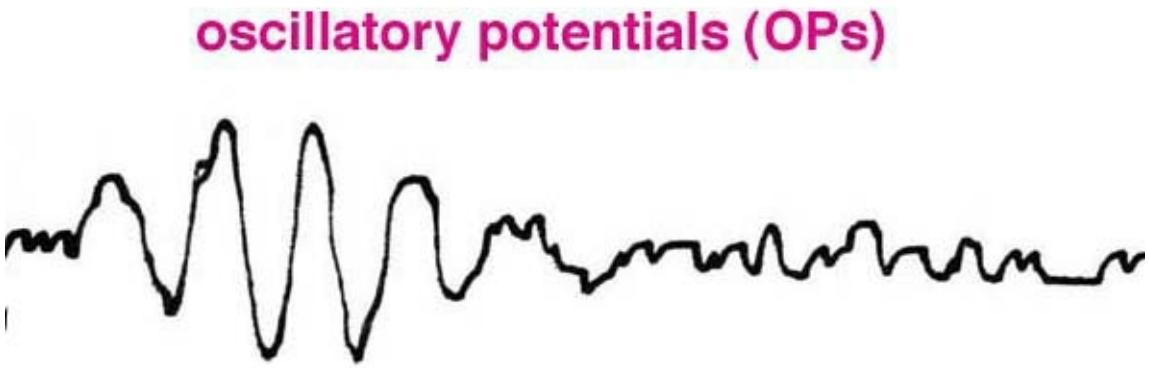

Figure 10. Oscillatory potentials.

extinguished, similar in appearance to the response to scotopic dim blue flash. Both scotopic and photopic b-wave peak implicit times are usually prolonged. Almost always, it is impossible to record OPs.

Early in the clinical onset of RP, with the exception of severe expressions such as Leber's congenital amaurosis or X-linked RP (Fig. 14), there are recordable ERGs, at least to bright photopic stimuli. Some individuals with dominantly inherited RP maintain recordable ERGs throughout most of their lives. I have tested over 100 members of one extended family with dominantly inherited RP. Some of the affected members showed no ERG changes until their mid-teens. Expression of RP in all forms of inheritance varies considerably, even between siblings. Female carriers of the X-linked form can show fundus changes and somewhat abnormal ERGs.

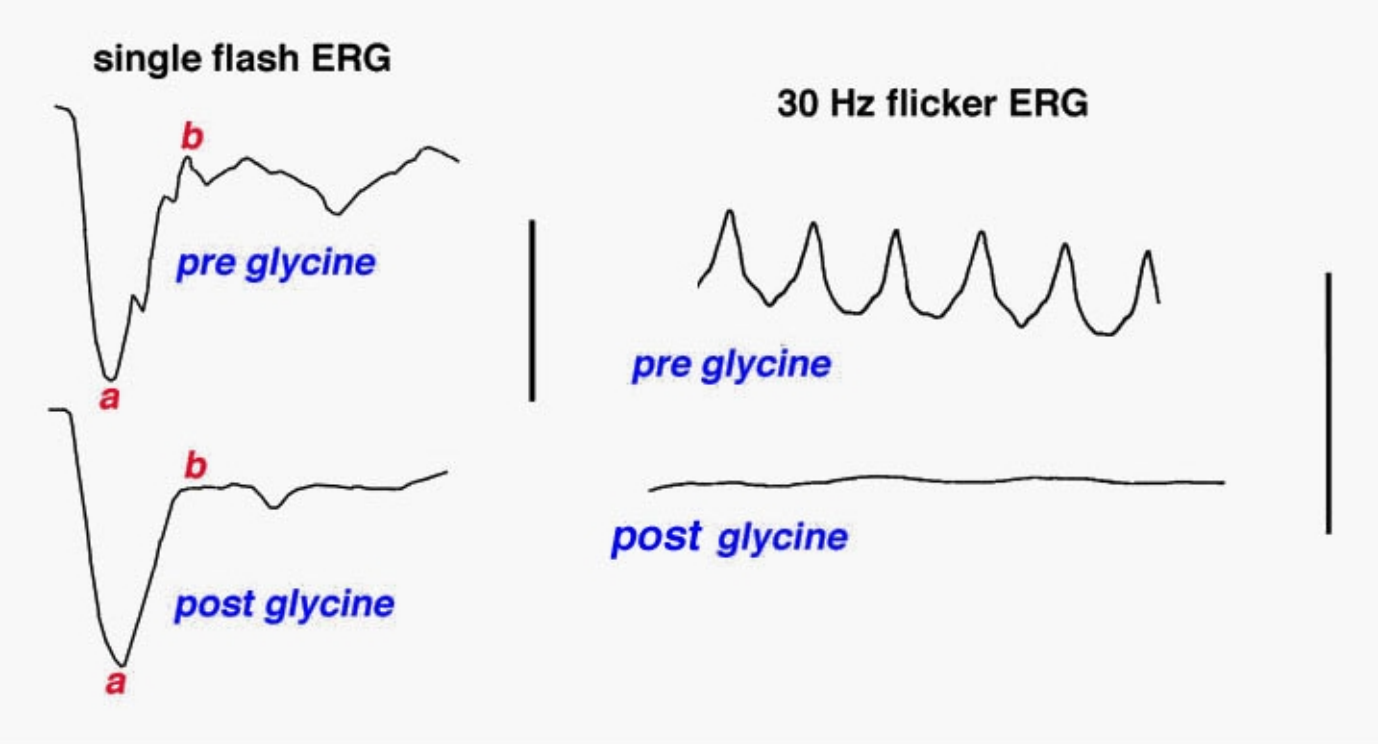

Figure 11. Patient with glycine overload.

Atypical cases of RP are common. There are occasional cases of RP without the usual pigment changes in the fundus (retinitis pigmentosa sine pigmento). Often these cases represent early stages of the disease. Sector RP usually results in a subnormal ERG proportional to the area of retina involved. Paravenous RP (Fig. 15) is associated with a poor ERG most of the time, but again, similar to sector RP, the ERG may be attenuated proportional to the extent of retinal involvement.

RP is seen as a component of a number of syndromes with variability in expression. A common syndrome is Usher's. Usher's syndrome is congenital deafness plus RP. Usher's syndrome may comprise over 20% of RP cases not associated with other syndromes (16).

Myotonic dystrophy (MD) can show ocular changes similar to RP (Fig. 16). Even without fundus changes, the ERG in MD patients is usually moderately affected like that seen in early dominantly inherited RP (17). It is interesting to note that minimally affected individuals without neurological symptoms usually have significant attenuation of their dim flash scotopic ERG b-wave amplitudes. Thus, the ERG can be used to identify the minimally affected parent with MD (Fig. 16, the mother) in cases where neither parent of a child with MD exhibits neurological symptoms.

There are a number of central nervous system syndromes with RP-like ocular involvement. Prominent among these are the mucopolysaccharidoses, such as the Hurler, Scheie, and Hunter syndromes, which often have abnormal ERGs early in the disease. Another group is the neuronal ceroid lipofuscinoses, such as Batten's disease, which have abnormal ERGs, usually attenuated b-waves.

There are syndromes that may include RP. The following list summarizes many of these syndromes:

- Alagille syndrome: ERG normal or subnormal
- Albers-Schonberg syndrome (osteopetrosis): ERG often abnormal
- Alport's syndrome: ERG normal or subnormal
- Alstrom's syndrome: ERG abnormal

- Ataxia with isolated vitamin E deficiency (AVED) and RP: ERG abnormal
- Bassen-Kornzweig syndrome (a-beta-lipoproteinemia): ERG abnormal
- Cockayne's syndrome: ERG often abnormal
- Cystinosis: ERG abnormal in older children
- Flynn-Ard syndrome: ERG sometimes abnormal
- Friedreich's ataxia: ERG sometimes abnormal
- Hallervorden-Spatz syndrome: ERG often abnormal
- Infantile phytanic acid storage disease: ERG usually abnormal
- Jeune's syndrome: ERG usually abnormal
- Joubert's syndrome: ERG abnormal
- Kearn's-Sayres syndrome: ERG some abnormal
- Laurence-Moon-Bardet-Biedl syndrome: ERG usually abnormal
- Methylmalonic aciduria with homocystinuria: ERG some abnormal
- Mucopolysaccharidoses (Hurler, Scheie, Hunter): ERG often has b-wave attenuation
- Myotonic dystrophy: ERG abnormal, dim scotopic ERGs
- Neuronal ceroid lipofuscinosis: (Haltia-Sanavouri, Jansky-Bielschowsky, Batten's): ERG often has b-wave attenuation
- Neuropathy ataxia and retinitis pigmentosa (NARP): ERG abnormal
- Refsum's disease: ERG often abnormal
- Saldino-Merzbacher syndrome: ERG usually abnormal
- Senior-Loken syndrome: ERG usually abnormal
- Spinocerebellar atrophy Type 7 (SPA7): ERG abnormal
- Usher's syndrome: ERG abnormal
- Zellweger's syndrome: ERG usually abnormal

In the differential diagnosis of RP, there are a number of disorders in which the ERG can be used to distinguish the correct diagnosis. Pigment in the retina is prominent in many infectious diseases and may not solely be an indication of RP. Syphilis, particularly the congenital form, can mimic the fundus appearance of RP (Fig. 17), but the ERG is usually normal or only slightly subnormal.

Rubella and viral infections, such as mumps, measles, and herpes, can produce pigment changes in the retina (Fig. 18). These ERGs are usually normal.

Stationary Rod Dystrophies

Congenital stationary night blindness (CSNB) is found in several forms. Although rare, CSNB is more often seen in the form with a normal-appearing retina and may be inherited in any fashion. Within this form are two types. Type 1 has an abnormal dim scotopic ERGs, but the bright-flash ERG maintains OPs on the ascending limb of the b-wave. Type 2 (Fig. 19) has a very abnormal, dim scotopic ERG, and the bright-flash scotopic ERG has a large a-wave and no b-wave (Fig. 20). OPs are also missing.

CSNB with retinal lesions is quite rare. Oguchi's disease is CSNB with an unusual golden-to-rust coloration of the fundus that is reversed with long dark adaptation. This is called Mizuo's sign and requires 2-3 hours of dark adaptation. The ERG resembles CSNB type 2 with no b-wave, although cases have been reported that the ERG returns to normal after hours of dark adaptation. Another rare form of night blindness is stationary albipunctate degeneration, also referred to as fundus albipunctata. This disorder includes stationary night blindness with white dots scattered throughout the fundus. The ERG b-wave is attenuated but returns to normal after long dark adaptation. A third form is Kandori's syndrome, characterized by large, irregular, hyperfluorescent flecks in the peripheral and central retina. In nyctalopia, the ERG is similarly affected as in stationary albipunctate degeneration.

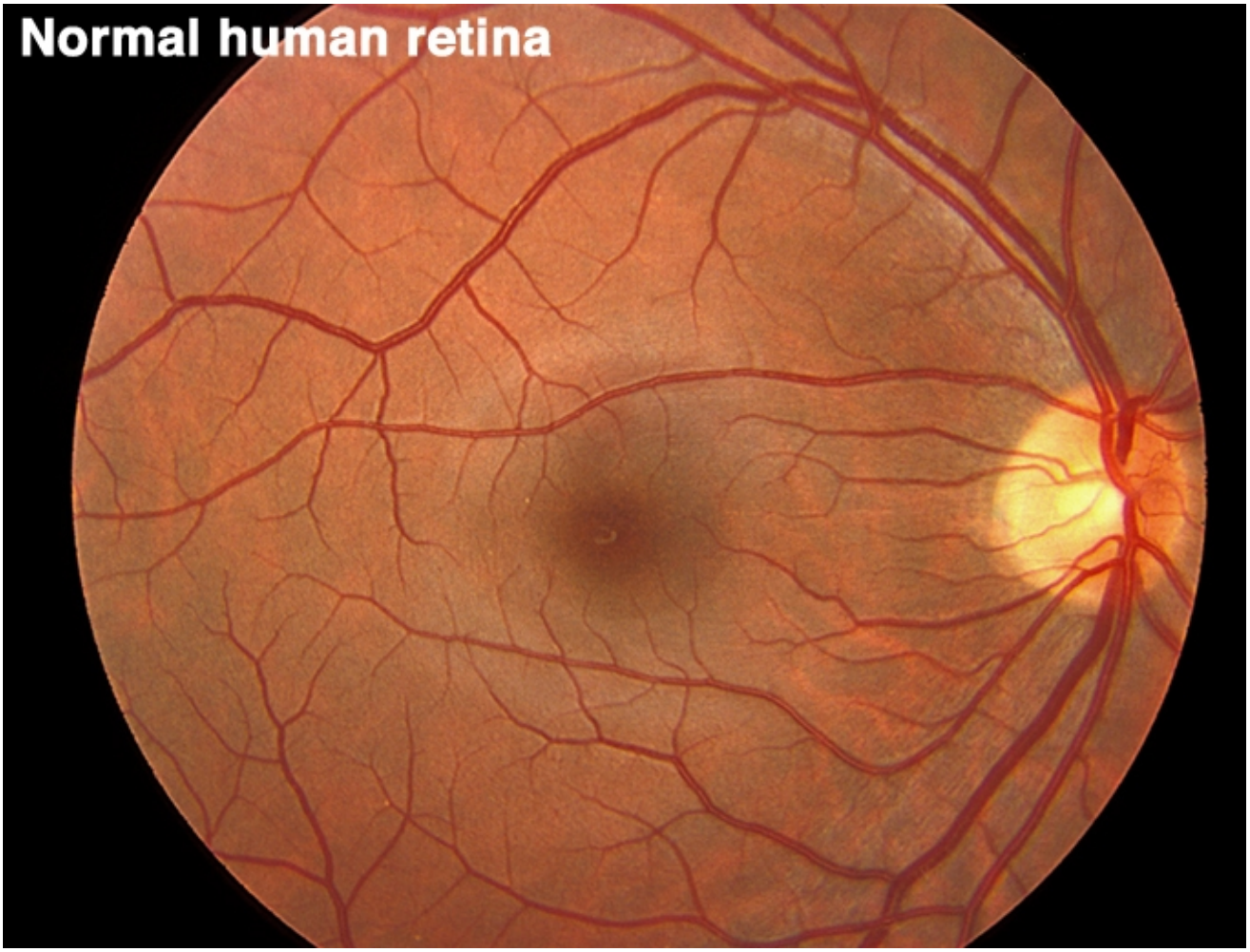

Figure 12a. Fundus photo of a normal human retina.

Other retinal atrophies

The bright flash ERG b-wave is selectively attenuated in:

- Juvenile retinoschisis
- Coat's disease
- Central retinal vein occlusion and central retinal artery occlusion
- Myotonic dystrophy
- Congenital stationary night blindness type 2
- Oguchi's disease
- Lipopigment storage diseases (Batten's disease)

Choroideremia represents an X-linked, diffuse atrophy of the choroid and pigment epithelium. In its mature form, the fundus appearance is white to yellow-white with some small islands of choroid (Fig. 21). Carriers are asymptomatic except for more subtle peripheral fundus abnormalities (Fig. 22). ERGs are usually abnormal.

Gyrate atrophy (Fig. 23) is a recessively inherited atrophy of the pigment epithelium and choroid caused by a deficient mitochondrial enzyme ornithine aminotransferase (OAT).

Figure 12b. Fundus photo of a patient with retinitis pigmentosa.

Gyrate atrophy is less extensive than choroideremia, and the fundus usually shows scalloped borders to degenerative areas (Fig. 23). ERGs are abnormal and progressly deteriorate according to the extent of degeneration of retinal pigment.

X-linked juvenile retinoschisis is a splitting or schisis in the central retina with a characteristic fundus appearance (Fig. 24). These patients have poor acuity. The ERG has a specific abnormality showing a normal a-wave but no b-wave. It is a negative ERG (Fig. 24). The picture is similar to that recorded in central retinal artery occlusion and congenital stationary night blindness type 2.

Patients with Creutzfeldt-Jakob disease (CJD) can also show selective loss of the b-wave (18), even in early stages. We have followed several patients with CJD that have shown unusual ERG waveforms (Fig. 24, a). Similar in appearance to the ERGs of retinoschisis, the b-wave is greatly attenuated (Fig. 24, a). In later stages, the a-wave and OPs are also affected. This pattern is seen in very few disorders, principally X-linked retinoschisis and congenital stationary night blindness type 2.

Except for some retinal dystrophies such severe RP or Leber's congenital amaurosis, most retinal disorders produce reduced, "graded" amplitude attenuation of the ERG, as we have seen in the above cases. However, a few disorders result in a completely extinguished ERG. They include the following:

- Leber's congenital amaurosis
- Severe retinitis pigmentosa
- Retinal aplasia
- Total detachment of retina

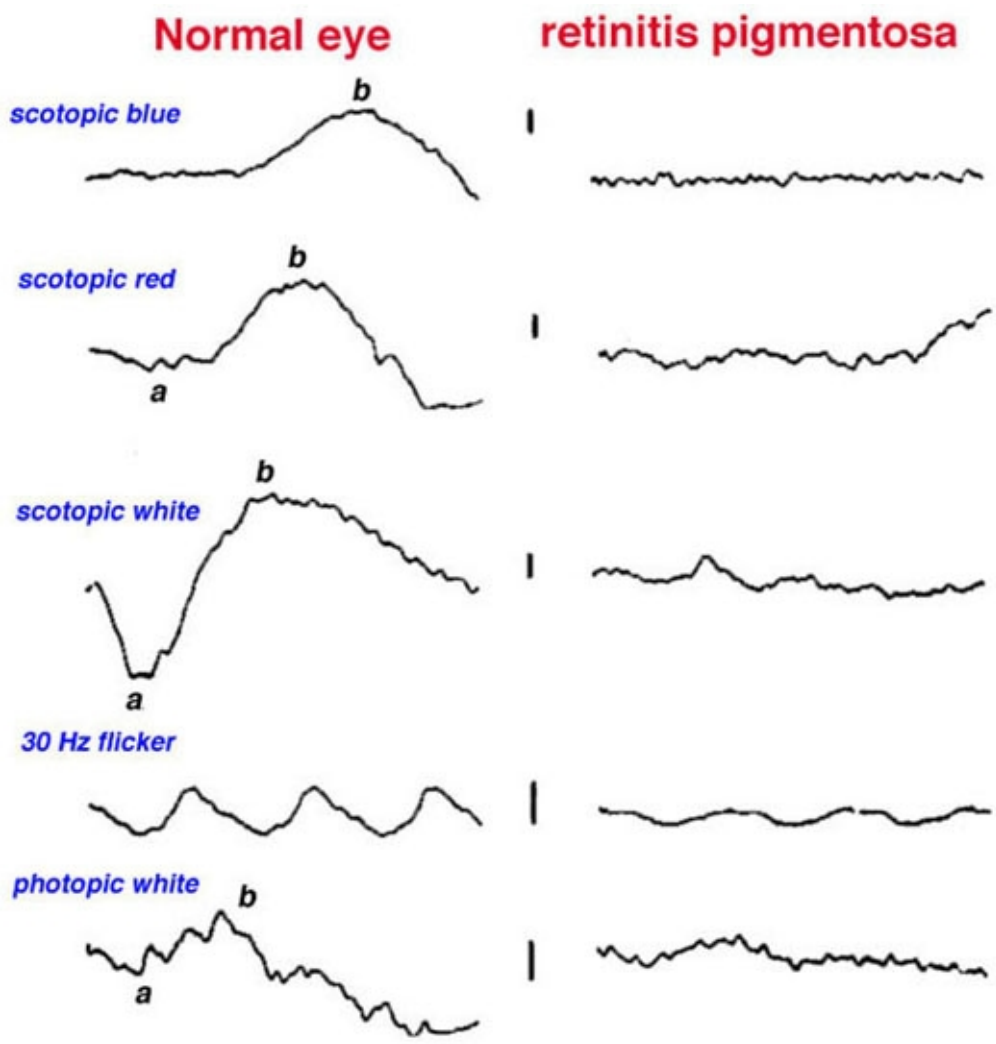

Figure 13. ERG recordings in a normal patient and one with retinitis pigmentosa.

- Ophthalmic artery occlusion

Leber's congenital amaurosis unfortunately presents with significant visual loss in the first year after birth. The fundus usually has a salt and pepper appearance. The ERGs are usually unrecordable.

The ERG in Cone Dystrophies

In contrast to RP, the ERGs of a patient with a cone dystrophy exhibit good rod b-waves that are just slower. However, the early "cone" portion (b_x) of the scotopic red flash ERG is missing. The scotopic bright-white ERG is fairly normal in appearance but with slow implicit times. The 30-Hz flicker and photopic white ERGs dependent upon cones are very poor. Cone dystrophies are inherited in all forms and include poor color vision and poor acuity. The most common fundus findings are a "bullseye" appearance or diffuse pigmentation in the macular area (Fig. 25). Many patients have nystagmus and photophobia. Cone-rod dystrophy appears to involve only cones early in the disease, but the ERGs usually show attenuated rod physiology after a while (Fig. 26).

Other dystrophies are the flecked retina disorders, such as fundus flavimaculatus (Fig. 27) and Stargardt's disease. The retinas display an abnormal accumulation of lipofuscin. The ERG in these disorders is normal except in very late stages, where it may become slightly subnormal.

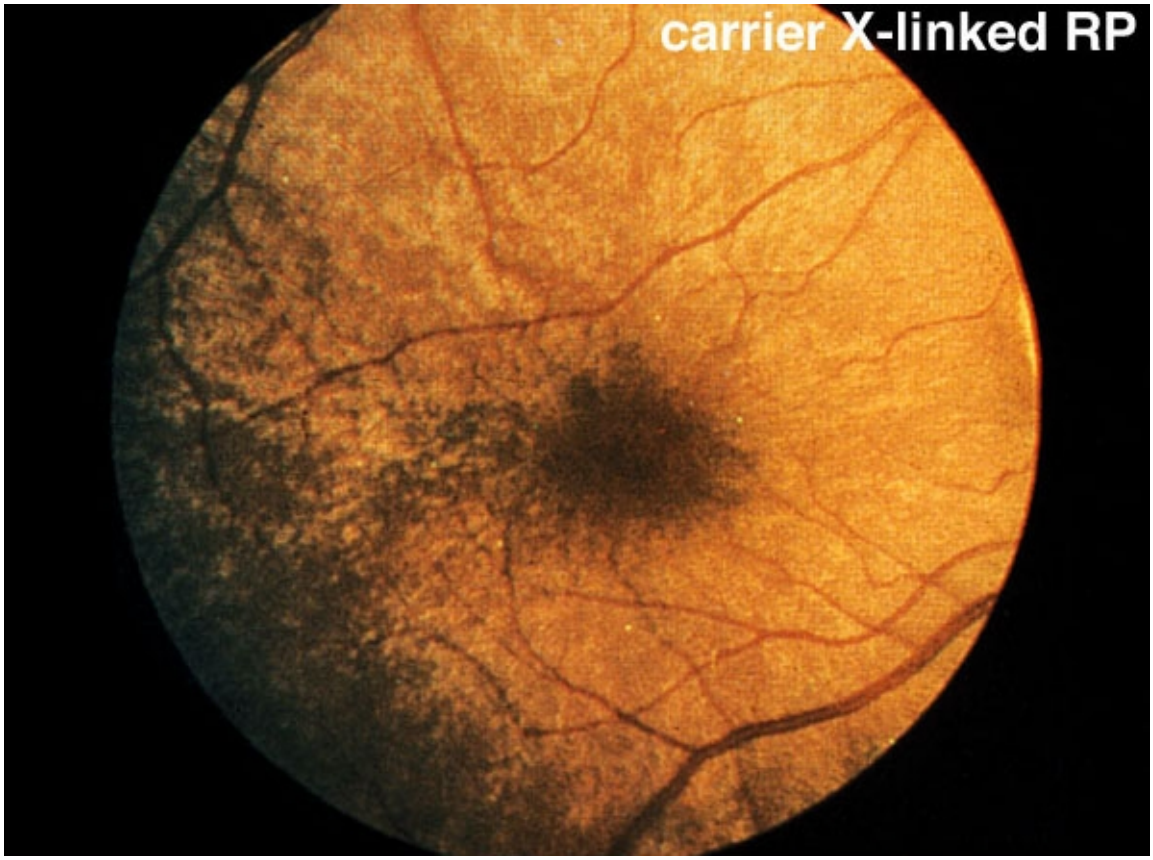

Figure 14. Fundus photo of patient with carrier X-linked retinitis pigmentosa.

ERGs in Retinal Vascular Disease

Vascular occlusions, such as central retinal artery thrombosis, produce a characteristic avascular appearance to select areas of the fundus (Fig. 28a) and an ERG with no b-wave (Fig. 28b). Ophthalmic artery occlusions usually result in unrecordable ERGs.

Foreign Bodies and Trauma

The ERG is useful to assess cases of retinal foreign bodies and trauma to estimate the extent of retinal dysfunction. Foreign bodies affect retinal function, depending on the extent of tearing of the retina, and the location and composition of the object. A small piece of stainless steel or plastic outside the macula may have a minor effect on the retina. However, a piece of copper or iron (Fig. 29) would likely have deleterious affects within a few weeks (Fig. 30a and Fig. 30b). In general, if b-wave amplitudes are reduced 50% or greater compared with the fellow eye, it is unlikely that the retinal physiology will recover unless the foreign body is removed.

The ERG can be used to estimate the extent of functional retina in cases of retinal detachment. An interesting case is shown in Fig. 31a and Fig. 31b. The patient had a small retinal detachment of the macular area in one eye (Fig. 31a, arrows point to circle of detachment). With the new techniques of optical coherence tomography (OCT), which gives an optical image like a vertical section plane, the detached portion of the retina in the foveal and macular area can be clearly seen, in comparison with the normal attached macular area in the fellow eye. In general, ERG b-wave amplitudes correspond to the amount of attached healthy retina, although the detached retina may function for some time.

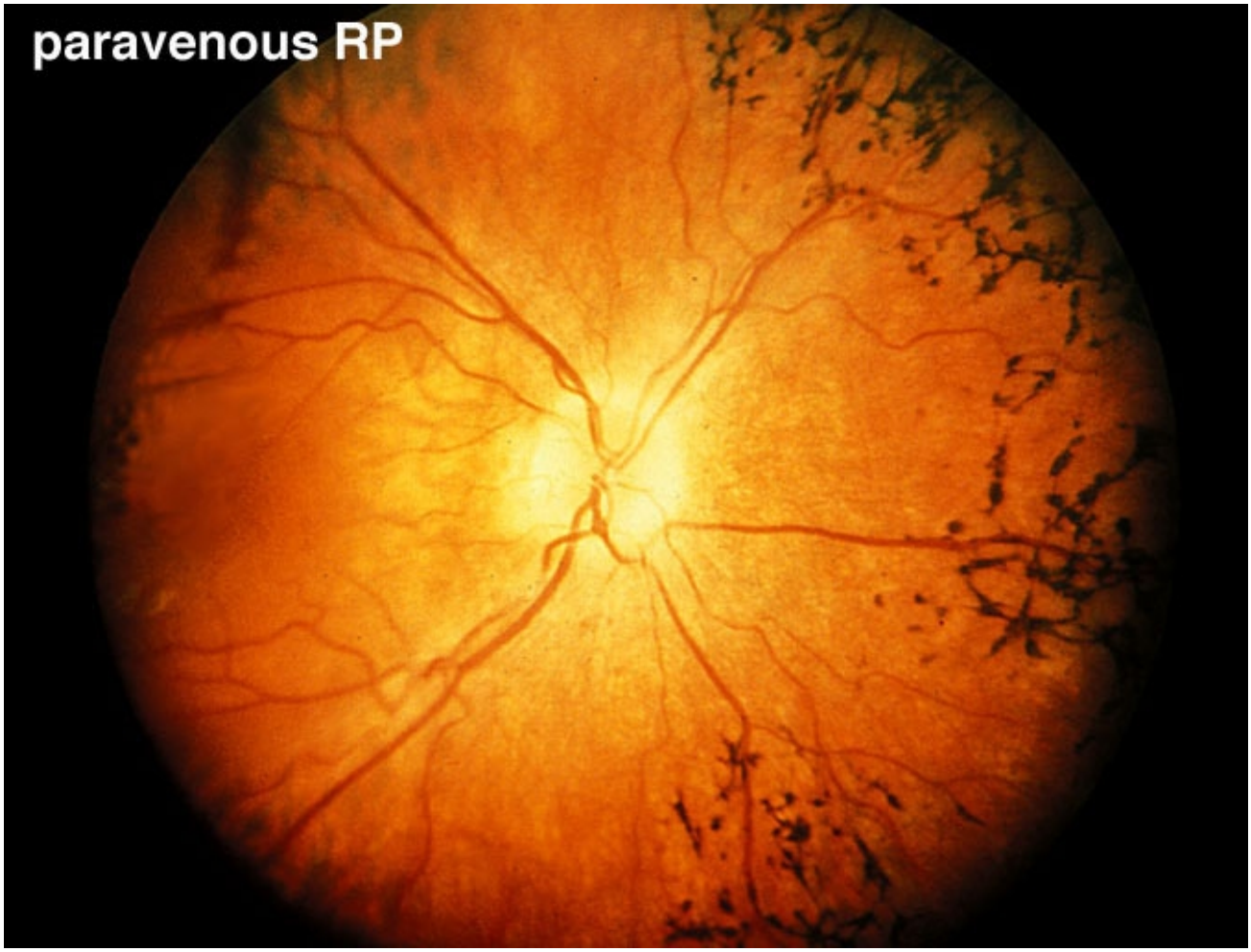

Figure 15. Fundus photo of a patient with paravenous retinitis pigmentosa.

Drug Toxicities

A number of drugs given in high doses or for long periods of time can produce retinal degeneration with pigmentary changes. Traditional culprits are thioridazine (Mellaril), chlorpromazine (Thorazine), and the antimalarial chloroquine. These are drugs usually taken at high dosages for many years and can end up damaging the retina and producing a retinopathy. Chloroquine retinopathy shows as a characteristic "bullseye" appearance of the macula (Fig. 32). The ERGs become abnormal in these cases (Fig. 33).

Hydroxychloroquine (Plaquenil) is usually less disruptive to the retina than chloroquine, but ERG changes can still occur. Other drugs can end up being accidentally toxic to the retina. Cisplatinum, used to treat brain tumors, sometimes reaches ophthalmic vascularization (Fig. 34) and causes a reduction in ERG waveform in the affected eye (OD in this case) (Fig. 35).

An interesting case was seen in our clinic, where an intranasal steroid injection affected the retina of the patient's right eye (OD) only. The fundus photo shows a cherry red spot in the macula (Fig. 36). The ERG response was diminished in size, particularly following dim scotopic flashes (Fig. 37).

Talc retinopathy is also seen occasionally (Fig. 38). Again, the global ERG is attenuated in such cases (Fig. 39).

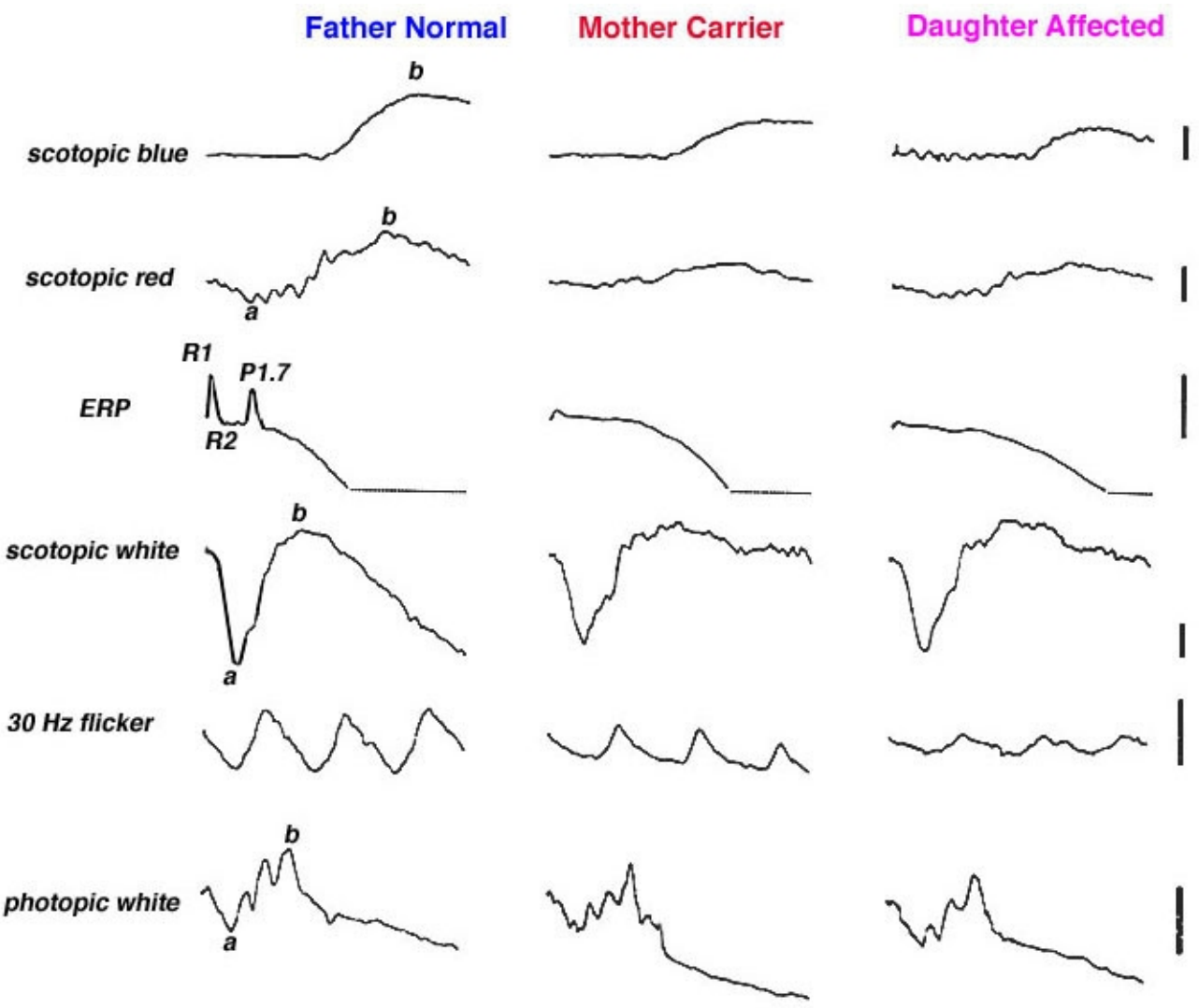

Figure 16. ERG of a family with a child with myotonic dystrophy.

Systemic Disorders and the ERG

Systemic metabolic disorders are reflected in retinal physiology. Liver and kidney disease and drugs that affect those organ systems, usually reduce ERG b-wave amplitudes, particularly in scotopic dim flash ERGs. For example, deferoxamine, an iron-chelating drug used to reduce iron overload, can be toxic to the retina. This is reflected in reduced a- and b-waves of the ERG (Fig. 40).

The Multifocal ERG (mfERG)

A limitation of the traditional global or full-field ERG is that the recording is a massed potential from the whole retina. Unless 20% or more of the retina is affected with a diseased state, the ERGs are usually normal. In other words, a legally blind person with macular degeneration, enlarged blind spot, or other central scotomas will have normal global ERGs.

The most important development in the ERG field in recent years is the multifocal ERG (mfERG) recording system (19). This system allows assessment of ERG activity in small areas of retinal dysfunction. With this method, one can record mfERGs from hundreds of small retinal areas (100 μm) simultaneously in less than 10

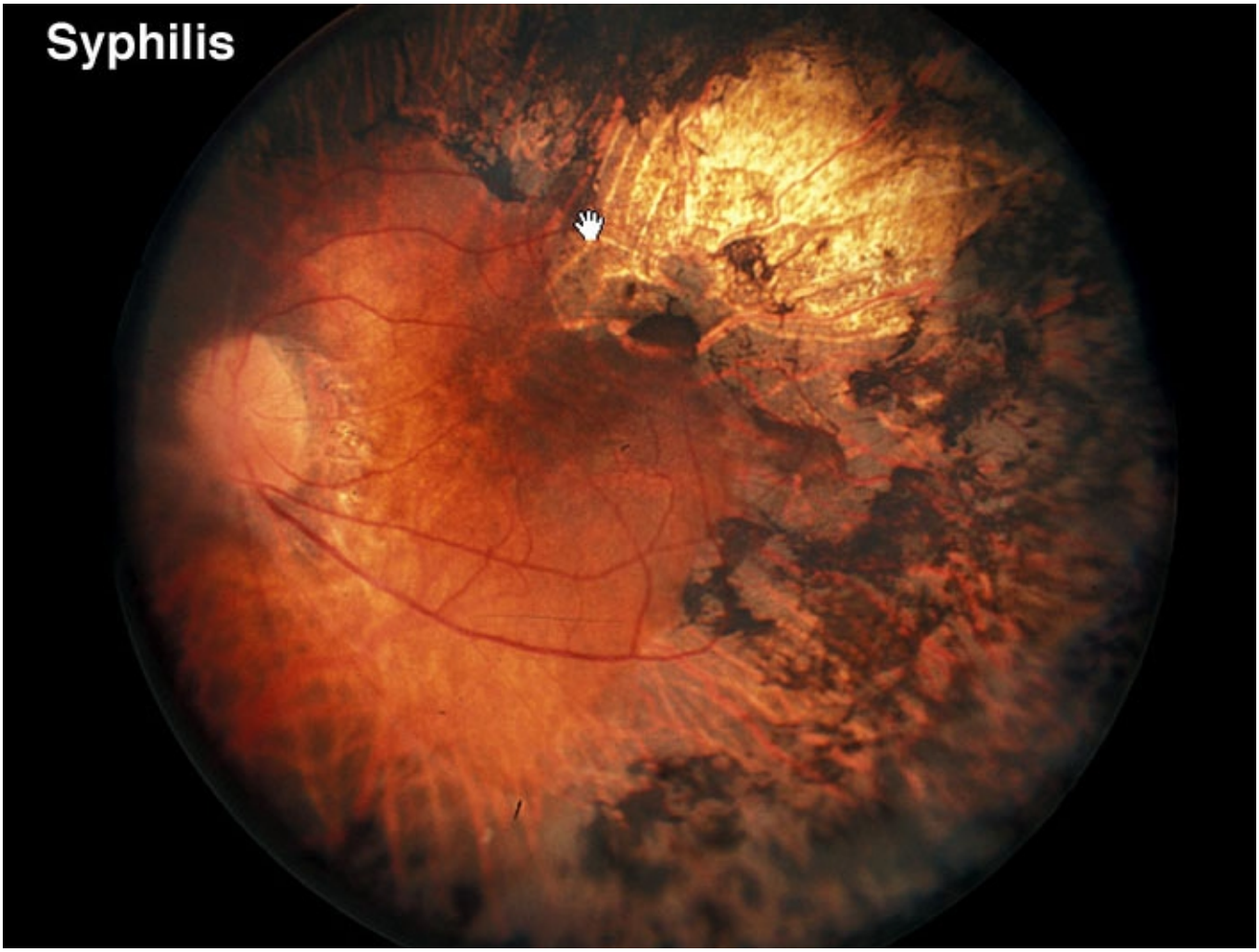

Figure 17. Fundus photo of patient with syphilis.

minutes per eye (20). A bipolar Burian speculum contact is usually used to record ERGs from the cornea from a dilated eye. Scotomas of only a couple of millimeters in diameter can be mapped, and the extent of retinal dysfunction can be quantified very accurately.

Below are the mfERGs of a patient tested at the Moran Eye Center (Fig. 41b and Fig. 42). The patient is an elderly woman with macular degeneration. The fundus photograph of another patient with age-related macular degeneration (AMD) is seen in Fig. 41a. In Fig. 41b are 103 multifocal ERGs from approximately the central 50 degrees of retinal field. In Fig. 42 are the b-wave voltages from these 103 locations transformed into a 3-D color plot. The lower far right (Fig. 42) shows a plot of a normal patient for comparison. The top color transformation is the difference between the patient's multifocal ERGs and a normal group, which points out the worst areas of retinal function. Colors reflect standard deviations (S.D.) from average ERG amplitudes. These plots can be rotated from 3-D to 2-D so that they resemble visual field plots.

One of the best uses of mfERGs is for distinguishing between retinal and central etiology of visual problems in patients with no apparent abnormalities in the ocular fundus. These types of patients can include MEWDS (Multiple Evanescent White Dot Syndrome) and AZOOR (acute zonal occult outer retinopathy). Figure 43 is example of 17-year-old male diagnosed with AZOOR associated with a viral prodrome. The mfERGs are clearly showing the retinal abnormalities coincident with the visual field losses (Fig. 43). In contrast, the only visible fundus abnormalities were small, easily overlooked pinpoint hyperfluorescent lesions in Indocyanine Green Chorioangiography (ICG).

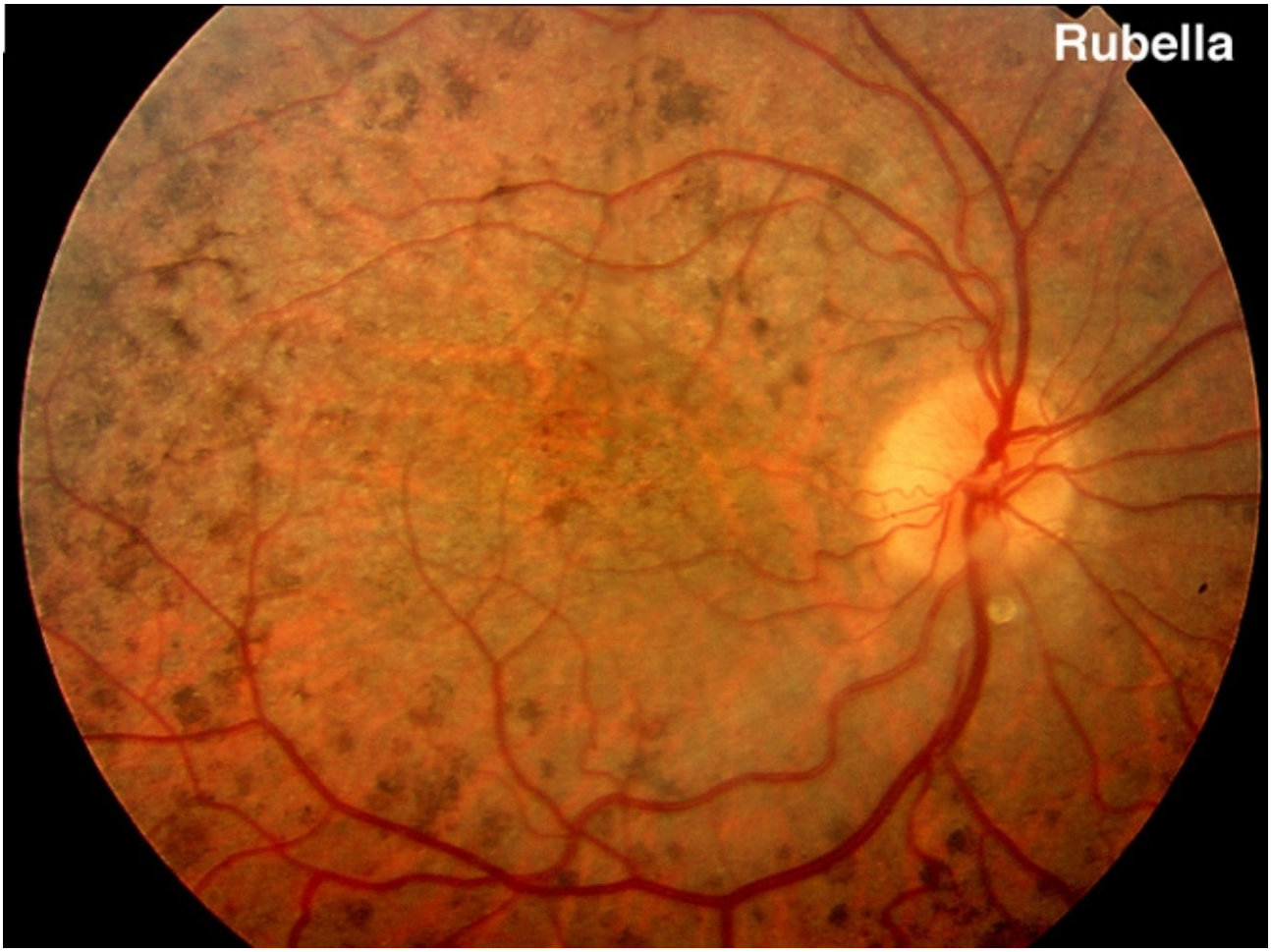

Figure 18. Fundus photo of patient with rubella.

The mfERG method is a very reliable test and really helps in following the progression of a macular (or other limited retinal area) disorders.

The Electrooculogram (EOG)

The electrooculogram (EOG) measures the potential that exists between the cornea and Bruch's membrane at the back of the eye. The potential produces a dipole field with the cornea approximately 5 millivolts positive compared with the back of the eye, in a normally illuminated room. Although the origin of the EOG is the pigment epithelium of the retina, the light rise of the potential requires both a normal pigment epithelium and normal mid-retinal function. Elwin Marg named the electrooculogram in 1951 (21), and Geoffrey Arden (3) developed the first clinical application. With the cornea constantly positive, movement of the eye produces a shift of this electrical potential. By attaching skin electrodes on both sides of an an eye (Fig. 44), the potential can be measured by having the subject move his or her eyes horizontally a set distance (Fig. 45). The eyes are usually dilated. Skin electrodes are attached near the lateral and medial canthus of each eye (Fig. 44). A ground electrode is attached usually to either the forehead or earlobe. It is helpful, but not necessary, that the patient have a chin rest to reduce head movement. Either inside a Ganzfeld, or on a screen in front of the patient, small red fixation lights are place 30 degrees apart (Fig. 46). The distance the lights are separated is not critical for routine testing. Any set distance subtending from 20 to 40 degrees of visual angle is satisfactory.

The patient should be light adapted such as in an well-illuminated room, and their eyes dilated. After the electrodes are attached, the procedure is explained and the patient is asked to practice several times while

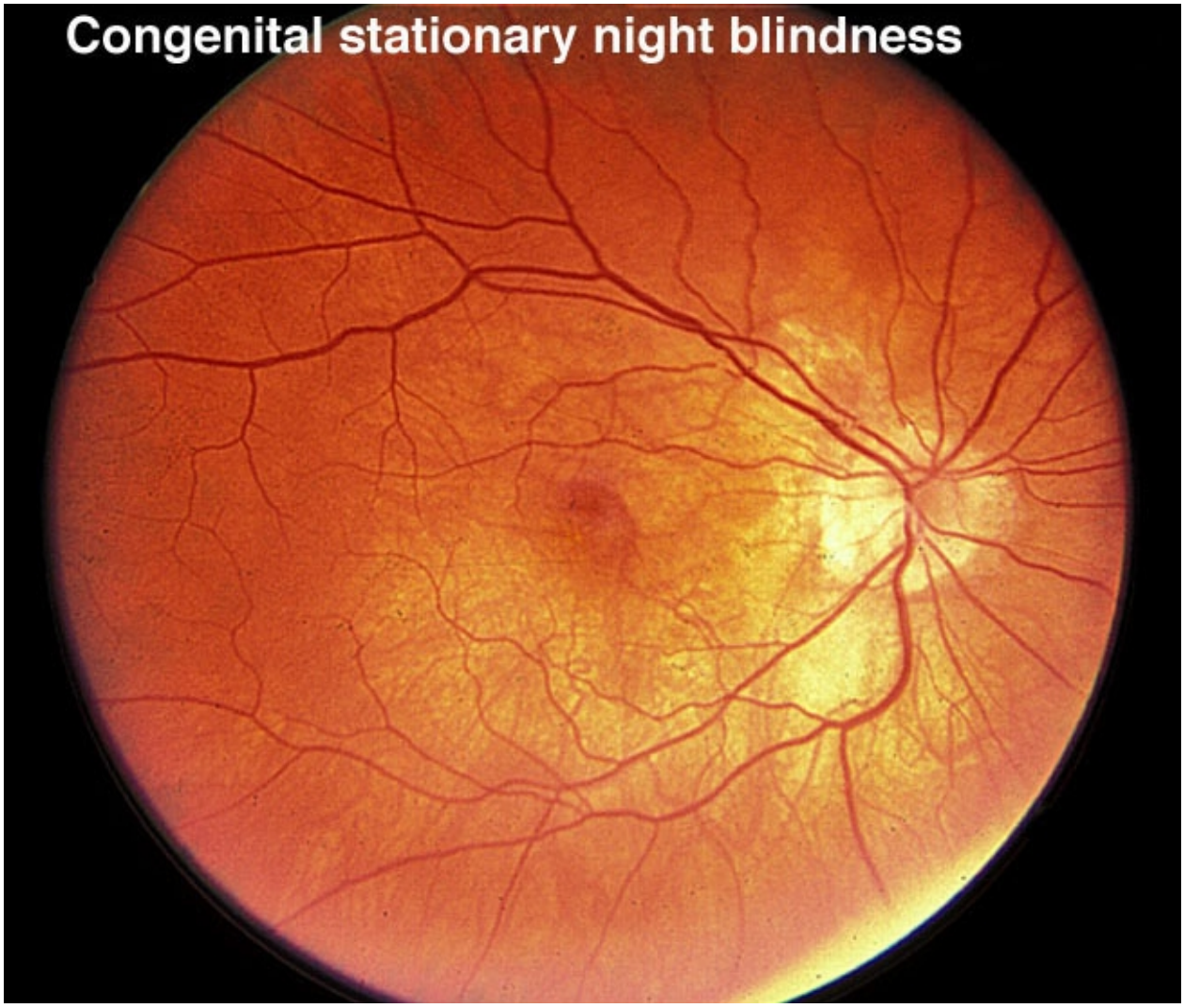

Figure 19. Fundus photo of patient with CSNB type 2.

baseline data are recorded. The procedure is simply that the patient keeps his or her head still while moving the eyes back and forth, alternating between the two red lights. The movement of the eyes produces a voltage swing of approximately 5 millivolts between the electrodes on each side of the eye, which is charted on graph paper or stored in the memory of a computer. In Fig. 47 are 10-sec periods of eye movement back and forth between two red LED lights placed 30 degrees apart inside a Ganzfeld.

After training the patient in the eye movements, the lights are turned off. About every minute, a sample of eye movement is taken as the patient is asked to look back and forth between the two lights (Fig. 47). Some laboratories have the patients move their eyes the entire testing period. After 15 minutes, the lights are turned on, and the patient is again asked about once a minute to move his or her eyes back and forth for about 10 sec. The top of Fig. 48 shows segments of eye movement that have been cut from 10-sec samples from a normal person. The chart (Fig. 48) graphs the change in voltage in the eye through 15 minutes of dark adaptation and 15 minutes of bright light. Typically, the voltage becomes a little smaller in the dark, reaching its lowest potential after about 8-12 minutes, the so-called "dark trough." When the lights are turned on, the potentials rise, and the light rise reaches its peak in about 10 minutes. When the size of the "light peak" is compared with the "dark trough", the relative size should be about 2:1 or greater (Fig. 48). A light:dark ratio of less than about 1.7 is considered abnormal. Fig. 49 shows an abnormal response recorded from a patient with Best's disease.

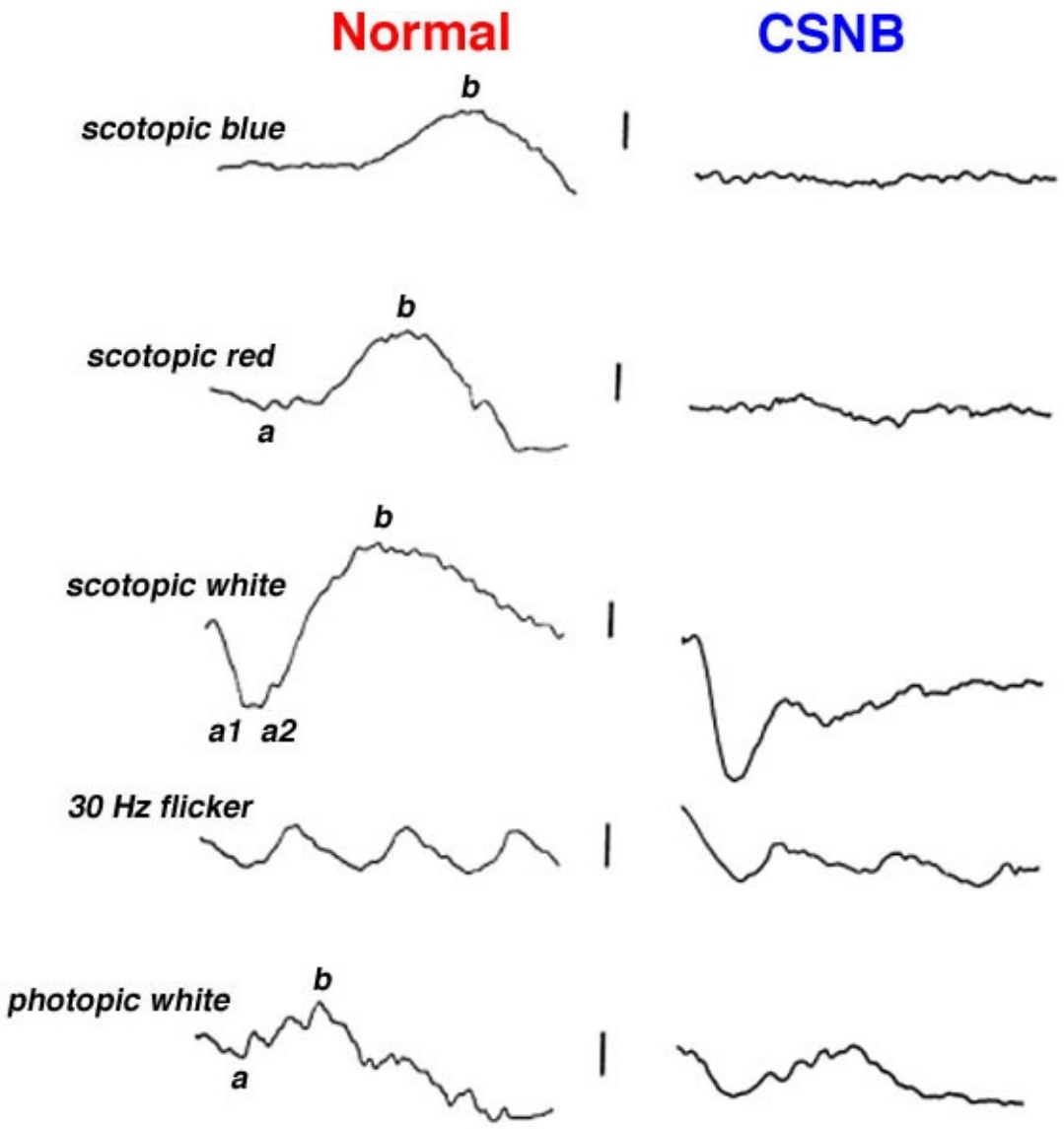

Figure 20. ERGs in a patient with CSNB type 2.

The EOG is redundant with the ERG in most retinal disorders. Retinal diseases producing an abnormal EOG will usually have an abnormal ERG, which is the better test for analysis of scotopic and photopic measures. The most common use of the EOG is to confirm Best's disease. Best's vitelliform macular dystrophy and variants of this disease are usually identified by the appearance of a retinal lesion resembling an egg yolk early in the disease (Fig. 50). In vitelliform macular dystrophy (Fig. 51), the ERG will be normal but the EOG will be abnormal.

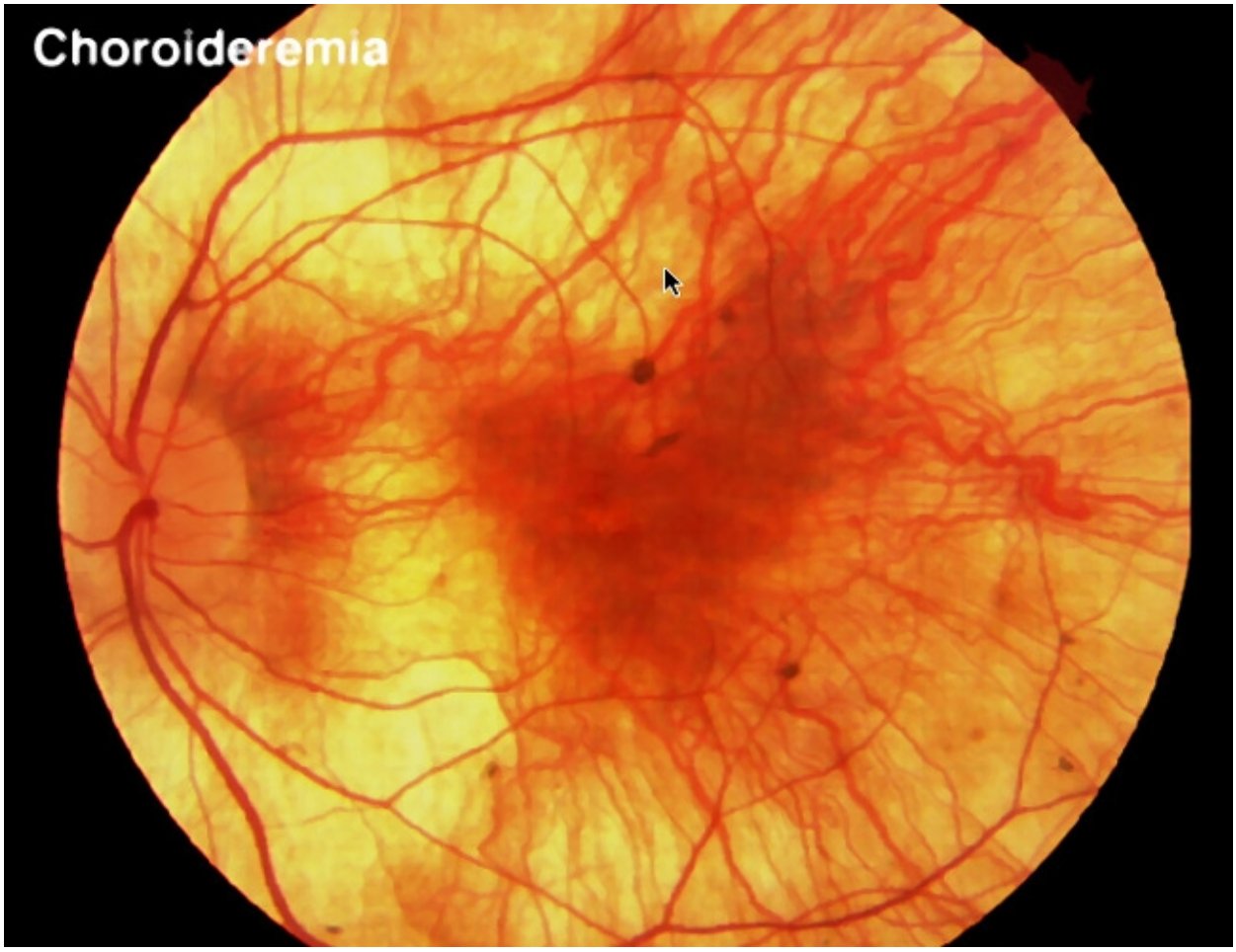

Figure 21. Fundus photo of patient with choroideremia.

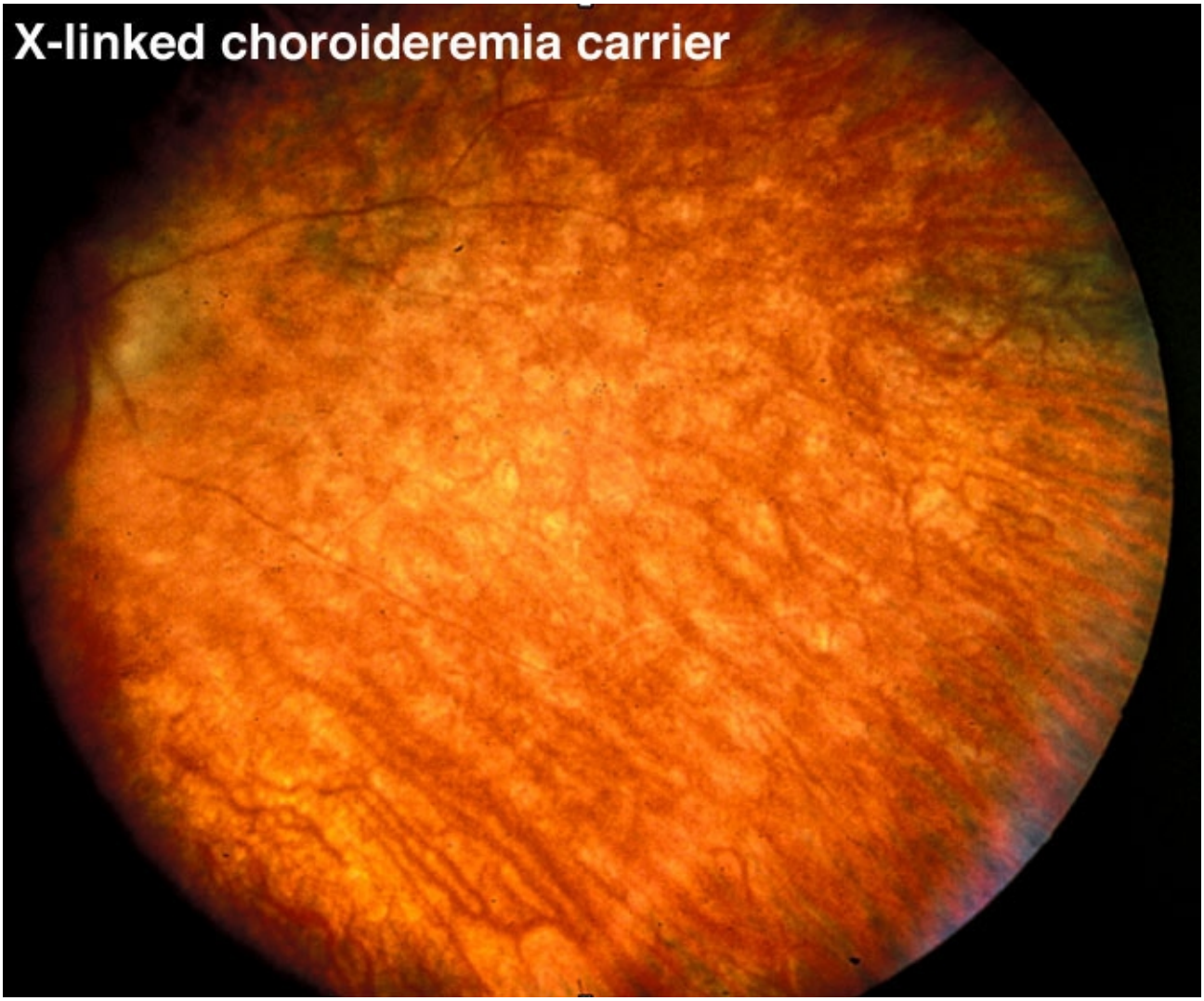

Figure 22. Fundus photo of a patient with X-linked choroideremia carrier.

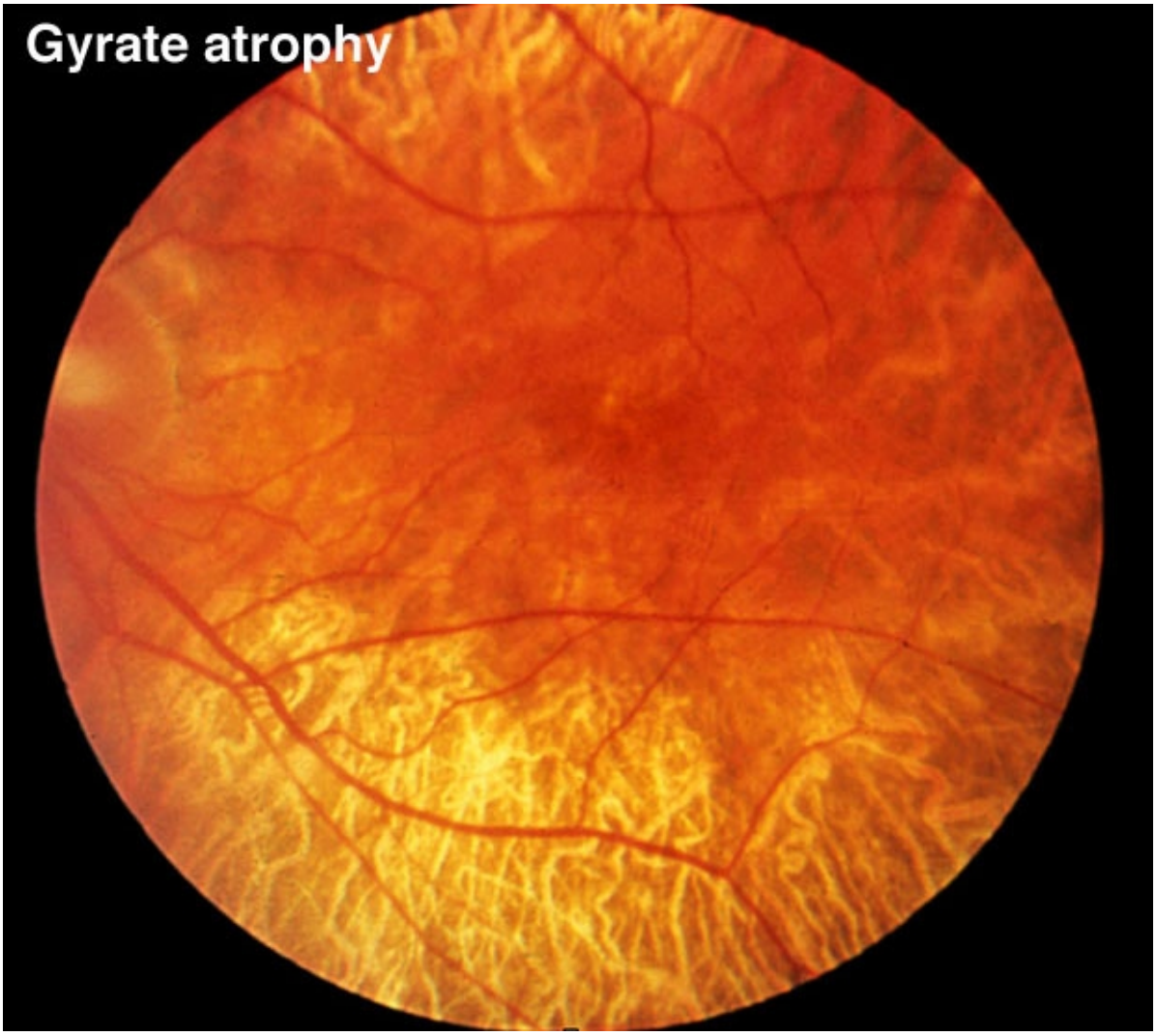

Figure 23. Fundus photo of a patient with gyrate atrophy.

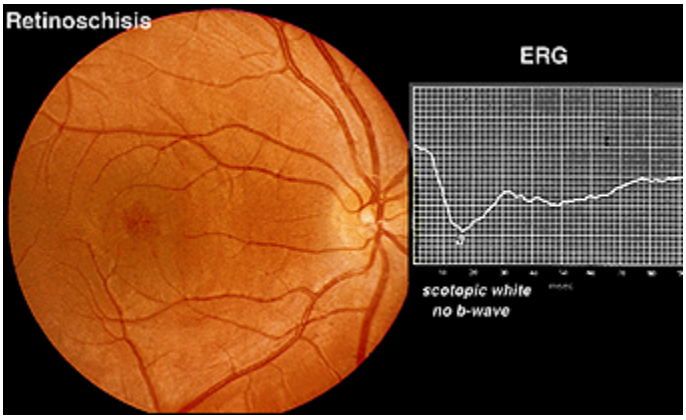

Figure 24. Fundus photo and bright-flash ERG of patient with retinoschisis.

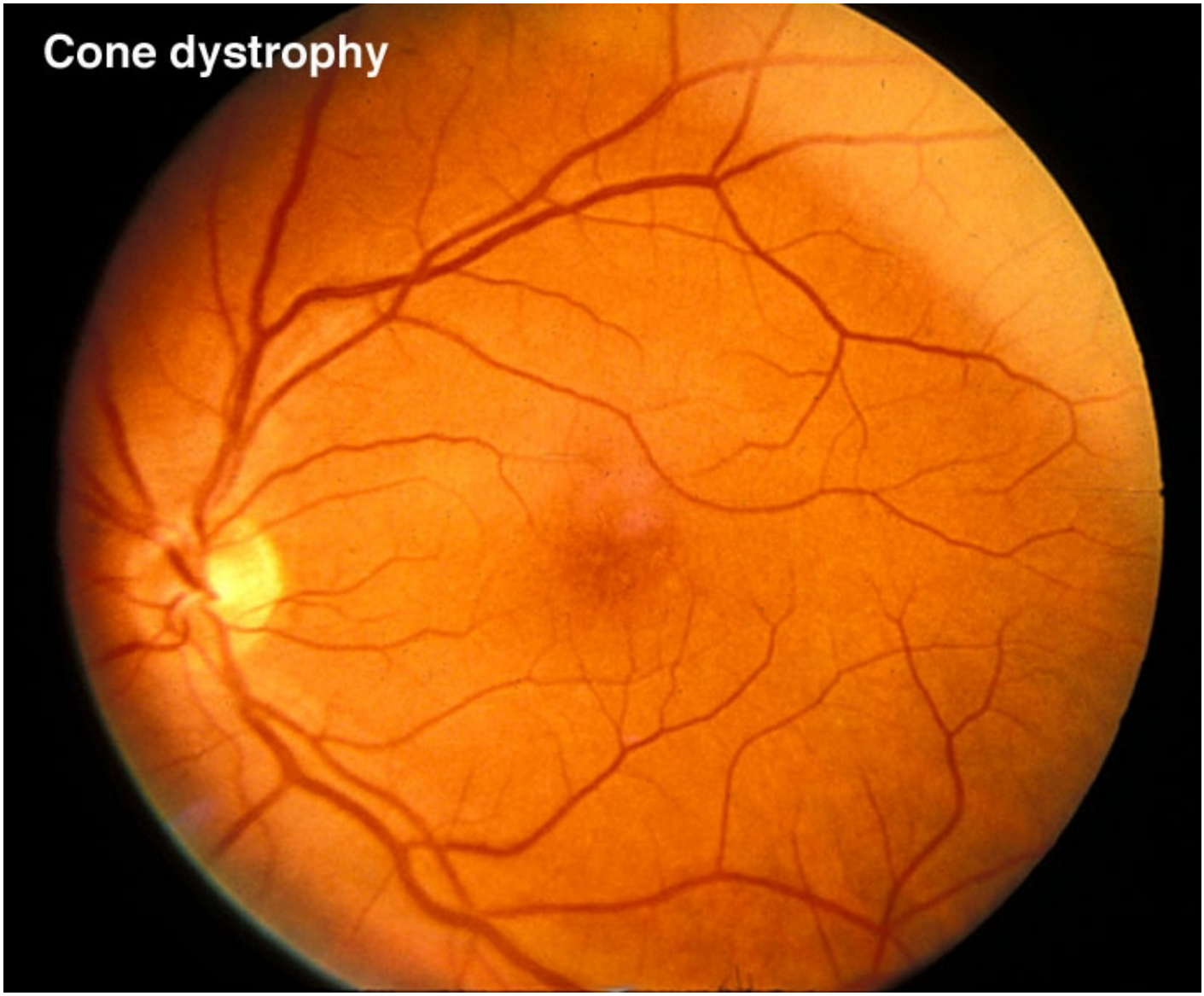

Figure 25. Fundus photo of patient with cone dystrophy.

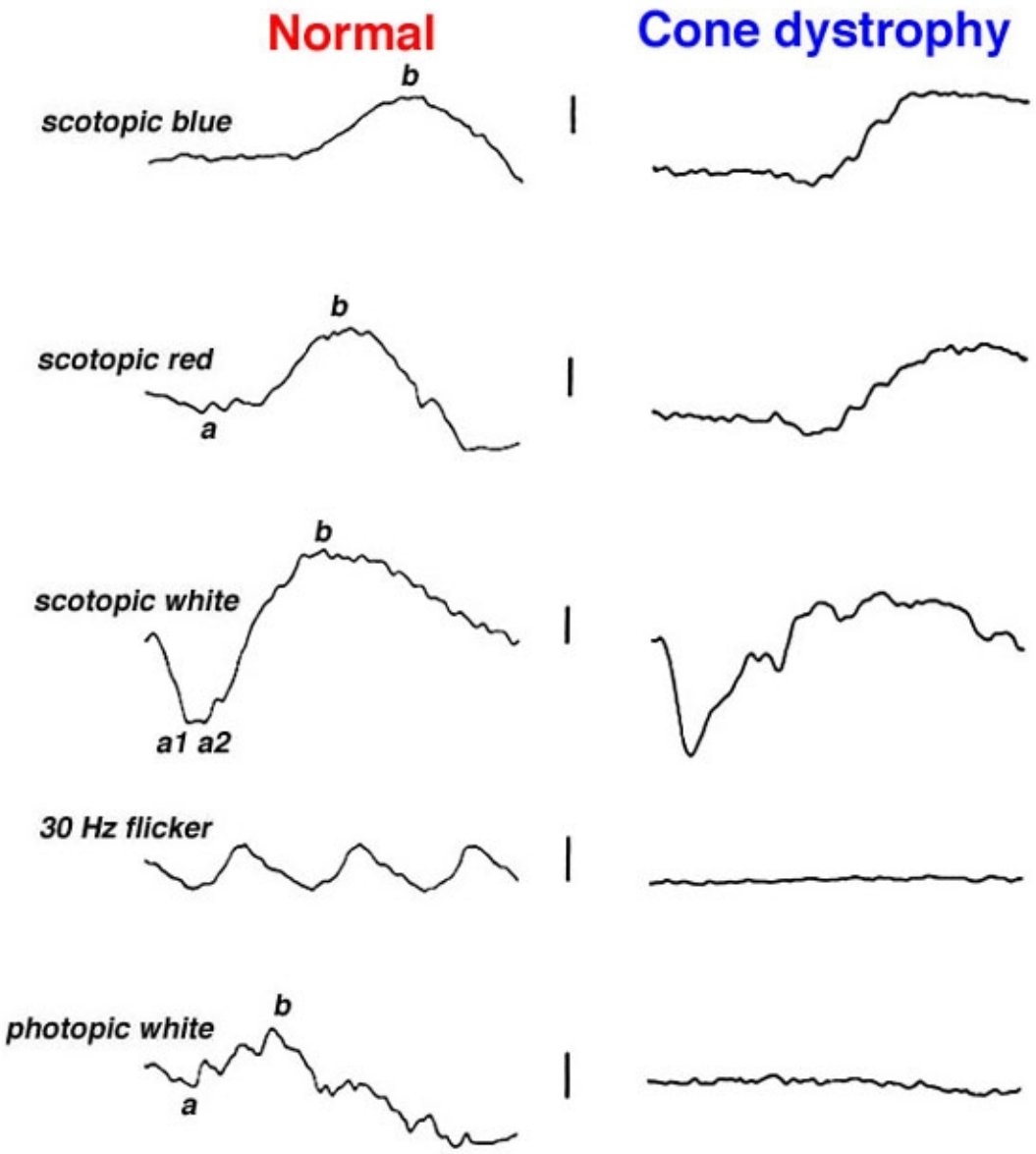

Figure 26. ERGs in a patient with cone dystrophy.

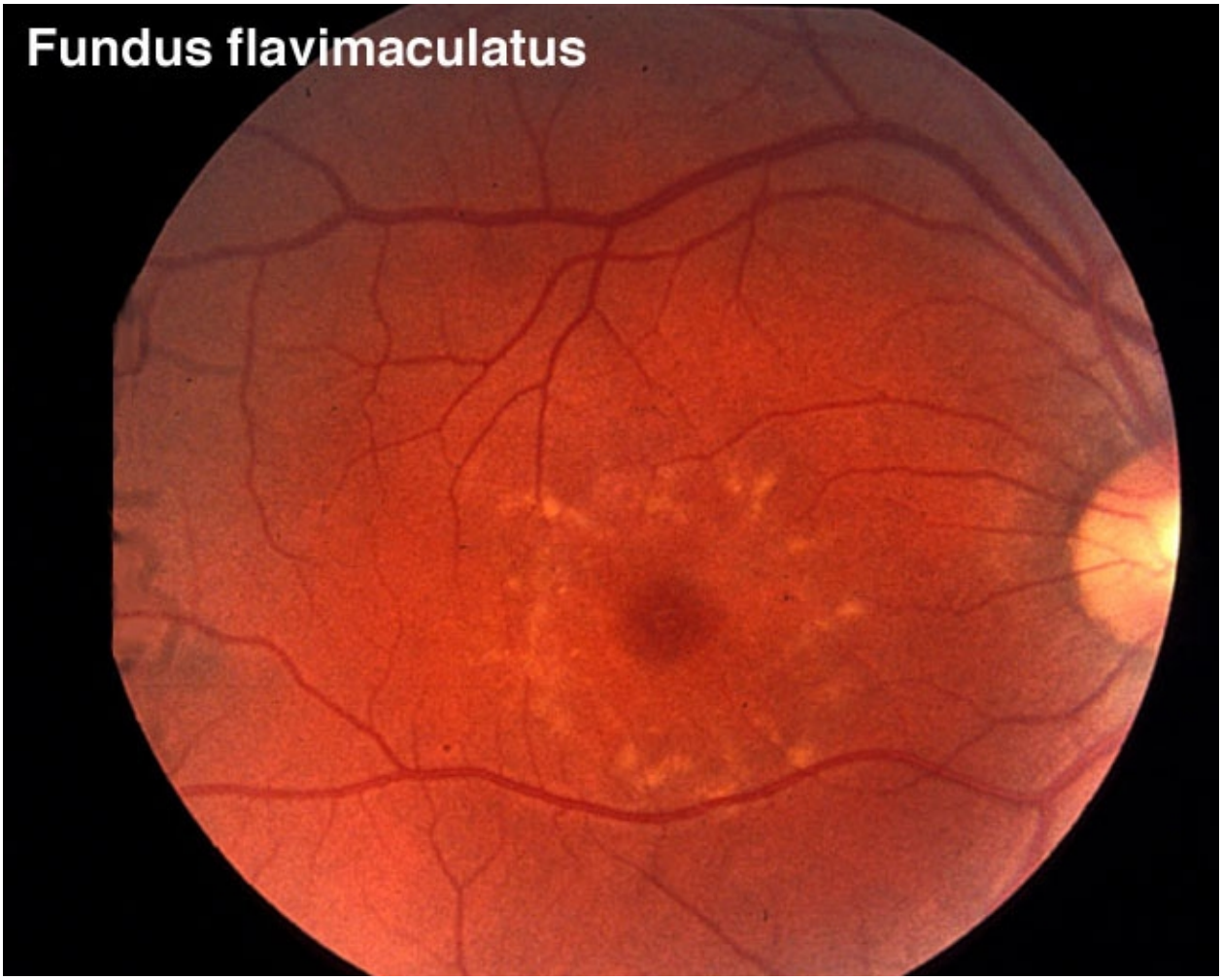

Figure 27. Fundus photo of patient with fundus flavimaculatus.

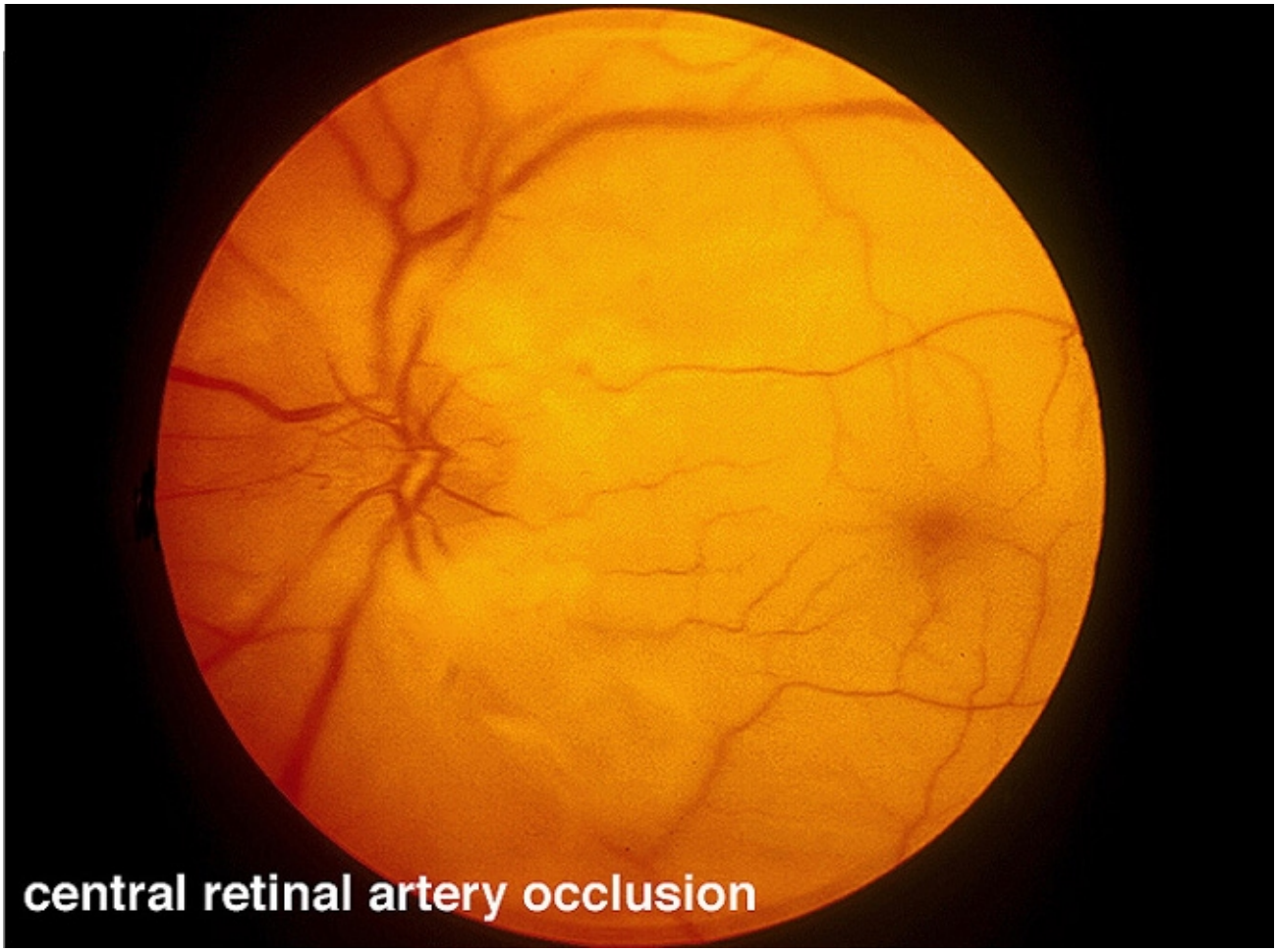

Figure 28a. Fundus photo of patient with central retinal artery occlusion.

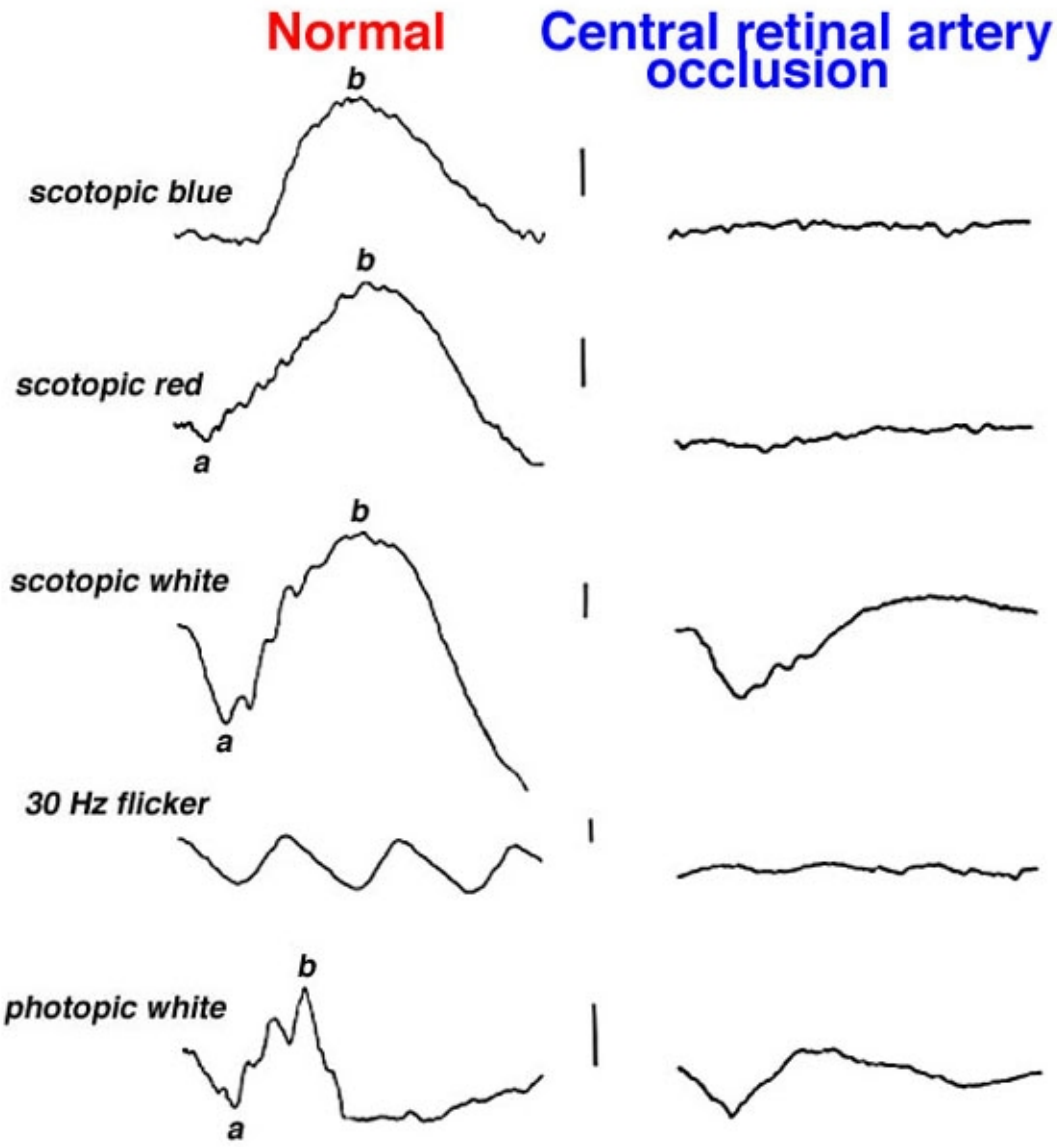

Figure 28b. ERGs in a patient with central retinal artery occlusion.

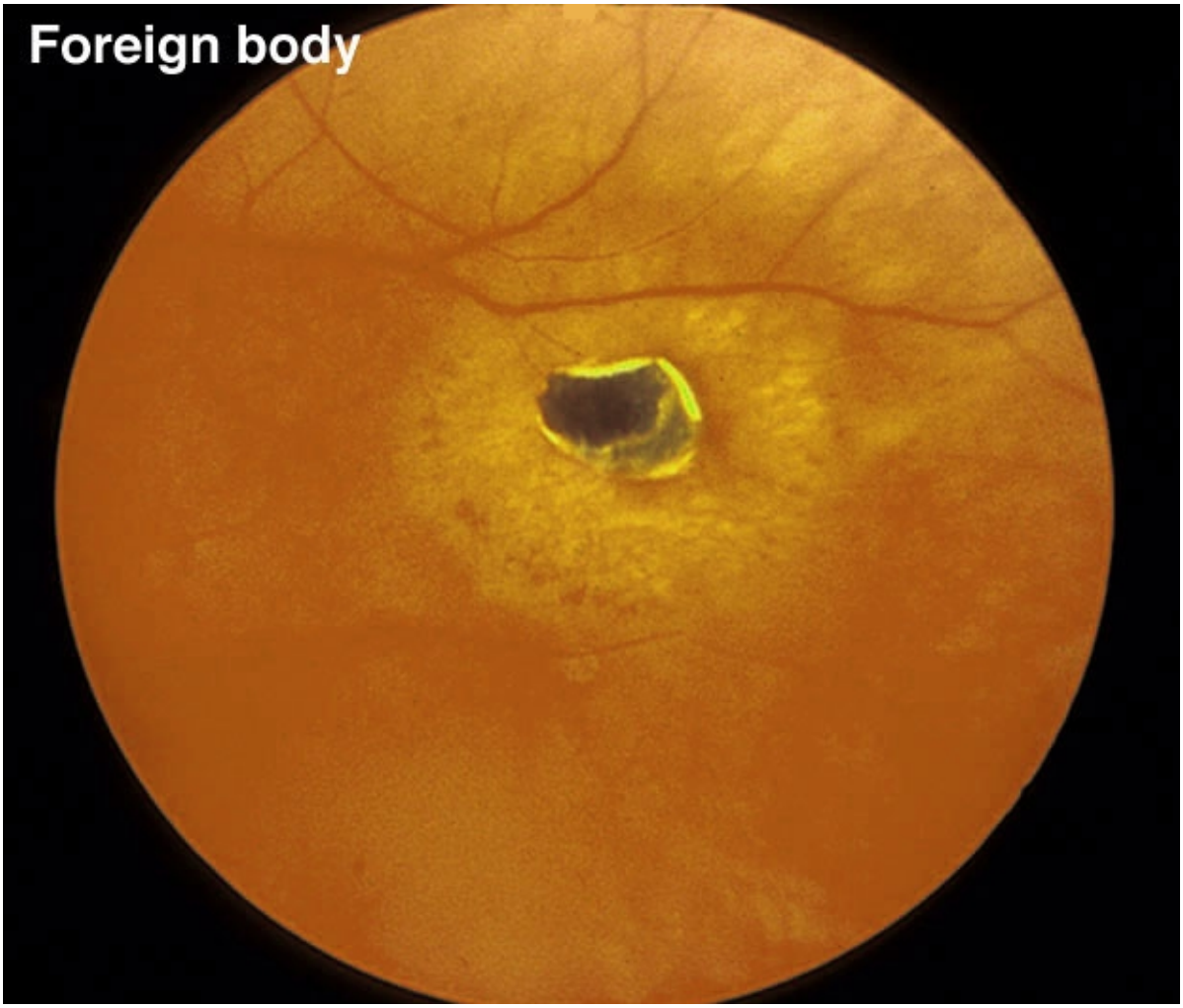

Figure 29. Fundus photo of a patient with a hole in the retina caused by a metallic foreign body.

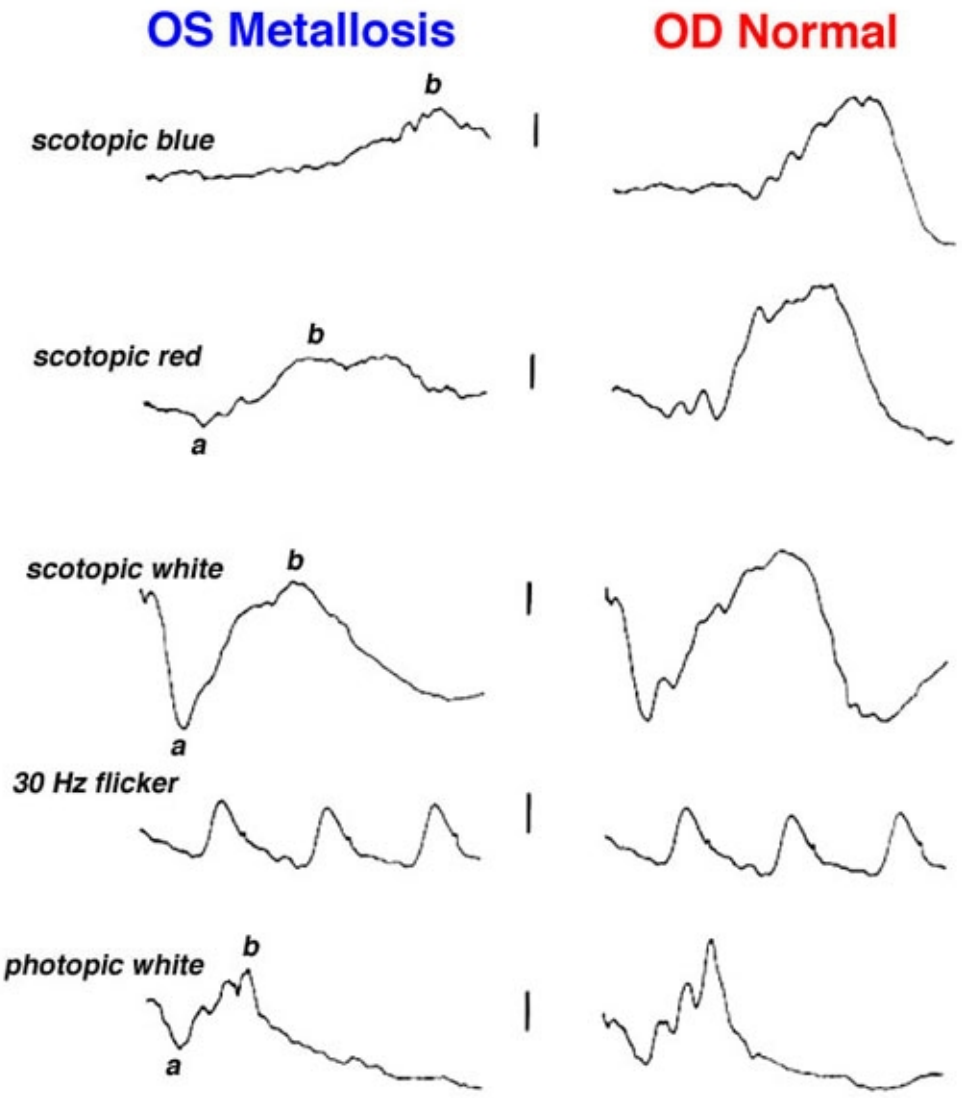

Figure 30a. The effect of the foreign body on the ERG waveform.

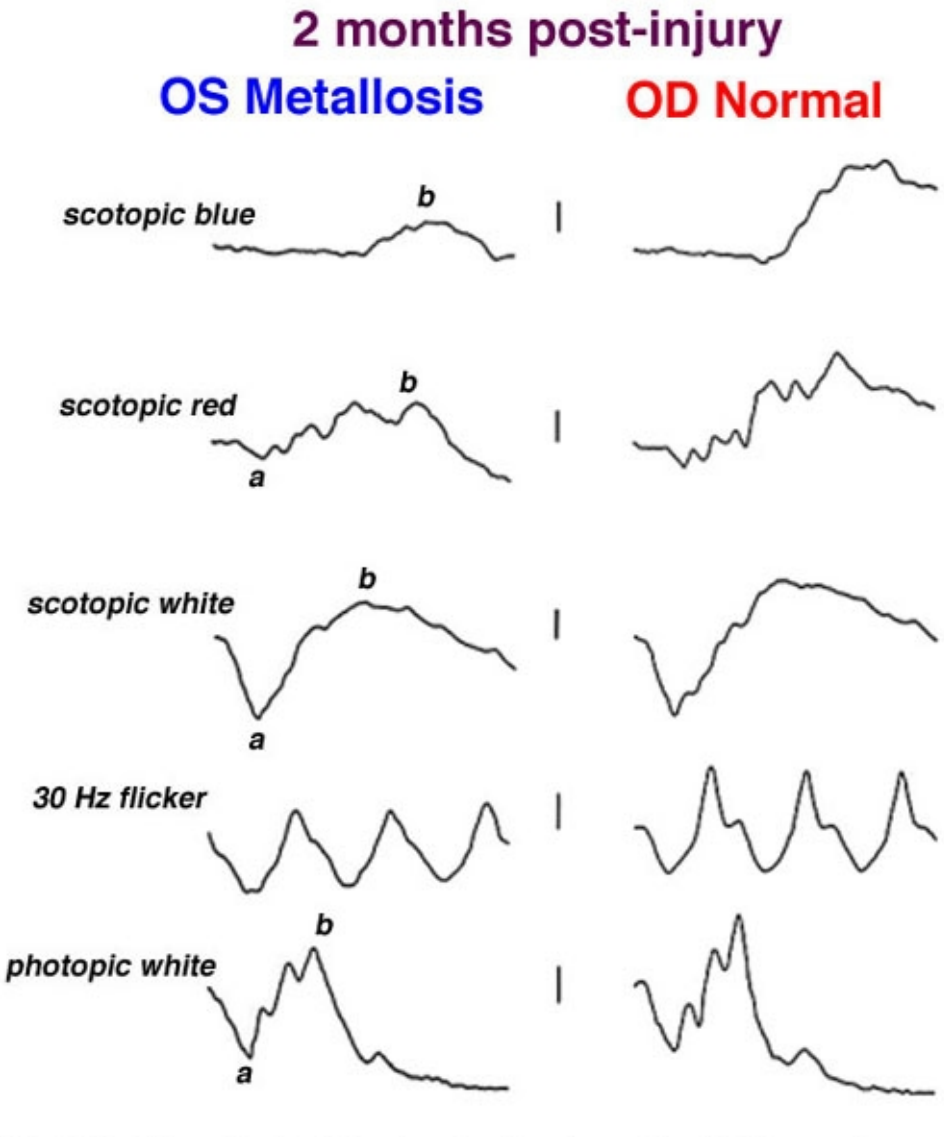

Figure 30b. The effect of the foreign body on the ERG waveform some weeks later.

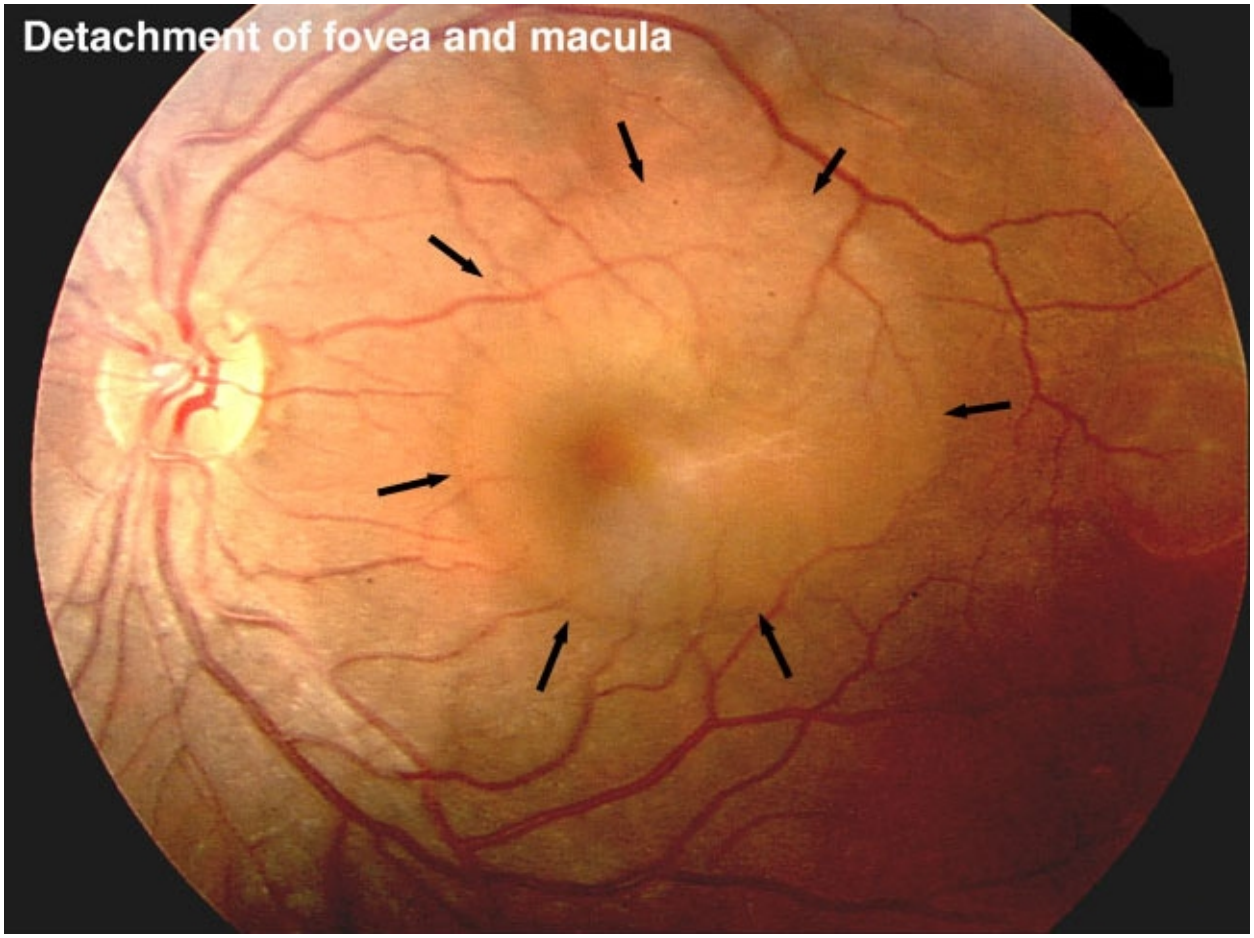

Figure 31a. Fundus photo of a patient with a retinal detachment at the fovea and macula in one eye.

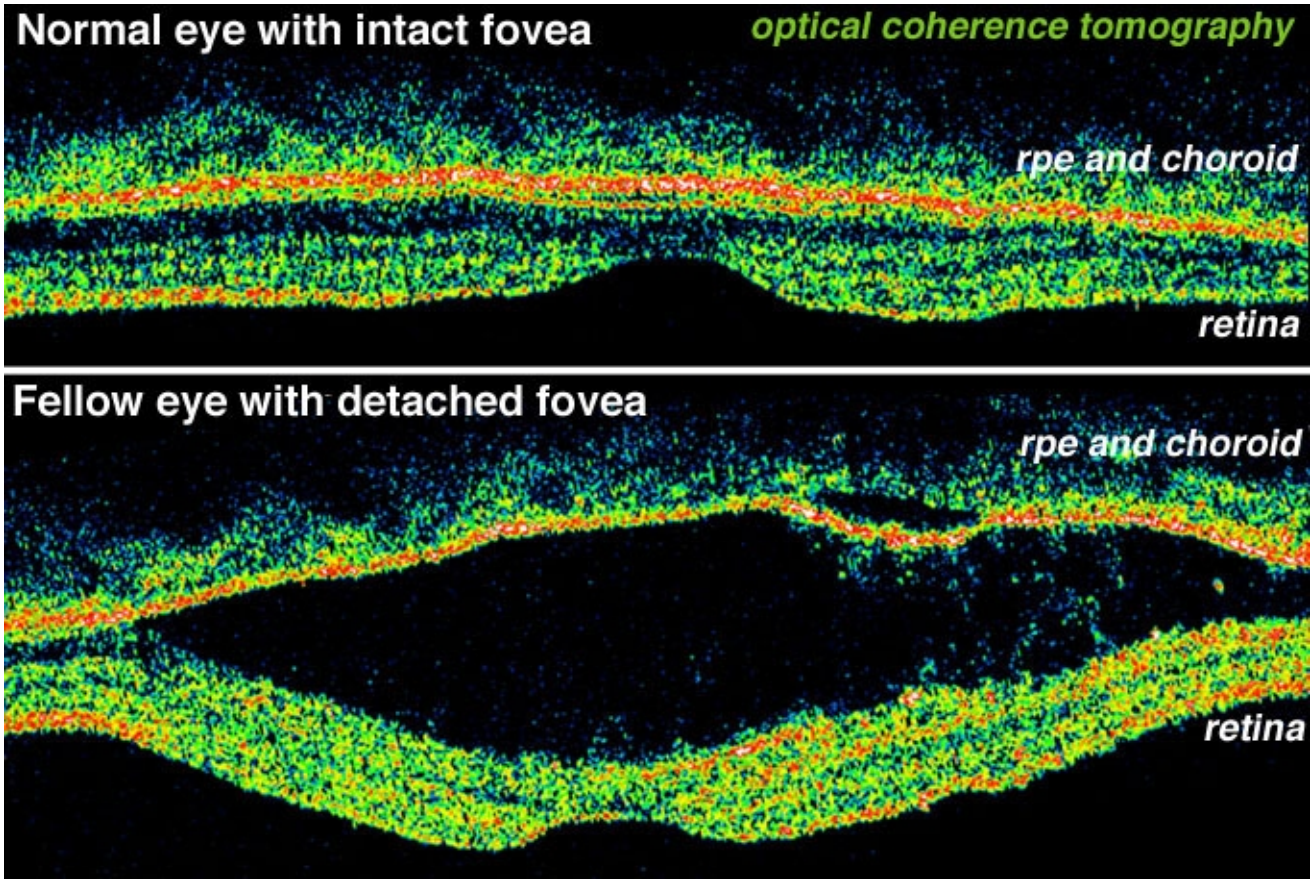

Figure 31b. Optical coherence tomography (OCT) images of the patient's normal macula and of the retina in the other eye with the macular detachment.

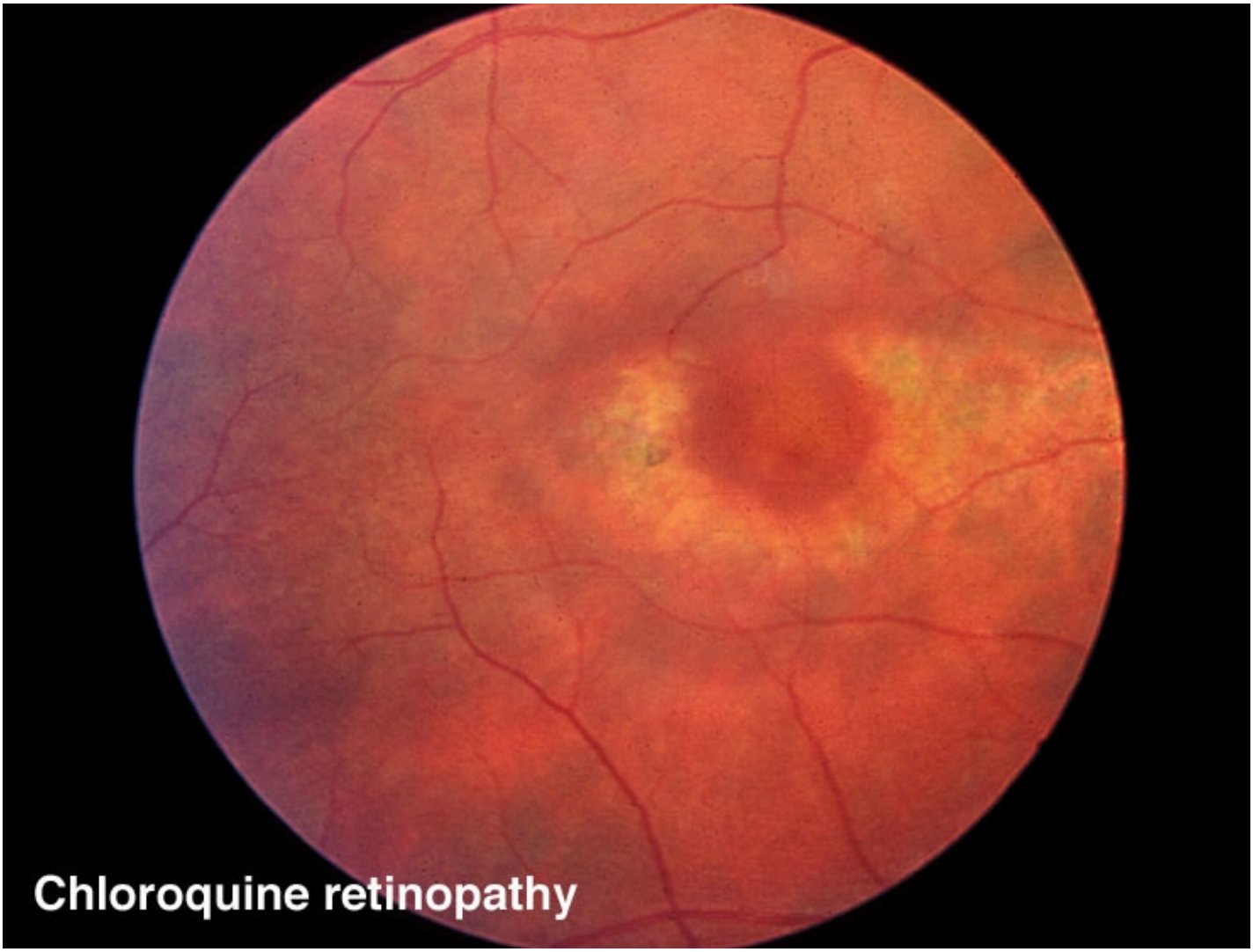

Figure 32. Fundus photo of patient with chloroquine retinopathy.

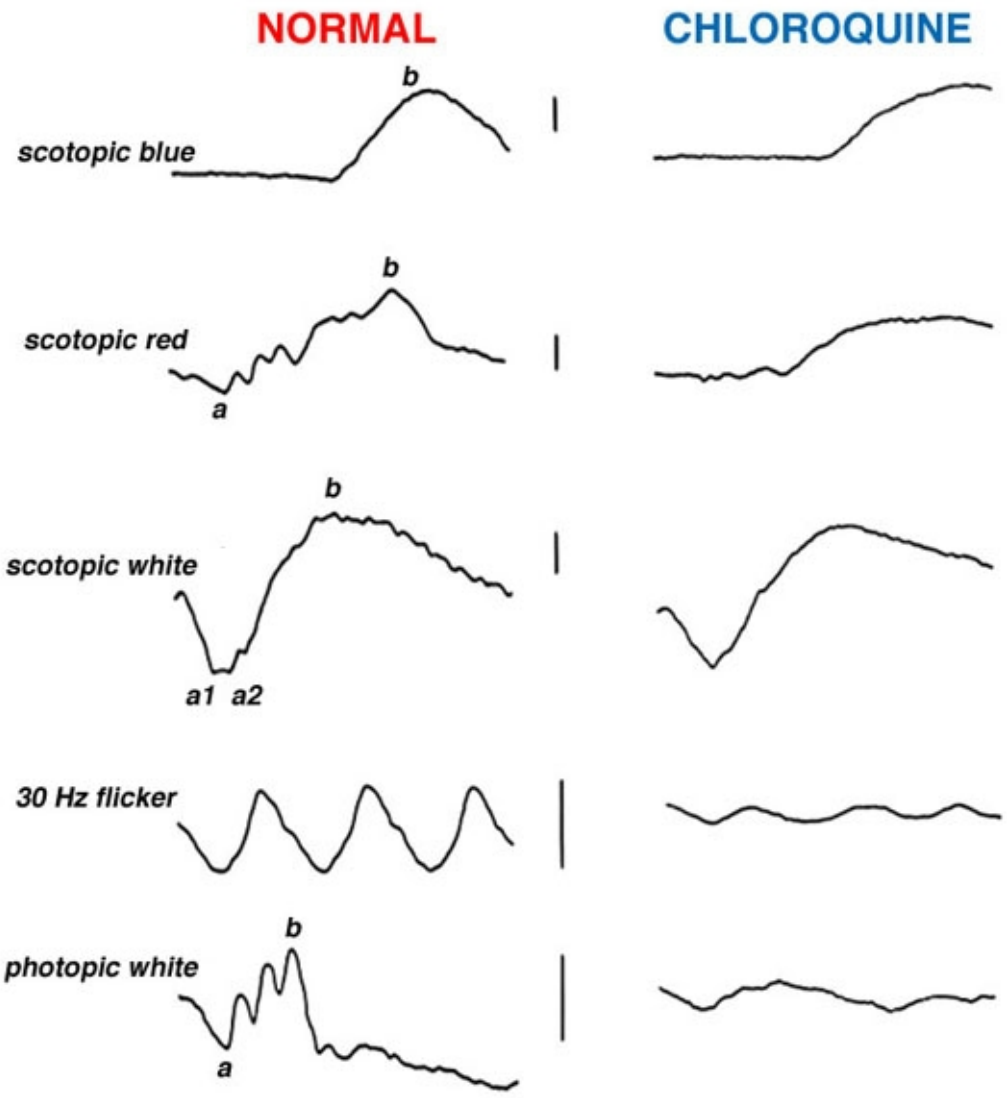

Figure 33. ERGs in a patient with chloroquine retinopathy.

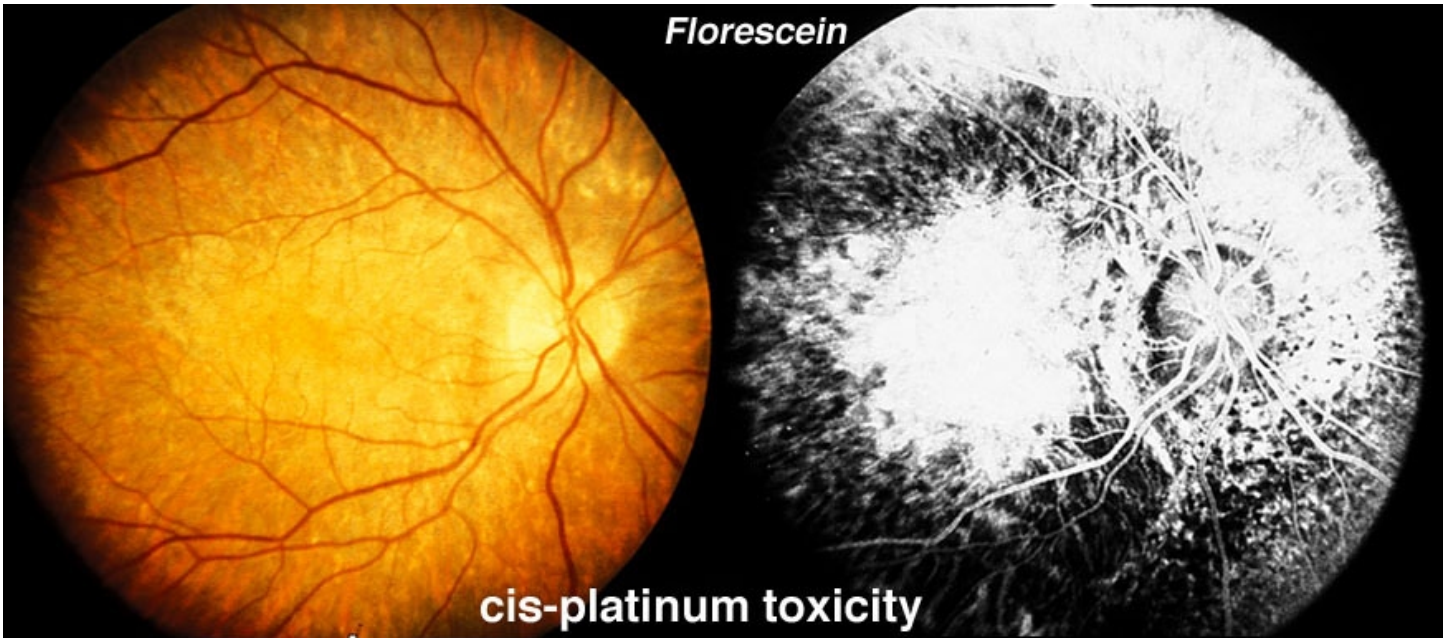

Figure 34. Fundus photo of patient with OD cisplatinum toxicity.

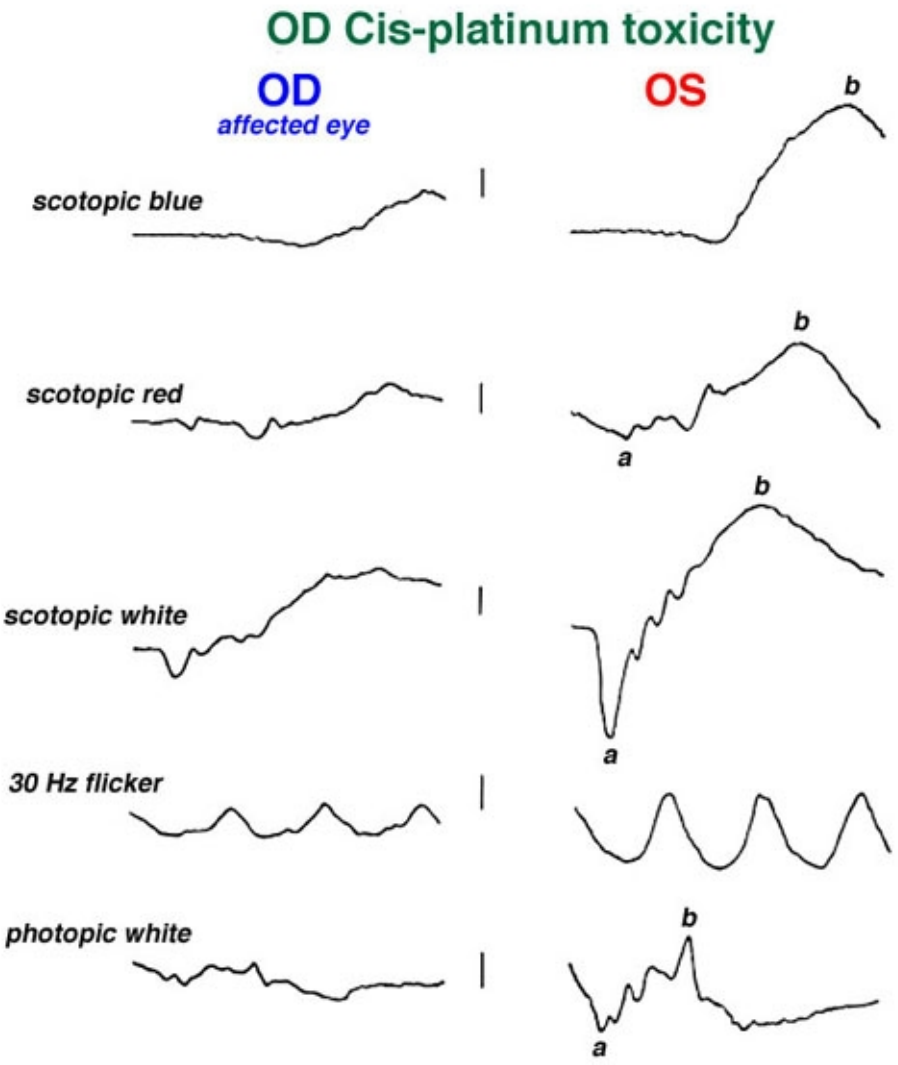

Figure 35. ERGs in a patient with OD cisplatinum toxicity.

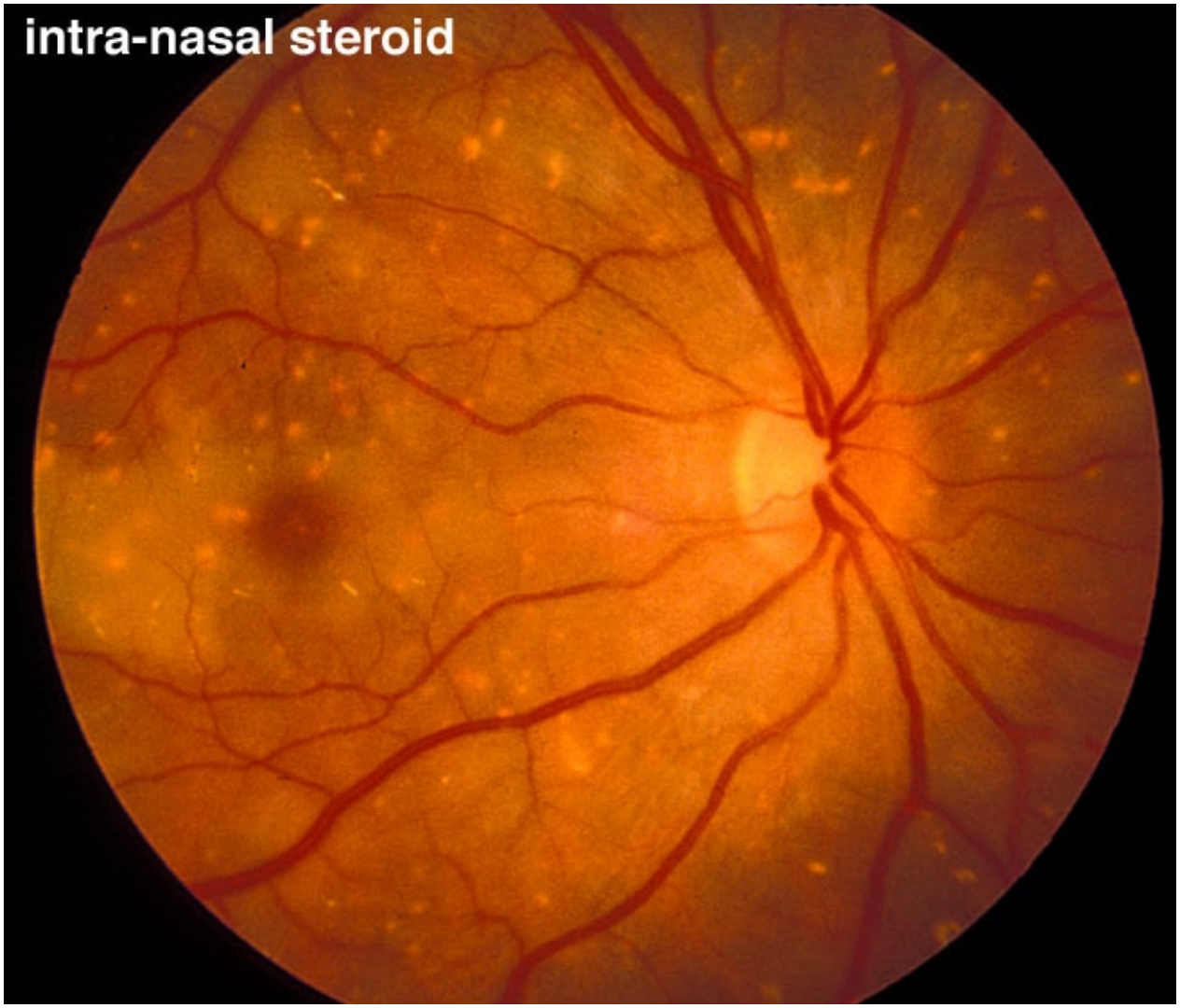

Figure 36. Fundus photo of patient with steroid retinopathy.

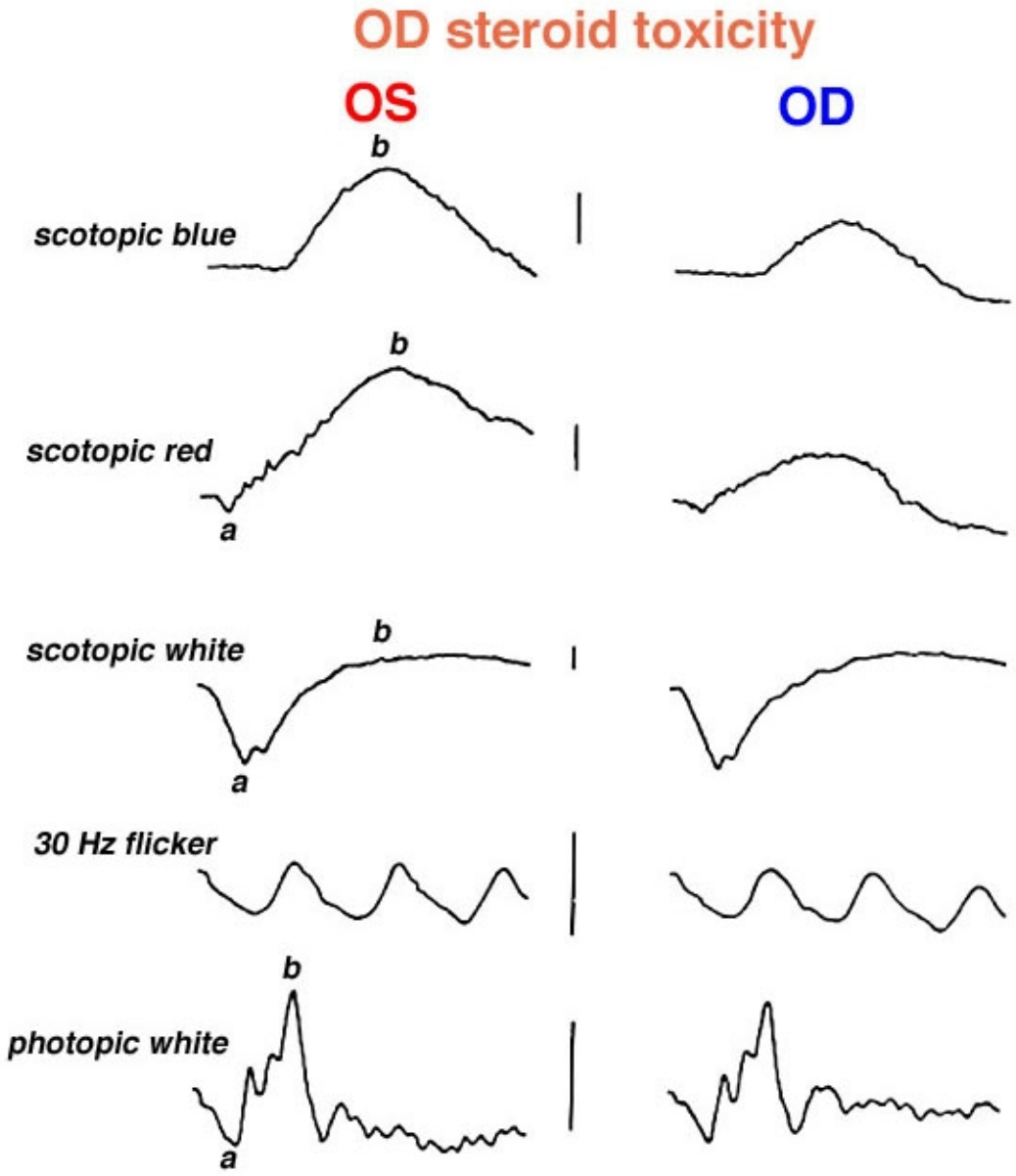

Figure 37. ERGs in a patient with steroid retinopathy.

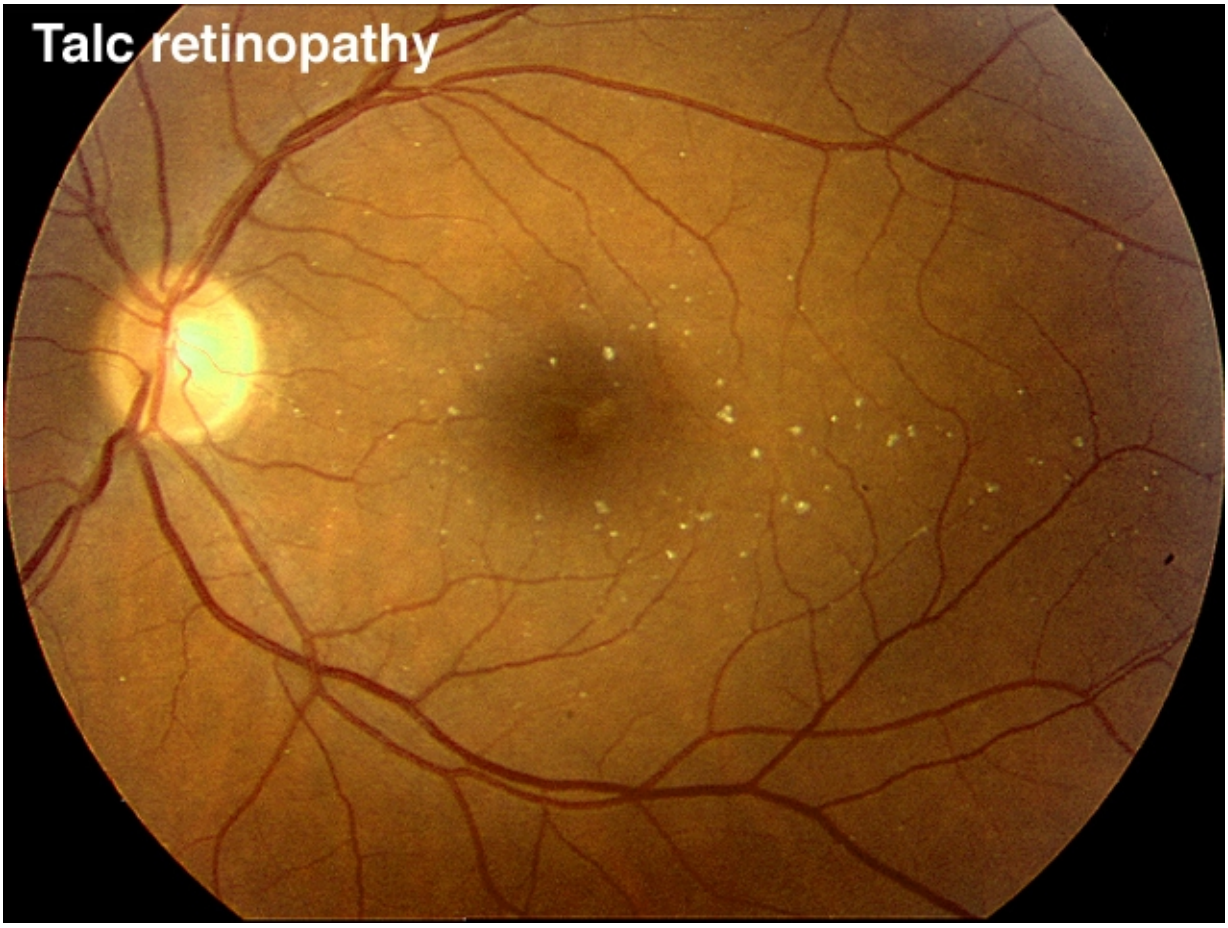

Figure 38. Fundus photo of patient with talc retinopathy.

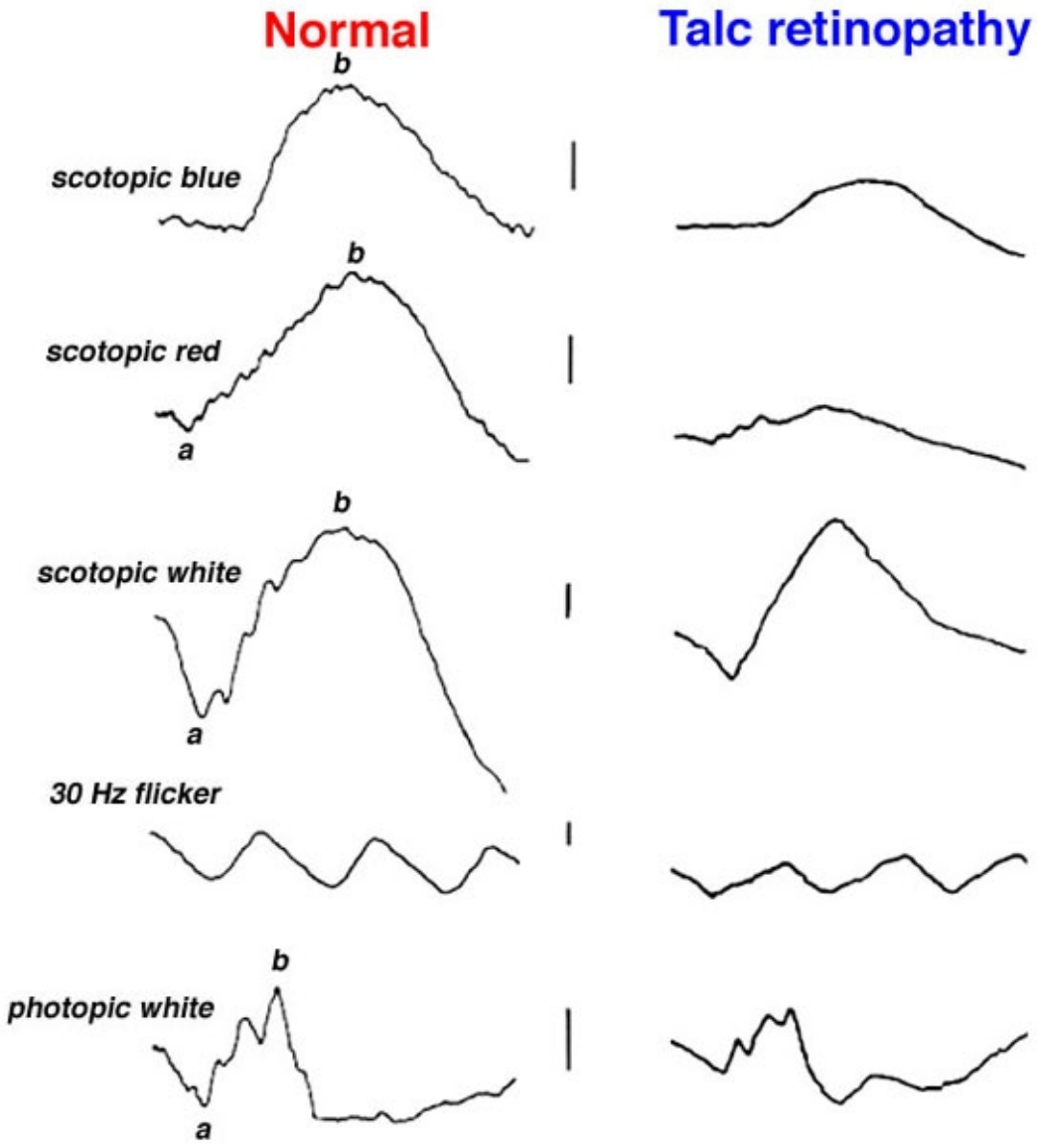

Figure 39. ERGs in a patient with talc retinopathy.

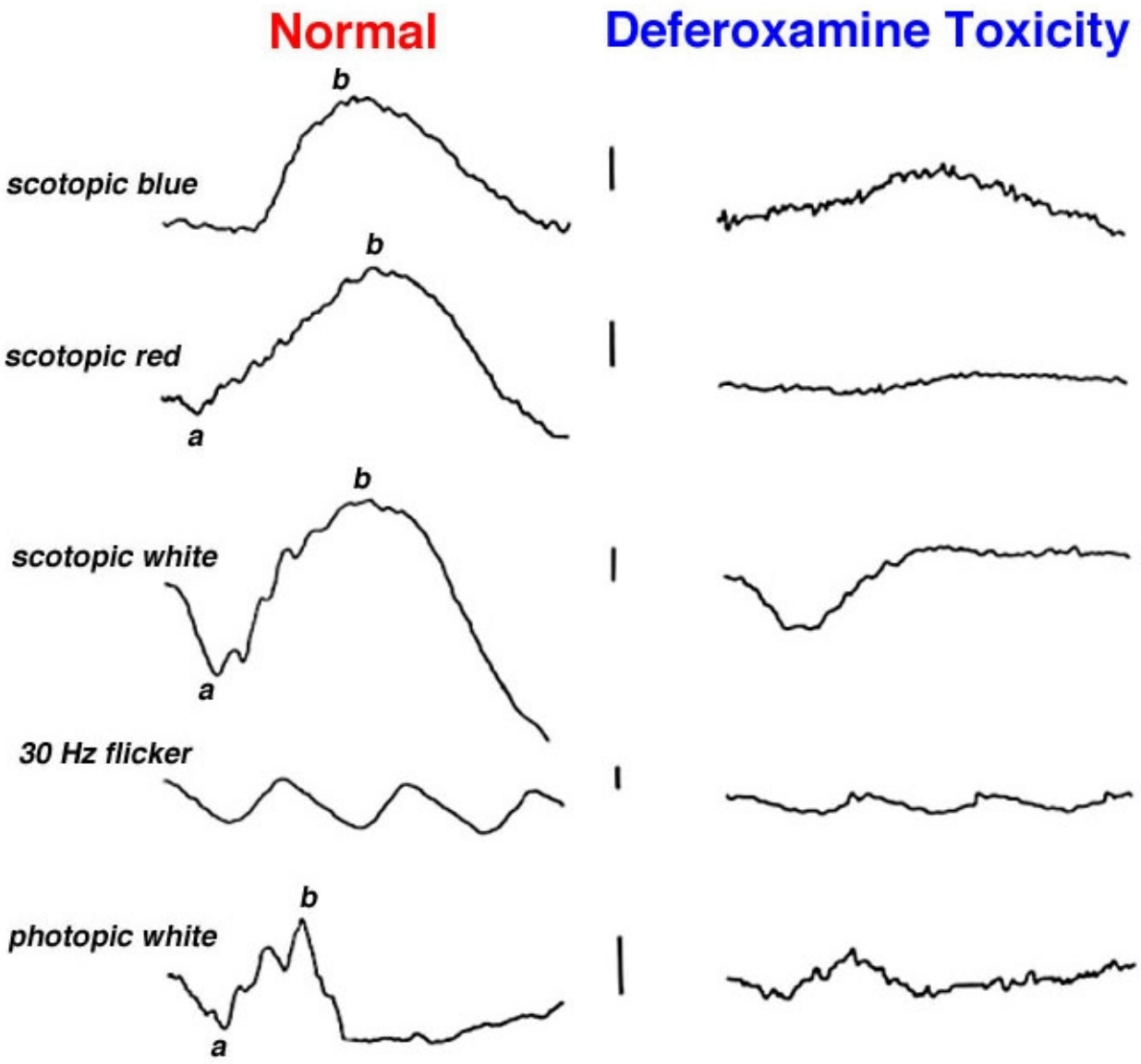

Figure 40. Deferoxamine toxicity effects on the ERG.

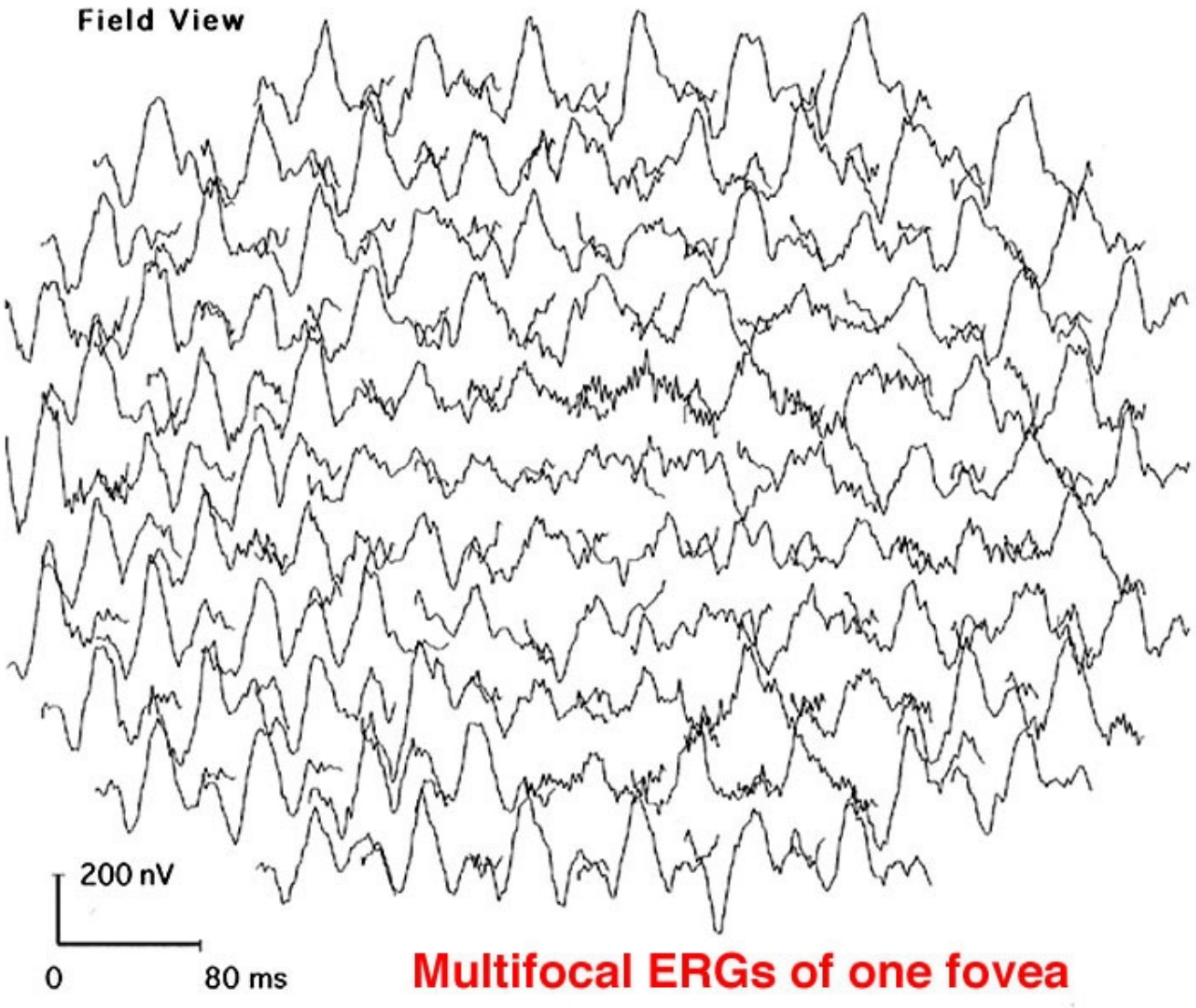

Figure 41b. Multifocal ERG recordings in a patient with age-related macular degeneration (AMD).

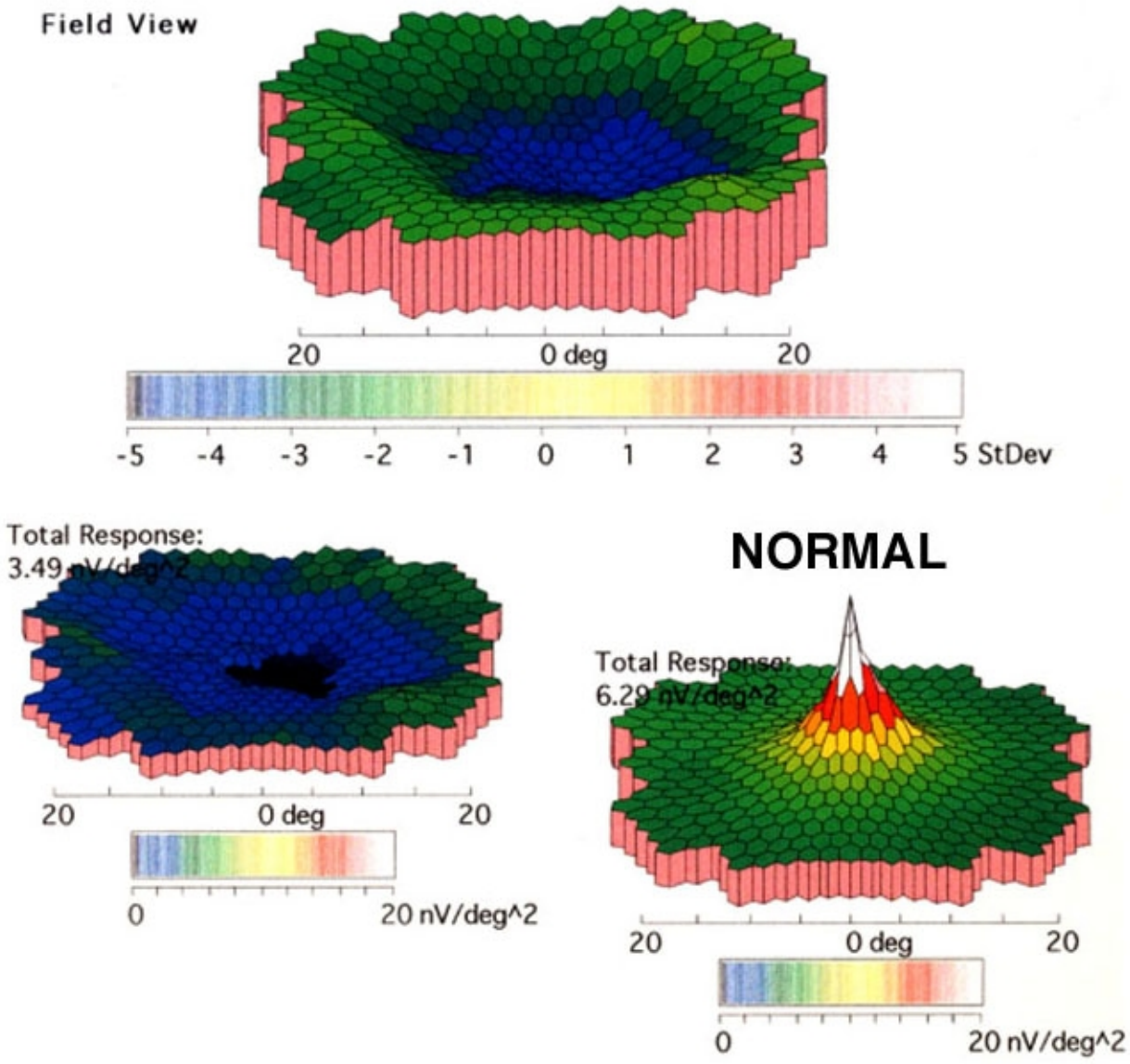

Figure 42. Multifocal ERG recordings transformed into 3-D maps of the macular area in a patient with AMD compared with a normal patient.

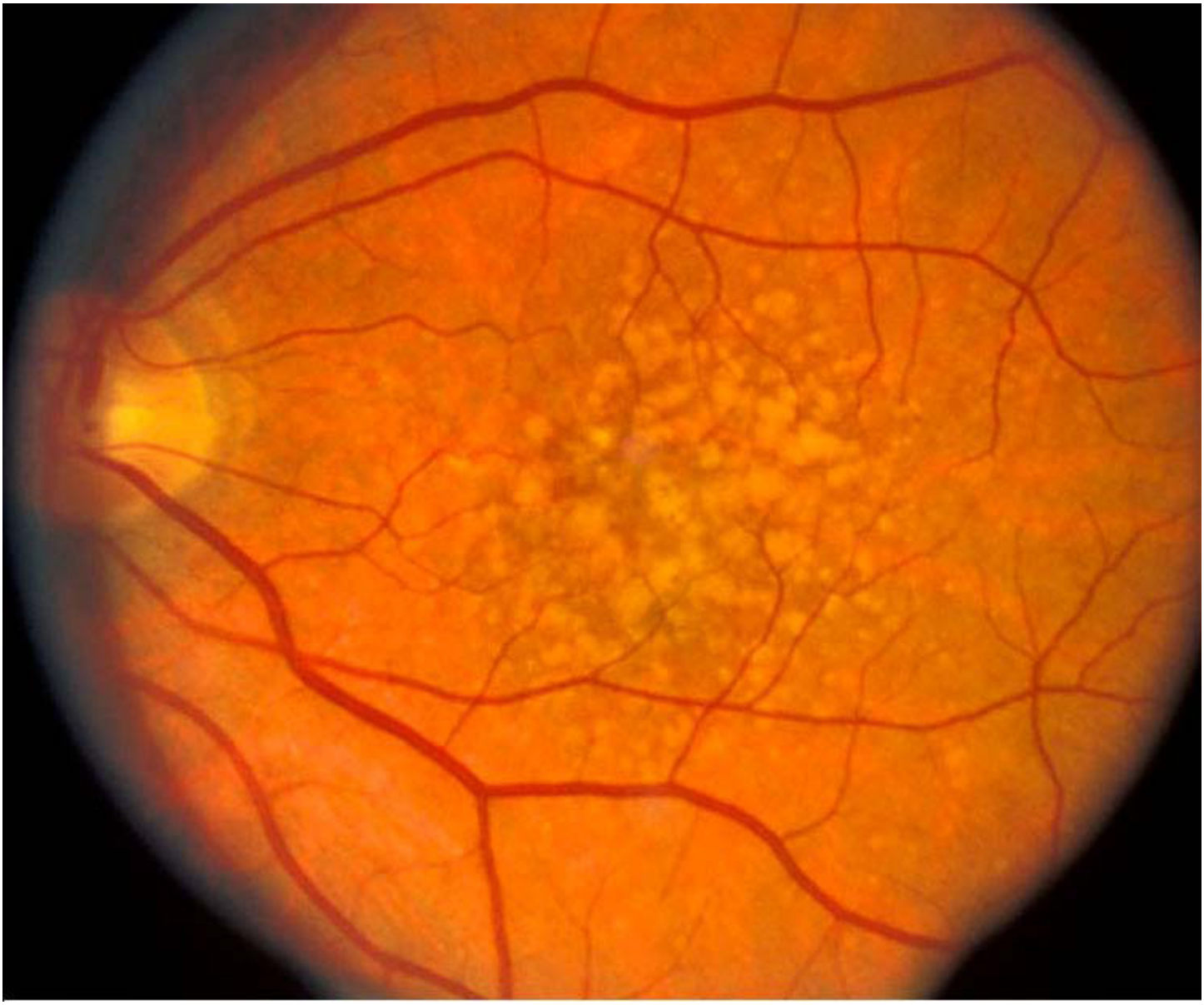

Figure 41a. Fundus photograph of a patient with age-related macular degeneration.

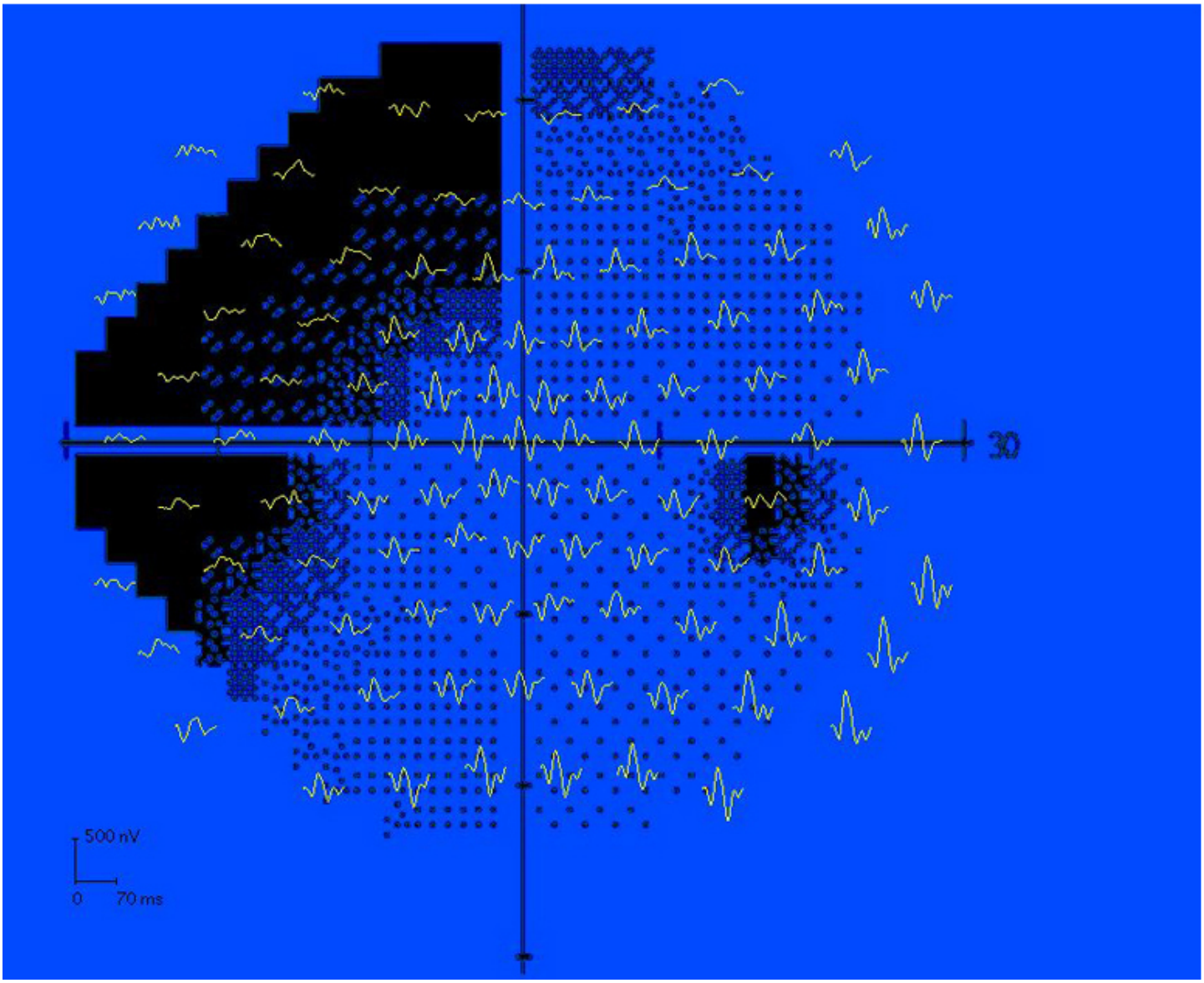

Figure 43. Multifocal ERGs (yellow) superimposed on Humphrey 24-2 visual field plot of the right eye in a patient with acute zonal accult outer retina. mfERG abnormalities match the visual field loss very well.

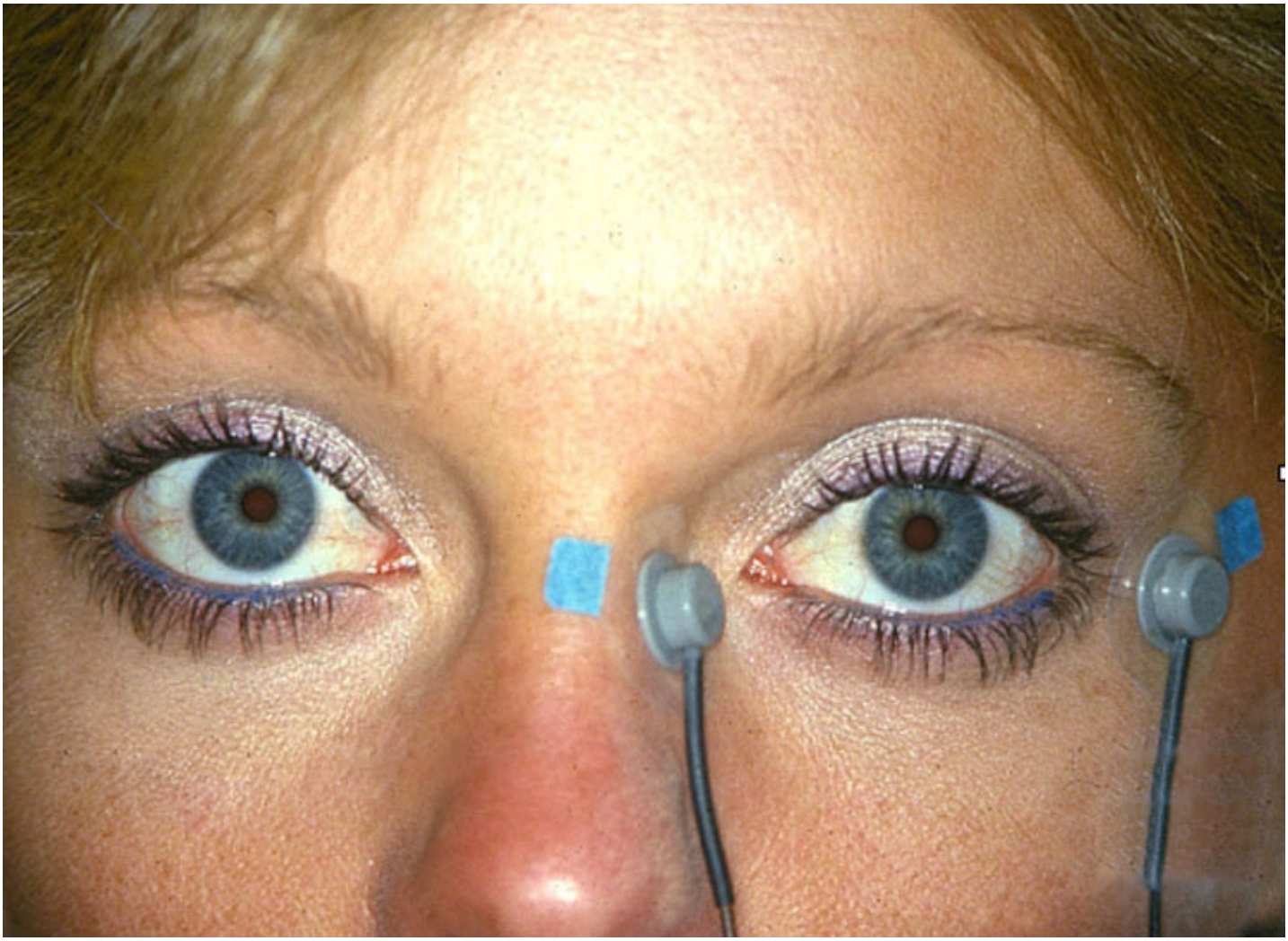

Figure 44. Placement of the electrodes for recording an EOG.

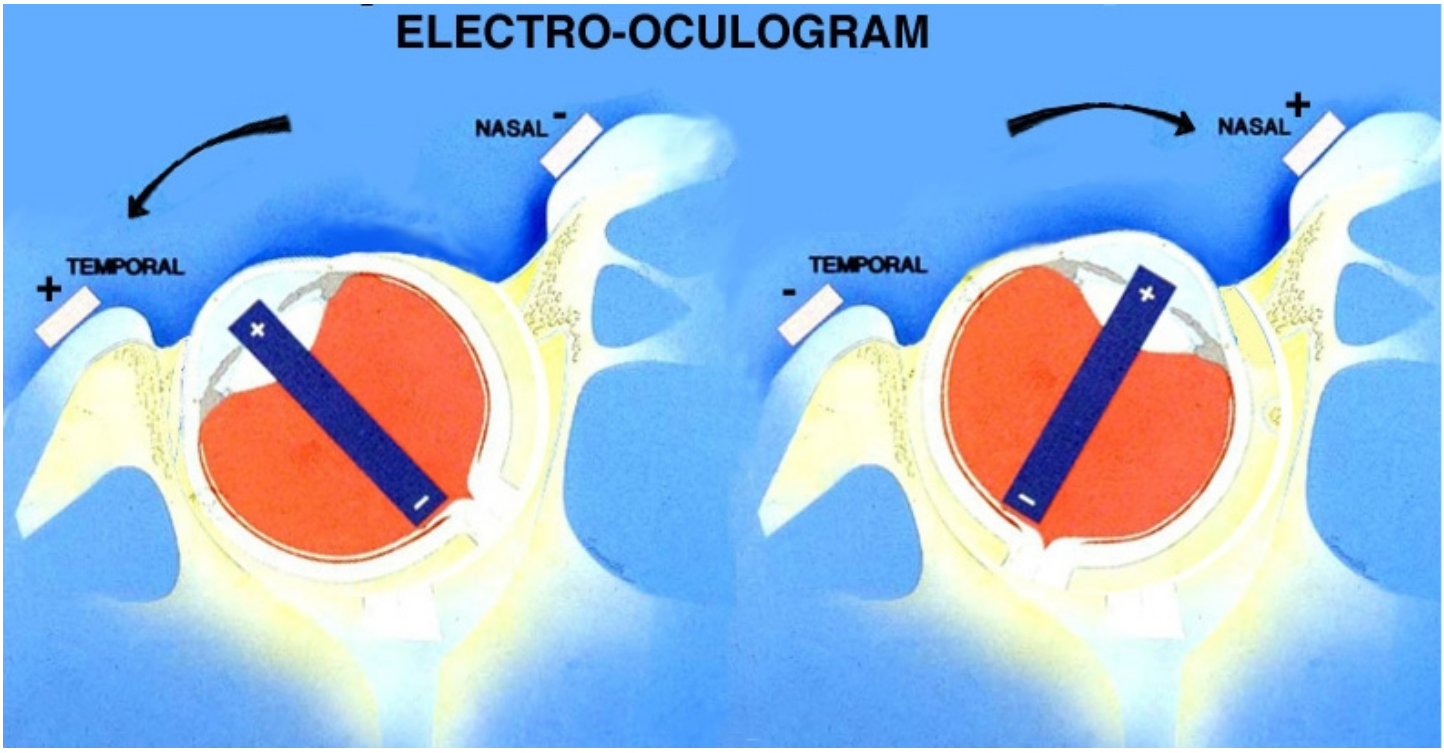

Figure 45. How the EOG potential is measured as the eyes turn toward and away from the skin electrodes.

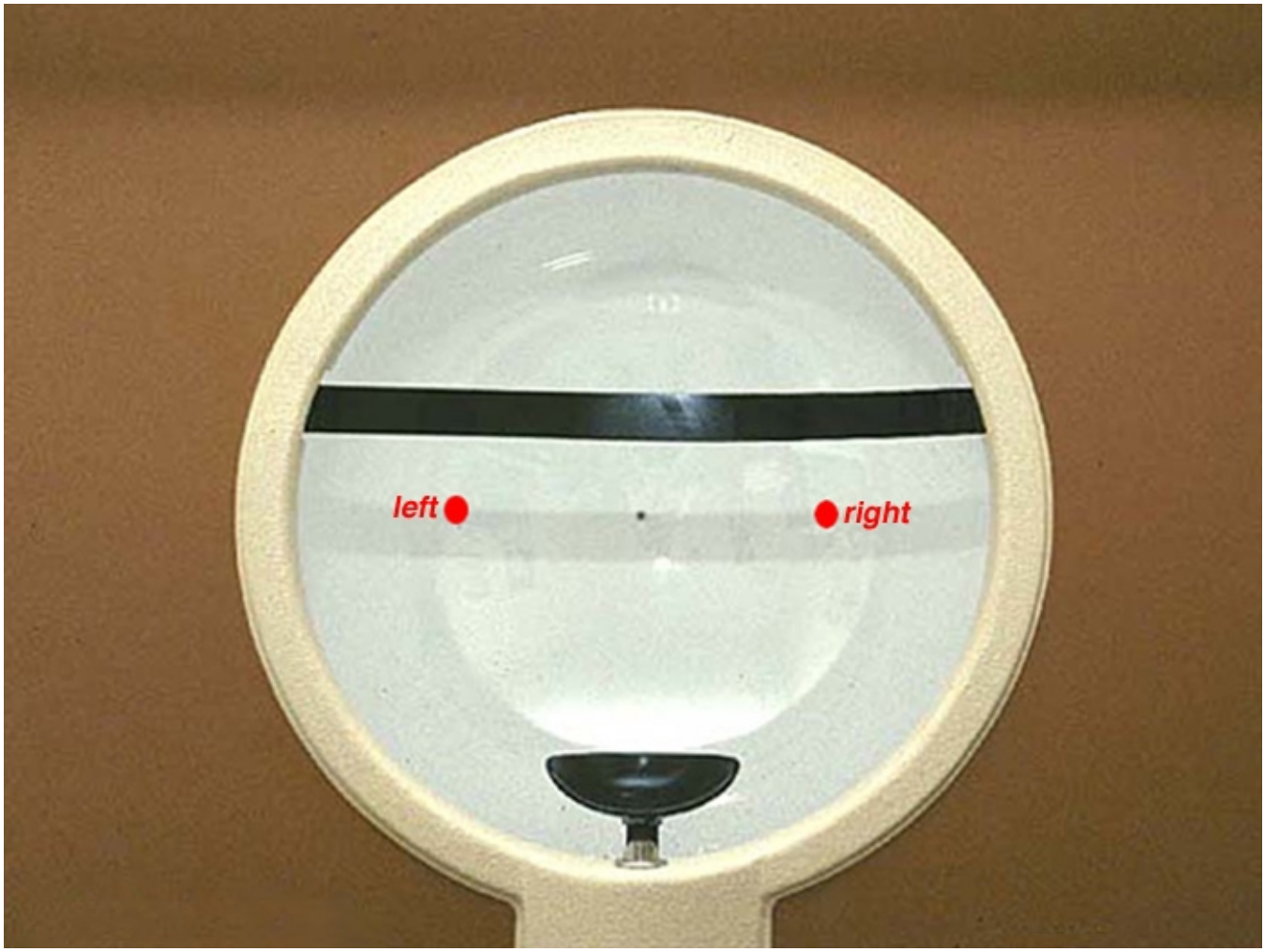

Figure 46. Ganzfeld used for stimulating the EOG waveform.

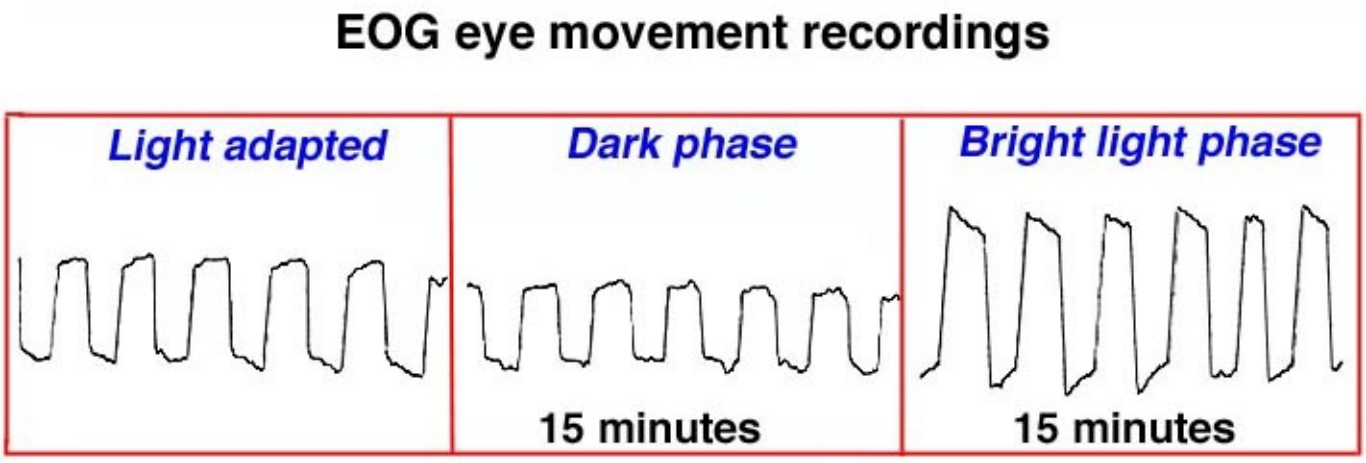

Figure 47. Light-adapted pre-EOG, dark adaptation phase and light-rise phase.

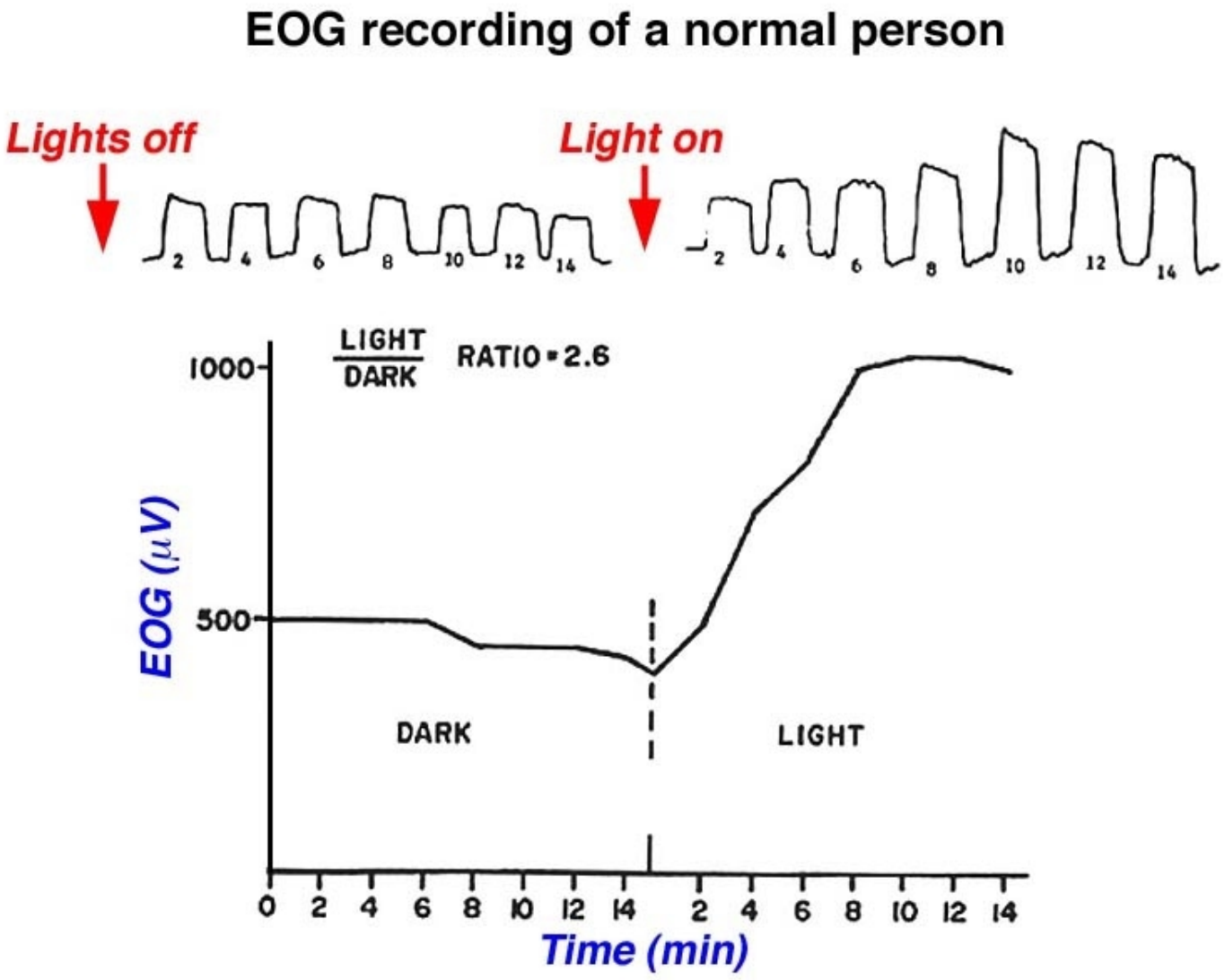

Figure 48. Normal EOG recording.

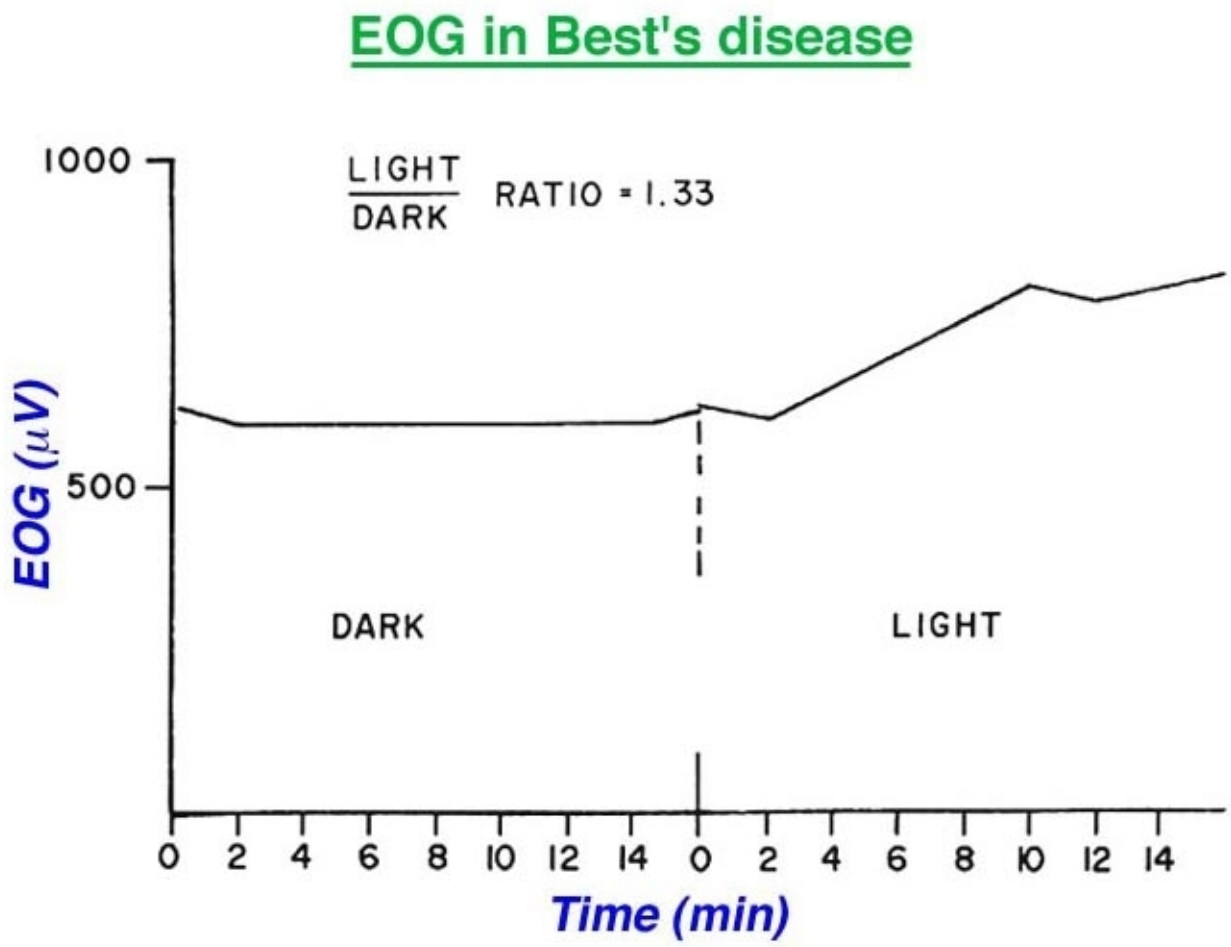

Figure 49. EOG from a patient with Best's disease.

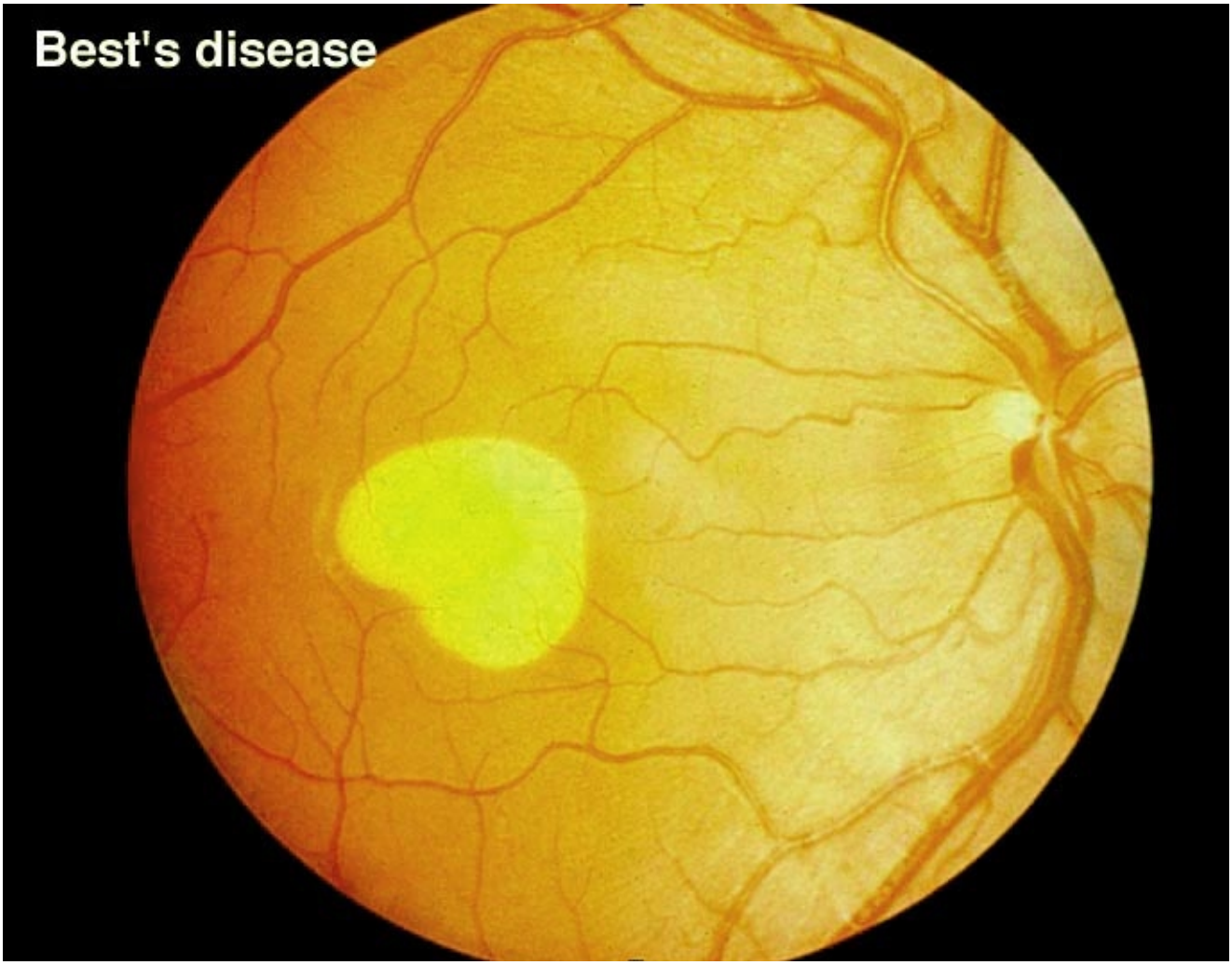

Figure 50. Fundus photo in Best's disease.

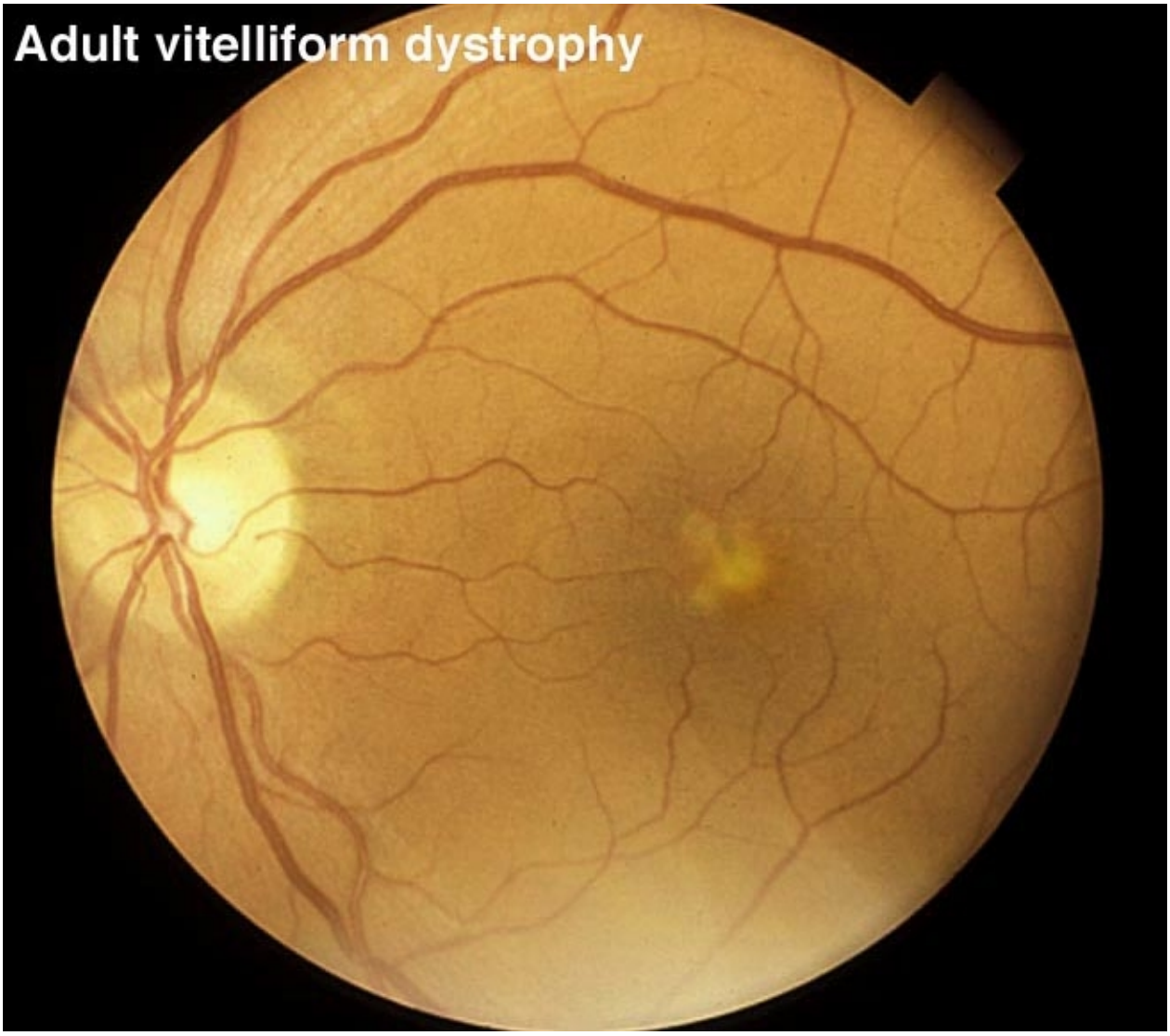

Figure 51. Fundus in adult viteliform dystrophy.

About the Author

Dr. Donnell Creel was born in Kansas City, Missouri. He attended the University of Hawaii and received his B.A and M.A. from the University of Missouri at Kansas City. His Ph.D. was in Neuropsychology from the University of Utah in 1969. Don's doctoral thesis and post-doctoral research centered on abnormal decussation of retinal ganglion cell fibers at the optic chiasm in albino mammals. In the early 1970s, he created a visual evoked potential test that detects this misrouting in human albinos. Later research demonstrated that melanin pigment in the inner ear is necessary for normal auditory function and that lack of pigment in albinos has consequences affecting normal cell development in the brainstem. Don has been in the Department of Ophthalmology, University of Utah Medical Center since 1980, and Director of Clinical Electrophysiology at the Moran Eye Center since its inception in 1993. Clinical research interests center around the application of visual and auditory evoked potentials and electroretinography.

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