ELSEVIER

DIAGNOSTIC AND SURGICAL TECHNIQUES

MARCO ZARBIN AND ELLIOTT FISHER, EDITORS

Electrophysiology in the Investigation of Acquired Retinal Disorders

Hendrik P. N. Scholl, MD, MA, and Eberhart Zrenner, MD

Department of Pathophysiology of Vision and Neuro-Ophthalmology, University Eye Hospital, Tübingen, Germany

Abstract. Electrophysiological research on acquired retinal disorders, both common and rare, is reviewed. Age is a major factor influencing electroretinogram (ERG) and electro-oculogram (EOG) findings. Bipolar or Müller cell death in the aging retina could account for much of the amplitude decline that is observed with age. In diabetic retinopathy, the oscillatory potentials can monitor the progression of the disease and indicate neuronal alterations rather than diabetic angiopathy of the retina. Human ERG studies on glaucoma concentrated on ERG measures that are dominated by inner retinal contributions. It has been shown that the pattern ERG can serve as a predictor of ocular hypertension's progression to glaucoma. In retinal disorders caused by endogenous intoxication, such as hepatic retinopathy, or exogenous intoxication from chronic lead exposure, ERG changes give an objective measure of the damage and allow to study the pathophysiological mechanisms that are involved. Inflammations of the choroid and the retina affect the standard ERG when they are diffuse. In central serous chorioretinopathy, functional disturbances can be revealed not only in the photoreceptors but also in the middle and inner retinal layers with the use of focal stimuli. Choroidal melanoma leads to large reductions of the EOG light peak–to–dark trough ratio through its influence on the transepithelial potential of the retinal pigment epithelium (RPE). In cancer-associated retinopathy, both the rod and cone ERGs are reduced. However, selective cone dysfunction has been described. In melanoma-associated retinopathy, the long flash ERG may reveal a specific pathophysiological mechanism, namely the affection of the ON-pathway with preservation of the OFF-pathway. ERG measurements can reveal vitamin A deficiency and are altered in cases with a mutation in the gene for the retinol binding protein in which other organs are not affected. Photochemical damage to the retina from light emission by the operating microscope can be assessed by electrophysiological methods. (**Surv Ophthalmol 45**:29–47, 2000.

Key words. acquired retinal disorders • aging • cancer-associated retinopathy • central serous chorioretinopathy • choroidal melanoma • chorioretinits • diabetic retinopathy • electrophysiology • electroretinogram • electrooculogram • glaucoma • hepatic retinopathy • lead • photochemical damage • retinol binding protein • vitamin A deficiency

0039-6257/00/$–see front matter
PII S0039-6257(00)00125-9

Since Karpe[62] introduced the electroretinogram (ERG) as a routine assessment technique in ophthalmology, many new stimulation and recording techniques have provided answers to pathophysiological and clinical questions. Basic research gave insight into the physiology and pathophysiology of the sources and components of the electrical signals that can be recorded at the cornea in normal subjects and in patients with retinal disorders, respectively. Many studies of retinal electrophysiology refer to hereditary retinal disorders. In retinitis pigmentosa (RP), ERG changes usually precede ophthalmoscopically visible fundus disease in all genetic patterns, and ERG abnormalities are the main criterion for the diagnosis of many hereditary retinal disorders.

Considering the wealth of information, we will not provide a comprehensive review of electrophysiological findings in acquired retinal disorders. Rather, we will cover only a selection of the investigational work that has been done in recent years. The basis for our selection is 1) research work related to common retinal disorders, such as glaucoma or diabetic retinopathy; 2) lesser known topics, such as hepatic retinopathy and photochemical damage to the retina; and (3) studies that have been very recently published. We further restricted our selection of electrophysiology to electroretinography and electro-oculography. In a short paragraph at the end of each section, the conclusions for clinical application are summarized. Because in most geographic locations, the very recent techniques, such as the multifocal ERG or the cone type specific (S-. M- and L-cone) ERGs, are not available, we restricted the conclusions to the ERG measures that are included in the standard of the International Society of Clinical Electrophysiology of Vision (ISCEV).[83,84]

Several aspects of acquired disorders will not be discussed, such as ocular trauma and opaque media (for a review, see Harding[49]), retinal detachment,[63] foreign metallic bodies in the eye,[69,104,114] and circulatory deficiencies (for a review, see Johnson[58]).

Effect of Age on Electrophysiologic Measurements

STANDARD ERG

Age is associated with a measurable decrement in the amplitude of the b-wave. Peterson[93] noted a linear reduction with age of the b-wave amplitude from about the age of 10 years, with the exception of women in the age group 40–49 years in whom a highly significant increase in the b-potential can be measured. Birch and Anderson recorded full-field ERGs in 269 normal subjects, including 10 normal infants tested within 1 week of birth and 30 healthy preterm infants tested at 4 months adjusted age.[12] Rapid development of the rod response is evident during the first 4 months of life, with a greater than tenfold increase in peak-to-peak amplitude. Between 4 months and adulthood, there is a further tripling of rod amplitude. Cone responses show a similar, but less dramatic, growth in amplitude between birth and age 4 months. Adult cone amplitudes are less than double those at age 4 months. For both rod and cone responses, amplitudes show a gradual decline with age up to 55 years, and a rapid decline thereafter. Best-fit exponential functions show that the age at which amplitude drops to one half that of the young adult level (ages 15 to 24 years) is 69 years for the rod response and 70 years for the cone response (Fig. 1).

Reduced amplitudes may reflect a general reduction in average retinal activity in older subjects. This could be related to the senile changes that have been found to occur both in the outer and inner layers of the retina[40] (for review, see Weale[123]). In an effort to provide further insight into the causes of amplitude reduction with age, Birch and Anderson obtained rod retinal illuminance vs amplitude functions.[12] They found log k, an index of sensitivity, to be only modestly decreased with age consistent with only modest decreases in photopigment optical density.[32,67] Thus, reduced sensitivity can account for only a small reduction in amplitude. A much larger contribution comes from the decline in V_{max}. Maximum amplitude varies with the number of functional b-wave generators.[13,126] Bipolar or Müller cell death in the aging retina[29] could account for much of the decline in amplitude.[12] It cannot be ruled out, however, that subtle preretinal media changes (e.g., yellowing of the lens with age) could also account for a decrease in amplitude as the consequence of their filter effects and the reduction of the amount of light reaching the retinal photoreceptors.

The effects of age on ERG timing are controversial. Weleber reported similar age-related reductions in ERG amplitude, but not in photopic and scotopic implicit times,[125] whereas Iijima found mild to moderate age dependency in both amplitudes and timing.[52] In the study of Birch and Anderson, implicit times were significantly correlated with age for the rod response, the maximal response, the single-flash cone response, and the 30-Hz flicker response.[12] In our clinic, we found age-related reductions in amplitude and prolongations of implicit times for nearly all responses of the ISCEV standard protocol.[53,54] For the rod response, the mean amplitude in the age group beyond 65 years is about 93% of the mean amplitude in the age group between 6 and 19 years, for the maximal response 95% and for the cone response 72%.

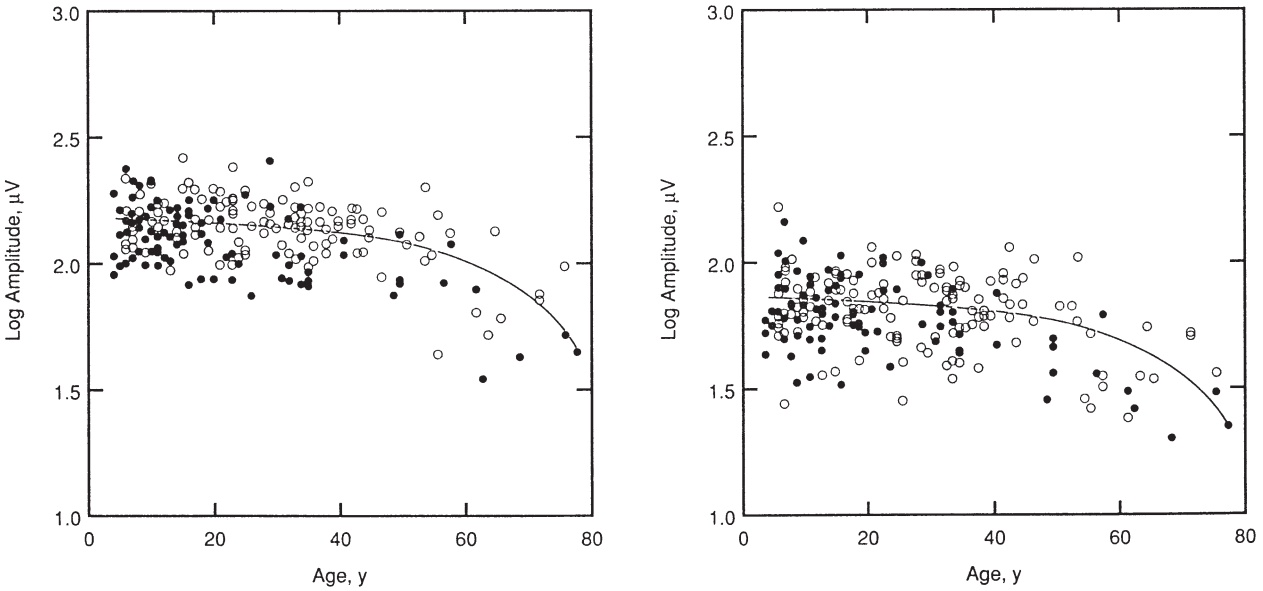

Fig. 1. Left: Variation of log ERG amplitude with age. Rod peak-to-peak amplitudes for subjects aged 5 years and older. Solid curve is best-fit exponential with half amplitude at age 69 years, right. *Right*: Cone peak-to-peak amplitudes to 30-Hz flicker for subjects aged 5 years and older. Solid curve is best-fit exponential with half amplitude at age 70 years. Open circles indicate female; solid circles indicate male. (Reprinted from Birch DG, Anderson JL[12] with permission of *Arch of Ophthalmol.*)

PATTERN ERG (PERG)

ERG measurements to periodic stimuli revealed that age-related changes in the visual system are not uniform across the spatio-temporal spectrum, but are greater at specific spatial and temporal frequencies. For the pattern ERG (PERG) Porciatti and coworkers tested the effect of spatial and temporal frequency.[96] They found systematically lower amplitudes for older subjects than for younger ones, but there was no systematic tendency for selective reduction in amplitude in the high, middle, or low spatial frequency regions. There was only a slight age effect on temporal frequency, that is, the amplitudes of the older subjects were relatively more depressed at the higher temporal frequencies. Their phase data suggest that there is little, if any, age-related latency difference in the PERG.

When considering amplitude and phase data in different age groups, one has to consider the different retinal illuminance, for example, the possible role of senile miosis. The effect of retinal illuminance on neural latency has long been known as the cause of the well known "Pulfrich effect."[98] The magnitude of the latency measured by psychophysical means is about 20 msec/log-unit,[100] similar to what Porciatti and coworkers observed.[96] Trick examined age-related alterations in retinal function, measuring PERGs and VEPs.[118] She found that the observed PERG alterations cannot be completely explained by the reduction in retinal illumination associated with senile miosis, but reflects age-related neurophysiologic changes. The most significant age-related differences in PERG amplitude were obtained when large checks were used. This suggests that slight differences in visual acuity or retinal image quality between younger and older subjects can not account for the reductions in PERG amplitude.

ELECTRO-OCULOGRAM (EOG)

The age effects on EOG parameters are controversial. Some authors report significant correlations of EOG parameters with age,[1,3,76] whereas others deny such changes.[28,129] In most studies, the slow oscillations and light peak–to–dark trough ratios(L/D, Arden index) are usually reported. Little is known about the fast oscillations. In a study in our clinic, age was not correlated with the L/D ratio, but the quotient of the fast oscillation was significantly correlated with age ($r = 0.32$, $P < 0.005$).[33] However, Weleber, who routinely measured the fast oscillations, did not find any significant correlations with age for all EOG parameters.[125]

CONCLUSIONS FOR CLINICAL APPLICATION

It is generally recommended that each laboratory establish a range of normal values for each electrophysiologic response. Because of the effect of age, it is crucial that the population of normal subjects comprises subjects of different ages.

Diabetic Retinopathy

Diabetic retinopathy affects the retinal blood vessels that develop in the complex metabolic milieu of systemic diabetes mellitus. The primary pathophysiologic process affects the permeability of the blood vessels because of a metabolic derangement. Retinal arterioles and capillaries close, and this leads to retinal ischemia and cell death (nonproliferative diabetic retinopathy [NPDR]). In proliferative diabetic retinopathy (PDR), there are secondary changes, including retinal edema and fibrovascular proliferation leading to ERG abnormalities.[15] However, it is also possible that abnormalities in retinal metabolism secondary to diabetes could cause retinal dysfunction without a microvascular basis for the ERG changes[60] (for a recent review, see Tzekov and Arden[120]).

STANDARD ERG A- AND B-WAVES

Studies on the parameters of the standard ERG in diabetic retinopathy remain equivocal. Juen and Kieselbach could reveal significant different ERG values for several ERG parameters in diabetics with and without retinopathy.[60] Holopigian and coworkers also found several ERG parameters to be abnormal in early diabetic retinopathy.[51] However, Jenkins and Cartwright reported normal or even supernormal amplitudes in the flash ERG of patients with early diabetic retinopathy.[57]

Nevertheless, the standard ERG can be of clinical value in diabetic retinopathy, as was shown by Bresnick and coworkers. They developed an electroretinographic protocol for diabetic retinopathy, which contains scotopic b-wave amplitude (and timing), oscillatory potential (OP) amplitude (and timing), and 30-Hz flicker timing.[15] They were able to show that in diabetic retinopathy, the reduction of amplitudes and the delay of peak implicit times in the ERG are related to the severity of retinopathy.[18,20]

PATTERN ERG

Arden and coworkers[4] recorded PERGs and OPs from the eyes of diabetic patients with various degrees of milder retinopathy. They found reduced amplitudes only in the presence of cotton-wool spots and angiographic evidence of capillary nonperfusion. Their scatter of results in the OPs was larger, so they suggested that PERG provides more reliable data than OPs. On the other hand, Wanger and Persson could not find any flash ERG or PERG changes that would distinguish between the presence or absence of retinopathy in diabetic patients.[122] Also in the study of Jenkins and Cartwright,[57] the PERG amplitudes of patients with early diabetic retinopathy were within normal limits.

OSCILLATORY POTENTIALS

Reductions in the amplitudes of OPs have been reported in diabetic retinopathy,[17,18,60] although Wanger and Persson[122] could not find any such changes. In studies by Bresnick and coworkers,[16,17,19] the amplitude of the OPs predicted the progression of eyes with NPDR or mild PDR to severe PDR. Abnormal OP amplitudes indicate a high risk of developing proliferative diabetic retinopathy and are correlated with the rate of progression of diabetic retinopathy.[16,17,19] However, the clinician has to consider that OPs have a high intra- and interindividual variability.[4,71]

There is evidence that individual OPs have different neural generators. For example, individual OPs have different retinal depth profiles, with the earlier OPs arising more proximally within the retina than the later ones.[121] Holopigian and coworkers[51] examined the amplitudes of the individual OP wavelets. Their results did not show selective changes in OP amplitude, but did show a uniform reduction for all OPs. From these results and from their results concerning the standard ERG changes, which have been mentioned above, they suggest that additional retinal sites must be affected in early diabetic retinopathy.

Shirao and Kawasaki[108] point out that in early diabetic retinopathy a prolongation of the peak latency of the OPs can be diagnosed much earlier than a reduction of the OP amplitude. The natural course of diabetes is an incipient prolongation of the peak latency, which is followed by the reduction of amplitude and prolongation of the interpeak intervals (Fig. 2). Both the prolongation of the peak latency and the reduction of amplitude of the OPs can quantitatively represent the diabetes-induced retinal dysfunction.

They investigated the OP abnormalities in Streptozotocin-induced diabetic rats and found that the peak latency of the second OP (OP2) began to be protracted as early as 2 weeks after diabetogenesis. From the rapidity of the OP changes in experimental diabetes in the absence of retinal vascular dysfunction, they concluded that the prolongation of the OP peak latency at the preretinopathy stage may not be attributable to diabetic angiopathy, but rather to certain neuronal alterations.

S-CONE ERG

Greenstein and coworkers[45] reported that diabetes decreases the sensitivity of the S-cone pathway more selectively than RP or open-angle glaucoma, suggesting that the S-cone pathway is more vulnerable to hypoxia than L- or M-cone pathways. Yamamoto and coworkers[127] used the method of Gouras and MacKay[43] in diabetic patients with and without retin-

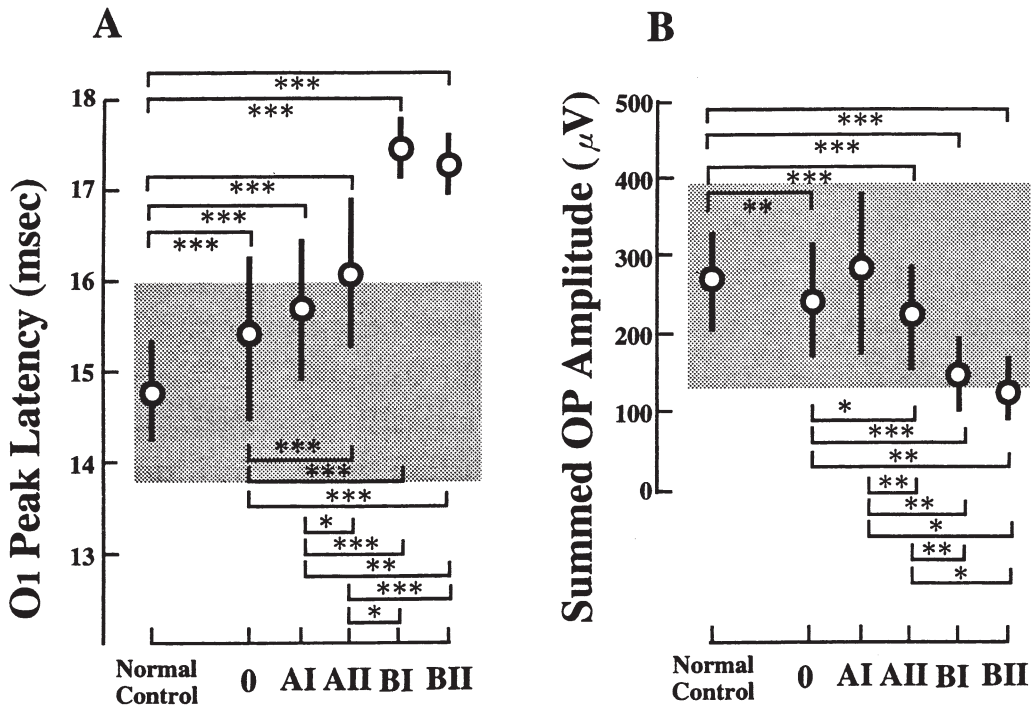

Fig. 2. Mean (M) and standard deviation (SD) of (A) the peak latency of the first OP peak and (B) the summed amplitude of the OPs (O_1-O_4) in normal subjects, diabetic eyes at pre-retinopathy stage and at overt retinopathy stage. Stage 0: no funduscopic or angiographic abnormality; Stage A I: funduscopic microaneurysms only; Stage A II: Stage A I plus at least one of dot hemorrhages or hard exudates; Stage B I: at least one of large soft exudates, small but multiple exudates or superficial flame-shaped retinal hemorrhages, plus angiographically confirmed non-perfusion area(s) or dye leakage; Stage B II: Stage B I plus diffuse retinal edema or marked venous dilatation. beThe shaded areas indicate the normal range (M ± 2 SD in the control subjects). Open circles and vertical bars indicate M and 1 SD, respectively. *P < 0.05; **P < 0.01; ***P < 0.001. (Reprinted from Shirao Y, Kawasaki K[108] with permission of *Prog Retin Eye Res.*)

opathy. They found that both retinopathic and non-retinopathic diabetes reduce the amplitudes of the b-waves of the S-cone ERG and decrease its sensitivity significantly. On the other hand, the L- and M-cone amplitudes were not decreased in either stage of diabetes.

ERG RECORDINGS OF THE FOVEAL CONES

Weiner and coworkers[124] examined patients with NPDR, with and without clinically significant macular edema (CSME). They could show that slowing and decreased amplitudes of the foveal cone responses are significantly associated with the presence of CSME in eyes with NPDR. Early changes in the foveal ERG may, therefore, indicate developing CSME and could be a potential tool for early detection of significant diabetic maculopathy, before loss of central vision has occurred.

MULTIFOCAL ERG

An important feature of beginning diabetic retinopathy is its focal nature. Standard ERG recording techniques measure an overall response of the retina. Therefore, small areas of retinal dysfunction may go undetected in the recording of the overall retinal response, because when large stimuli are used, small abnormalities will not affect responses evoked from a retina that is predominantly normal. For simultaneous ERG testing of multiple small retinal areas, Sutter and Tran[113] developed the Visual Evoked Response Imaging System (VERIS), which allows a fast, objective evaluation of retinal function, using a multifocal technique. Palmowski and coworkers[90] explored the efficacy of the multifocal ERG in detecting and localizing dysfunctional retinal areas in diabetes. They found reduced overall amplitudes and delayed latencies in the first-order response component in patients with NPDR, but not in diabetics without retinopathy. Because the first-order response components arise predominantly in the outer retina, there is obviously some impairment of outer retinal function in diabetes. The second-order response component apparently has substantial contributions from the inner retina. Since diabetic retinopathy is presumably a disease that affects the inner retina more, the second-order response component should be more suitable for detecting early disturbances. Amplitudes of the second-order

response component were indeed significantly reduced in diabetic patients with or without retinopathy. Looking at the waveforms, Palmowski and coworkers observed a difference between the normal subjects and the diabetic patients. This feature occurs at about 40 msec and was markedly reduced in amplitude even in the patients with no clinically apparent retinopathy (Fig. 3). They increased the base interval from 13 msec to 26 msec and found that the feature is reduced or absent both in patients with retinopathy and without. They concluded that the feature disappears because of a change in the dynamics of adaptive mechanisms.

EOG RESPONSES TO NONPHOTIC STIMULI FROM RPE

It has been electrophysiologically shown that the RPE is more susceptible to mild hypoxia than are the retinal neurons.[78] Diabetic retinal pigment epitheliopathy presumably occurs because of hypoxic conditions caused by diabetes. But the time courses and the L/D ratios of the conventional EOG do not essentially differ among the stages of retinopathy. The L/D ratio reflects not only the function of the RPE, but depends also on photoreceptor integrity and physical arrangement between the photoreceptors and the RPE.

For selectively testing the function of the RPE, Yonemura and Kawasaki[128] developed three kinds of non-photic EOG responses as novel function tests for the RPE: 1) responses to an increase in sodium bicarbonite concentration; 2) responses to an elevated osmolarity due to an addition of fructose; and 3) responses to the addition of Diamox. Shirao and Kawasaki[108] measured the time course of the EOG in normal control subjects and diabetics at various stages of retinopathy after injection of bicarbonate. The mean amplitude of the bicarbonate response

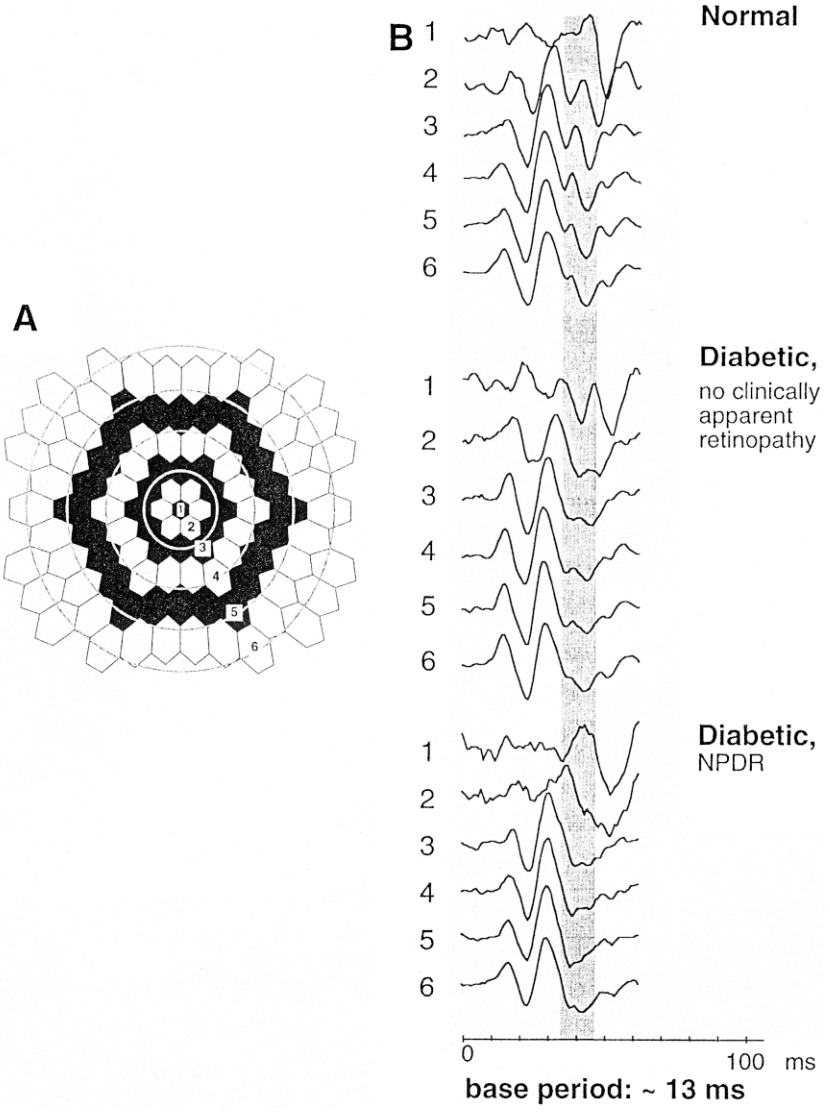

Fig. 3. First slice of the second-order response component with a stimulus base interval of ∼ 13.33 msec. *A:* Areas of approximately equal eccentricities whose responses, having similar waveforms, were averaged to achieve a better signal-to-noise ratio. *B:* Response average, derived from rings shown in A in a control subject, in a diabetic patient without retinopathy, and in a diabetic patient with retinopathy. A feature found in control subjects at a latency of ∼ 40 msec is marked in gray. It was greatly reduced or absent throughout the retina in nonproliferative diabetic retinopathy. (Reprinted from Palmowski AM et al[90] with permission of *Invest Ophthalmol Vis Sci.*)

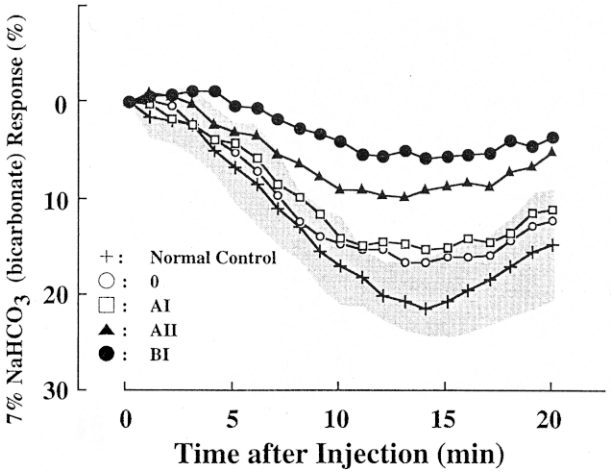

Fig. 4. Averaged time courses of the bicarbonate response in control subjects (+) and in diabetics (○, Stage 0; □, Stage A I; ▲, Stage A II; ●, Stage B I). Shaded area indicates the normal range. (Reprinted from Shirao Y, Kawasaki K[108] with permission of *Prog Retin Eye Res.*)

was significantly reduced in diabetics as early as the preretinopathy stage, and it progressively deteriorated as the retinopathy stage advanced (Fig. 4).

Pathologic function of the RPE apparently takes place very early in diabetes and can be detected only with non-photic stimuli as the bicarbonate response.

CONCLUSIONS FOR CLINICAL APPLICATION

To monitor the effects of diabetic retinopathy on retinal function, standard scotopic and photopic ERG measures can be used, as they are related to the severity of retinopathy. The most sensitive indicators, however, are the OPs. Abnormal OPs indicate a high risk of developing proliferative diabetic retinopathy. For the OPs, both amplitude and timing should be taken into account.

Primary Open-Angle Glaucoma (POAG)

Glaucoma primarily affects retinal ganglion cells. Whether or not there is also loss from other inner retinal cells such as amacrine cells is still under debate. Since inner retinal layers are morphologically destroyed by the disease, studies on the human ERG in glaucoma have concentrated on the cells located more proximally in the retina, which also contribute to the measurable potentials at the cornea. The PERG generally is viewed as the major signal reflecting ganglion cell activity, because it depends on the integrity of those cells[80] (for a review, see Berninger and Arden[9] and Zrenner[130]). It allows distinction between retinal/macular dysfunctions (P50 component) and optic nerve head disease (N95 component).[50] Inner retinal contributions to the flash ERG have been thought mainly to originate from amacrine cells, such as the OPs.[64,89] Another inner retinal contribution to the dark-adapted flash ERG, a negative-going potential called the scotopic threshold response (STR), also has been ascribed to amacrine cells.[86,111]

SCOTOPIC FLASH-ERG

Korth and coworkers examined dark-adapted flash-evoked ERG components in glaucoma patients.[70] They elicited small scotopic PII responses, using near-threshold intensities that were far below the standard flash intensity used for conventional ERG testing. Secondly, they elicited the STR. The

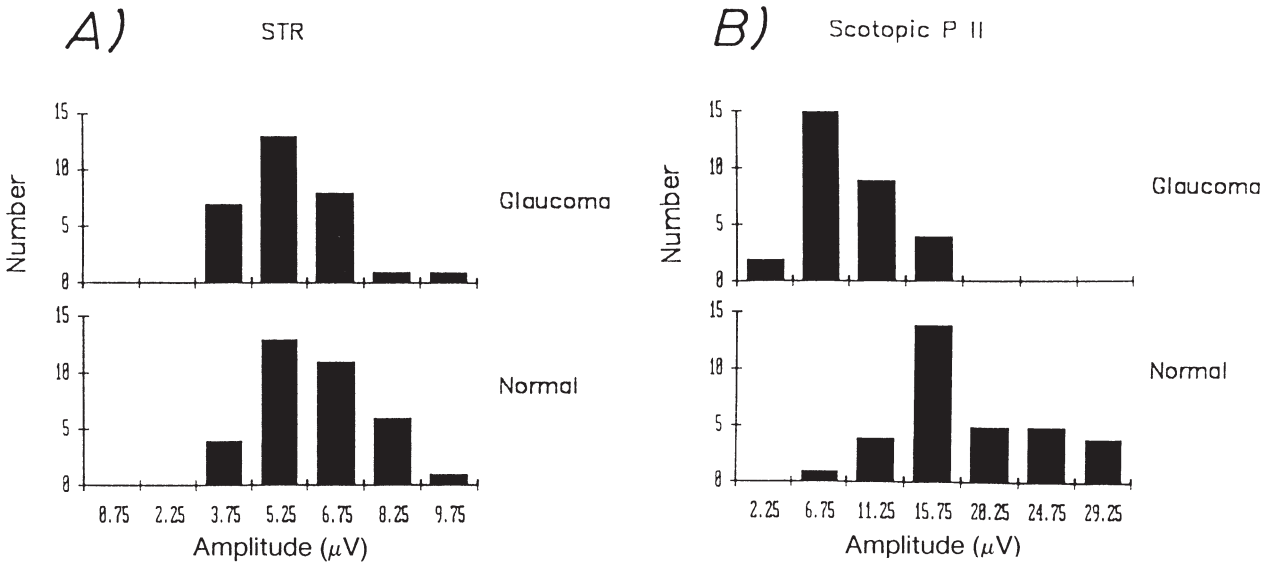

Fig. 5. Amplitude histograms of the STR (*A*) and scotopic PII (*B*) for the glaucoma patients and the normal controls. (Reprinted from Korth M et al[70] with permission of *Invest Ophthalmol Vis Sci.*)

scotopic PII amplitudes were significantly reduced in the glaucoma patients compared with the control group. The STR maximum amplitude is apparently not strongly affected by glaucoma (Fig. 5).

The peak time of both the PII and the STR were not significantly delayed. The preserved STR suggests that structures responsible for its generation are less damaged in glaucoma than the structures responsible for scotopic PII. Frishman and coworkers found that a sensitive, negative-going ERG component was abolished or greatly reduced in macaque monkey eyes with experimental glaucoma.[38] There was no consistent reduction of other wave forms of the scotopic ERG. So both studies found glaucoma-induced changes in scotopic ERG components, but they found different components to be affected. The conclusion to be drawn is that inner retinal neurons contribute to the scotopic ERG, but the relative balance of these components may vary appreciably across species.

PATTERN ERG

Bach and coworkers could show that the PERG can reveal ganglion cell damage that is not detected by conventional perimetry;[8] the PERG amplitude reductions in glaucoma were very much dependent on check size.[7] They could also show that the PERG amplitude parallels the morphometric measure of computerized disk analysis.[6]

A case example[132] demonstrates that the PERG is a much better indicator of the damage caused by POAG than the flash-ERG parameters of the ISCEV-standard. Patient SG (64-year-old female) had POAG in both eyes for 4 years. Several days before the electrophysiologic recordings, her intraocular pressures were 38 mm Hg in the right eye and 28 mm Hg in the left. Argon laser trabeculoplasty and beta-blocker therapy reduced the pressure to about 23 mm Hg in both eyes. Visual acuity was 6/18 in the right eye and 6/12 in the left. As shown in Fig. 6A, the PERG was reduced in both eyes. In contrast, cone responses (Fig. 6B) and rod responses (Fig. 6C) elicited by Ganzfeld stimuli were not affected.

Pfeiffer and coworkers performed a longitudinal prospective study in patients with high-risk ocular hypertension.[94] Initially, 17 eyes had a normal PERG and 17 eyes had a pathologic PERG. Within the observation period (maximally, 31 months), 5 of 29 eyes developed visual field loss, that is, conversion from ocular hypertension to glaucoma. All five eyes had a pathologic PERG during the first visit. Of the eyes that had a normal PERG on the first visit, none developed visual field defects. From their data they calculated a sensitivity of 100% for the prediction of the conversion of a patient from ocular hypertension to glaucoma with a specificity of 71%.

CONCLUSIONS FOR CLINICAL APPLICATION

Since the PERG at least partly reflects ganglion cell activity, it is the electrophysiologic measure of choice for functional testing of glaucoma. The PERG, which is a prognostic tool, should be helpful for the decision to treat or not to treat patients with ocular hypertension.

Toxic Conditions

There are a substantial number of toxic agents that affect the retina (for a review, see Grant and Schuman[44] and Zrenner[131]). Some prominent toxic agents whose effect can be shown by electrophysiologic means are chloroquine or hydroxychloroquine,[34] phenothiazines,[82] and vigabatrin.[5,25,72] In this section, two examples are chosen: 1) hepatic retinopathy (as an example of an endogenous toxicity) and lead intoxication (as an example for an exogenous toxicity).

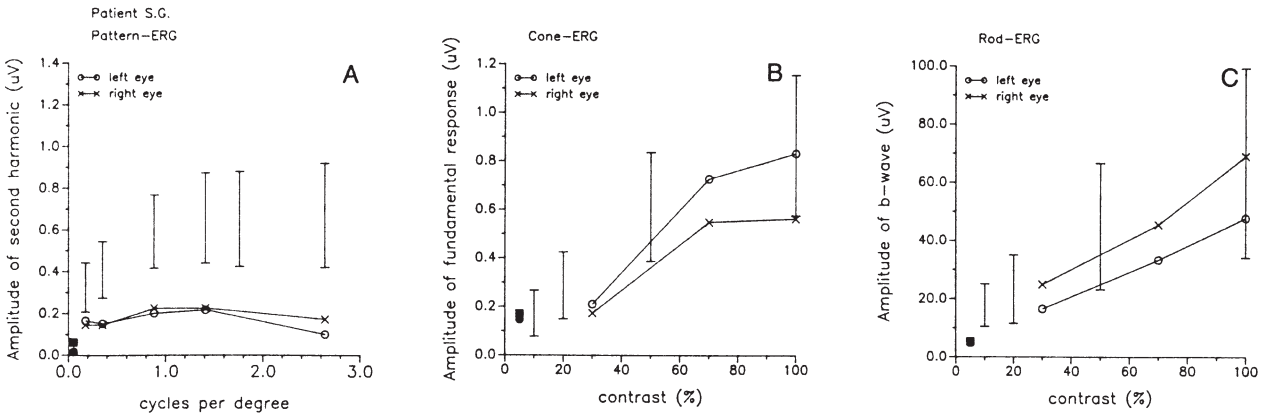

Fig. 6. PERG (*A*), cone-ERG (*B*), and rod-ERG (*C*) of a 64-year-old female patient (SG) who had primary open-angle glaucoma since the age of 4 in both eyes. (Reprinted from Zrenner E et al[132] with permission of *Doc Ophthalmol.*)

HEPATIC RETINOPATHY

Hepatic encephalopathy is a syndrome that is associated with hepatic failure. As a consequence of portal systemic shunts or impaired hepatocellular extraction, potentially neuroactive nitrogenous metabolites accumulate in the peripheral blood plasma. Of the many substances that have been implicated in the pathogenesis of hepatic encephalopathy, ammonia is thought to be a key factor.[22,22] Because ammonia is directly toxic to cultured astrocytes,[87,88] it will affect Müller cells within the retina. Impaired Müller cell function will influence the generation of ERG potentials.

Eckstein and coworkers[31] evaluated the retinal function of 11 patients who suffered from various stages of hepatic encephalopathy. Patients were vitamin A–substituted and classified into two groups depending on their stage of hepatic encephalopathy according to the criteria of Pappas and Jones[91]: group I included patients with stages 0–1 disease, and group II included stages 2–3. Group I patients showed normal scotopic b-waves, whereas group II patients showed significantly decreased amplitudes and increased implicit times. A-wave amplitudes were almost within normal limits for the group I patients and a-wave latencies were only slightly elevated. Group II patients showed significantly reduced a-wave amplitudes and increased latencies. Similar results were obtained under photopic conditions. B-wave amplitudes were only slightly reduced in group I, but significantly reduced in group II. Implicit times were significantly increased only in group II patients. The most sensitive indicator of retinal dysfunction caused by hepatic failure was the OP2. Amplitudes were reduced to about 95% of the controls in group I patients, but significantly reduced in group II patients. Implicit times were significantly increased in both groups.

CHRONIC EXPOSURE TO LEAD

Anorganic lead is a major environmental pollutant with a world production of 3.5 million tons and an annual release via gasoline of 300,000 tons per year. If lead is taken up in the early developmental stages of life, its effects on brain functions are longlasting and persist even after cessation of exposure.[47] Acute or subacute lead toxicity depends on the blood levels. With high blood levels (> 90 μg/100 ml blood), encephalopathy, papilledema, and abdominal symptoms are present. Medium blood levels (30–60 μg/100 ml blood) lead to a reduction of the rod-ERG amplitude and a disturbance of hemoglobine synthesis. "Subtoxic" blood levels (< 30 μg/100 ml blood) during childhood can result in developmental retardation and reduction of the intelligence quotient.

Ophthalmologic symptoms occur in only about 1–2% of all exposed persons. They comprise forms of optic neuritis possibly with papilledema, variable reduction of visual acuity that does not correlate with papilledema, central scotoma (rarely ring scotoma) of the visual field, palsy of the ocular muscles, disturbance of dark and light adaptation,[37] and color vision defects.

In the following case example, subject AM had been working in a printing office and was exposed to lead through inhalation. Symptoms occurred 10 years after exposure, with an increasing loss of visual acuity in both eyes. Lead blood level was 20 μg/100 ml blood at the time of presentation. Visual acuity was 2/20 in the right eye and 4/20 in the left. Visual field testing revealed a central scotoma in both eyes. Nagel anomaloscope testing revealed deuteranopia. Other clinical examinations, such as funduscopy, imaging by computed tomography (CT), and visual evoked potentials (VEP), did not reveal any pathologic signs. In the ERG, there was a reduction of amplitude and an increase of implicit times of the b-wave. Both features are more prominent for the rod and S-cone ERG (Fig. 7A) than for the L-cone ERG (Fig. 7B), which was more or less normal.

CONCLUSIONS FOR CLINICAL APPLICATION

The ERG is a sensitive and objective tool for detecting toxic effects on the retina. In the case reported above, the diagnosis of lead-related toxicity of the retina was made based mainly on the electrophysiologic deficits. In lead toxicity, it is very important to draw this conclusion because there is a therapeutic consequence. Lead toxicity can be treated with dimercaprol, calcium EDTA, or penicillamine.

Inflammatory Conditions

Various inflammatory conditions of the choroid and the retina affect the ERG to an extent that tends to correlate with apparent fundus abnormalities. Thus, patients with minimal to moderate fundus involvement from such conditions as syphilis or other types of chorioretinitis of unknown etiology in initial stages usually have either normal or only moderately subnormal ERG amplitudes. Both the a- and the b-wave are affected and the implicit times are normal.[10] In diffuse, generally chronic inflammatory states of the retina, the EOG L/D ratio is subnormal, its degree of abnormality generally correlating with the extent of clinically apparent disease and its noted effect on the ERG.[35] Patients with local forms of inflammatory disease of the fundus, including toxoplasmosis and histoplasmosis, generally show normal Ganzfeld ERG responses. Local inflammatory disease also does not affect the EOG.

Inflammatory disorders of the choroid and the

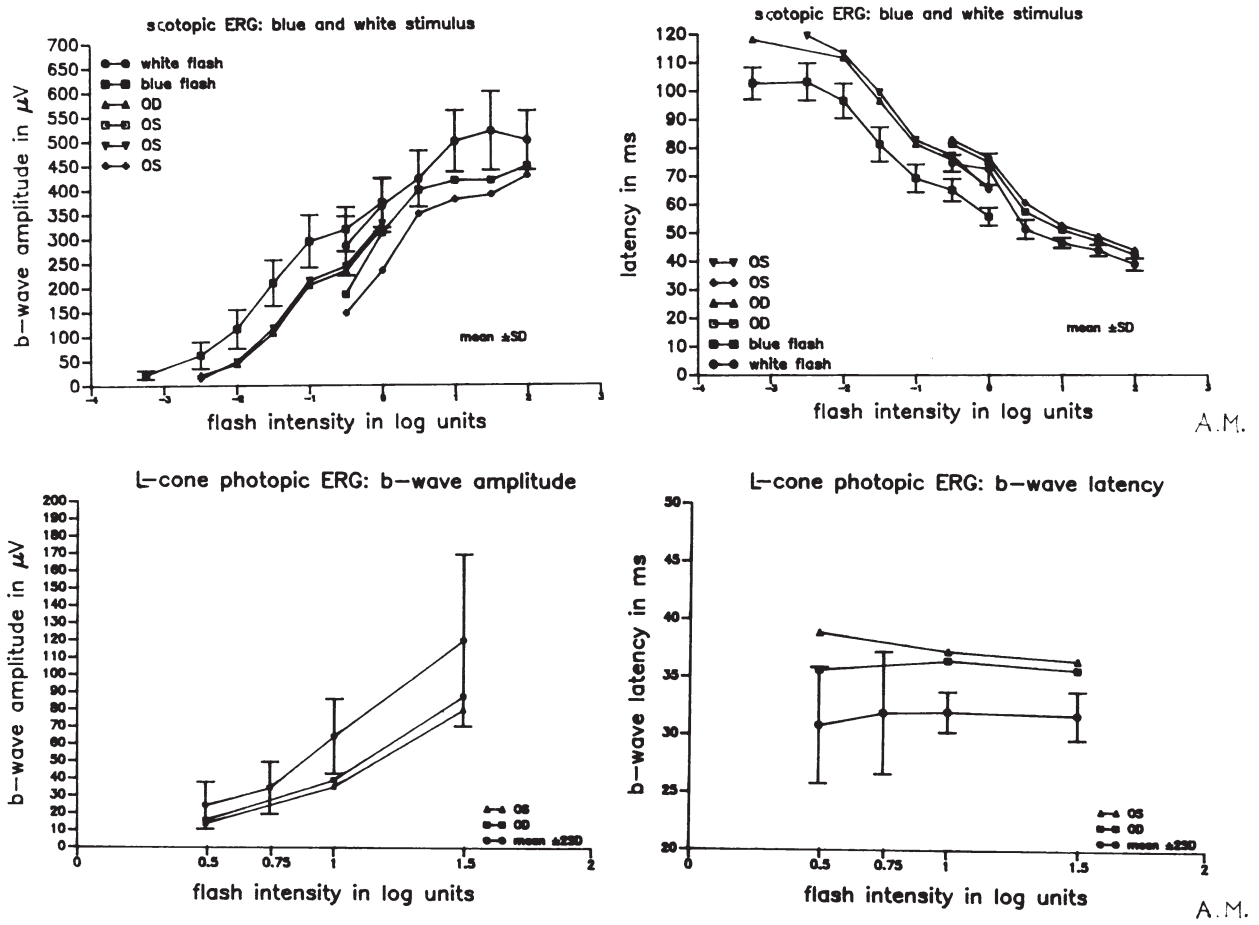

Fig. 7. Top: Scotopic ERG responses to white and blue stimuli in a subject (AM) with chronic exposure to lead per inhalation. B-wave amplitudes are significantly reduced (left) and b-wave latency is significantly prolonged (right). *Bottom:* Photopic ERG responses to red light flashes. B-wave amplitudes are subnormal but within normal limits. B-wave latencies are subnormal in the right eye and significantly increased in the left eye for lower flash intensities (right). For higher flash intensities, b-wave latencies are significantly increased in both eyes.

retina that lead to pigmentary degenerative changes typically have less marked ERG abnormalities than true RP. Thus, the ERG is useful in establishing a diagnosis, which can be difficult by fundus appearance alone. In posterior uveitis, the ERG is subnormal but usually not extinguished, as would be the case in RP with comparable fundus changes. Another feature is the unilateral involvement or the substantial difference in amplitude reduction in posterior uveitis, which contrasts the symmetric involvement in RP.

CENTRAL SEROUS CHORIORETINOPATHY

The pathogenesis of idiopathic central serous chorioretinopathy is still incompletely understood. Ophthalmoscopic findings showing an accumulation of serous fluid in the subretinal space suggest disturbance of the photoreceptors in the macula. In patients with idiopathic central serous chorioretinopathy, Miyake and coworkers[85] recently recorded a- and b-waves, as well as OPs, in the macular region, using focal stimuli. They found reduced a-wave, b-wave, and OPs, as well as prolonged implicit times for these ERG responses. Since the photoreceptors substantially contribute to the a-wave, their finding supports the presence of dysfunctional photoreceptors in this disease. Surprisingly, the b-wave and OPs had deteriorated even more severely than the a-wave (Fig. 8). Apparently, the functional disturbance occurs not only in the photoreceptors, but also, and probably more severely, in the middle and inner retinal layers, as the b-wave and the OPs reflect activity of these layers. They suggest that their results cannot be explained by receptor disorientation (Stiles-Crawford effect) or disturbance of photopigment regeneration. They reexamined patients 2–5 months after the macular detachment and visual acuity resolved. They found that the a- and b-wave had recovered almost to normal control levels. But the OPs remained smaller in the affected eye than in the fellow eye (Fig. 9). They conclude that the uncomplete recovery of the OPs indicates some subclinical abnormality in the middle and inner retinal layers.

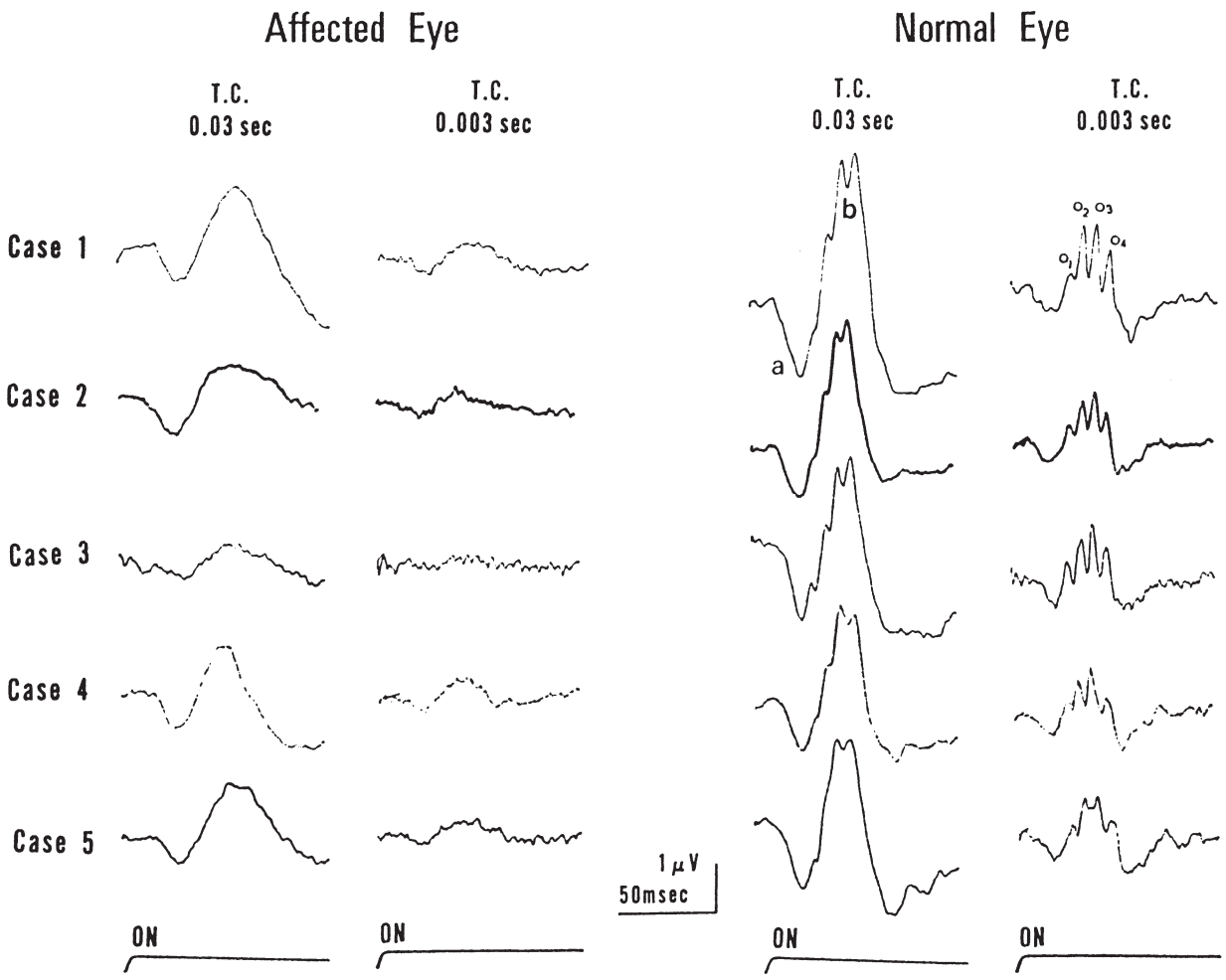

Fig. 8. Local macular ERGs in five representative patients with idiopathic central serous chorioretinopathy. The stimulus spot was 10° in diameter. Two different time constants (T.C.), 0.03 and 0.003 seconds, were used simultaneously. As compared with the normal fellow eyes (*Right*), the affected eyes (*Left*) show reduced amplitudes, particularly in the b-waves and OPs, and delayed implicit times. (Reprinted from Miyake Y et al[85] with permission of the *Am J Ophthalmol.*)

If the focal ERG of Miyake and coworkers reveals obvious electrophysiologic damage to the outer and inner layers of the retina, the multifocal ERG also should be promising. In a case study in our clinic, a 22-year-old woman suffered from idiopathic central serous chorioretinopathy 9 months prior to clinical testing in our department. Visual acuity was 20/20. Fluorescein angiography revealed a central blocking and two small defects of the RPE. In the multifocal ERG, the foveal response was moderately reduced and the parafoveal responses were markedly reduced. There was also a region with reduced amplitudes between the fovea and the blind spot, which was in good agreement with the perimetric results (Fig. 10). Asymmetric or focal impairment of the retina due to idiopathic central serous chorioretinopathy can be well demonstrated by multifocal ERG techniques.

UNCOMMON INFLAMMATORY DISORDERS WITH MARKED ERG ABNORMALITIES

In some presumed inflammatory disorders, functional impairment of the retina is more apparent by reductions in ERG amplitudes than might have been anticipated from the extent of clinically apparent disease. Two such examples are birdshot chorioretinopathy[101] and the multiple evanescent white-dot syndrome (MEWDS).[56] There are marked abnormalities in the scotopic and photopic ERG in both birdshot chorioretinopathy[39,61,97] and MEWDS.[110]

CONCLUSIONS FOR CLINICAL APPLICATION

In global inflammatory disease, the ERG will parallel the funduscopically visible fundus changes. The ERG can be helpful in distinguishing chorioretinitis from hereditary retinal degenerations (e.g., RP).

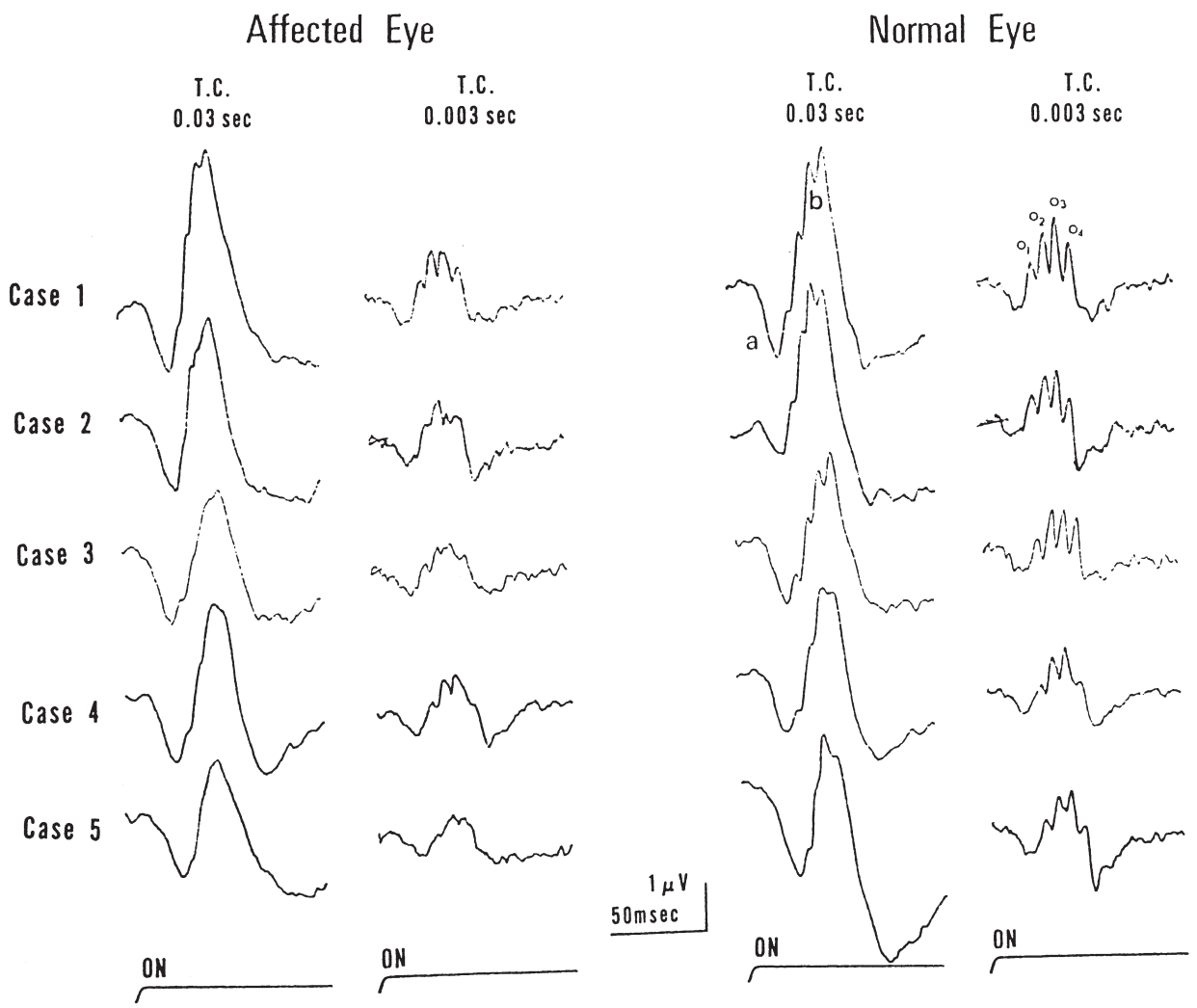

Fig. 9. Local macular ERGs in five patients in the convalescant stage of idiopathic central serous chorioretinopathy. The case numbers correspond to those used in Fig. 8. A- and b-waves in the affected eyes show nearly the same amplitudes as those in the normal fellow eyes. The amplitudes of the OPs, however, are smaller than those in the normal fellow eyes. (Reprinted from Miyake Y et al[85] with permission of the *Am J Ophthalmol.*)

There are uncommon disorders (birdshot chorioretinopathy, MEWDS), in which the ERG is unexpectedly abnormal. Detection of local inflammatory disease (e.g., idiopathic central serous chorioretinopathy) by the ERG requires local measurements (focal ERG, multifocal ERG).

Cancer

CHOROIDAL MELANOMA

Malignant melanoma of the choroid is one of the few primary eye diseases that is life threatening. Recent reviews are given by Shields[107] and Foulds.[36] The sensitivity of the RPE and its transepithelial potential to influences of the chemical milieu of the choroid and the outer retina make the transepithelial potential a likely indicator of nearby tumors. Whether the malignant melanoma originates in the choroid or in the RPE itself may make little difference in the responsiveness of the transepithelial potential. A reduction in the EOG L/D ratio in patients with malignant melanoma was first reported by Ponte and Lauricella[95] and Bohar and Farkas.[14] Subsequently, larger samples of patients were investigated, for example, 22 patients by Jones,[59] 54 patients by Staman,[112] and 30 patients by Markoff.[81] These studies all agreed that the presence of malignant melanoma resulted in large reductions in the EOG L/D ratio, whether or not retinal detachment was present and regardless of the size of the melanoma.[27]

CANCER-ASSOCIATED RETINOPATHY

Cancer-associated retinopathy (CAR) occurs most often in association with small cell carcinoma of the

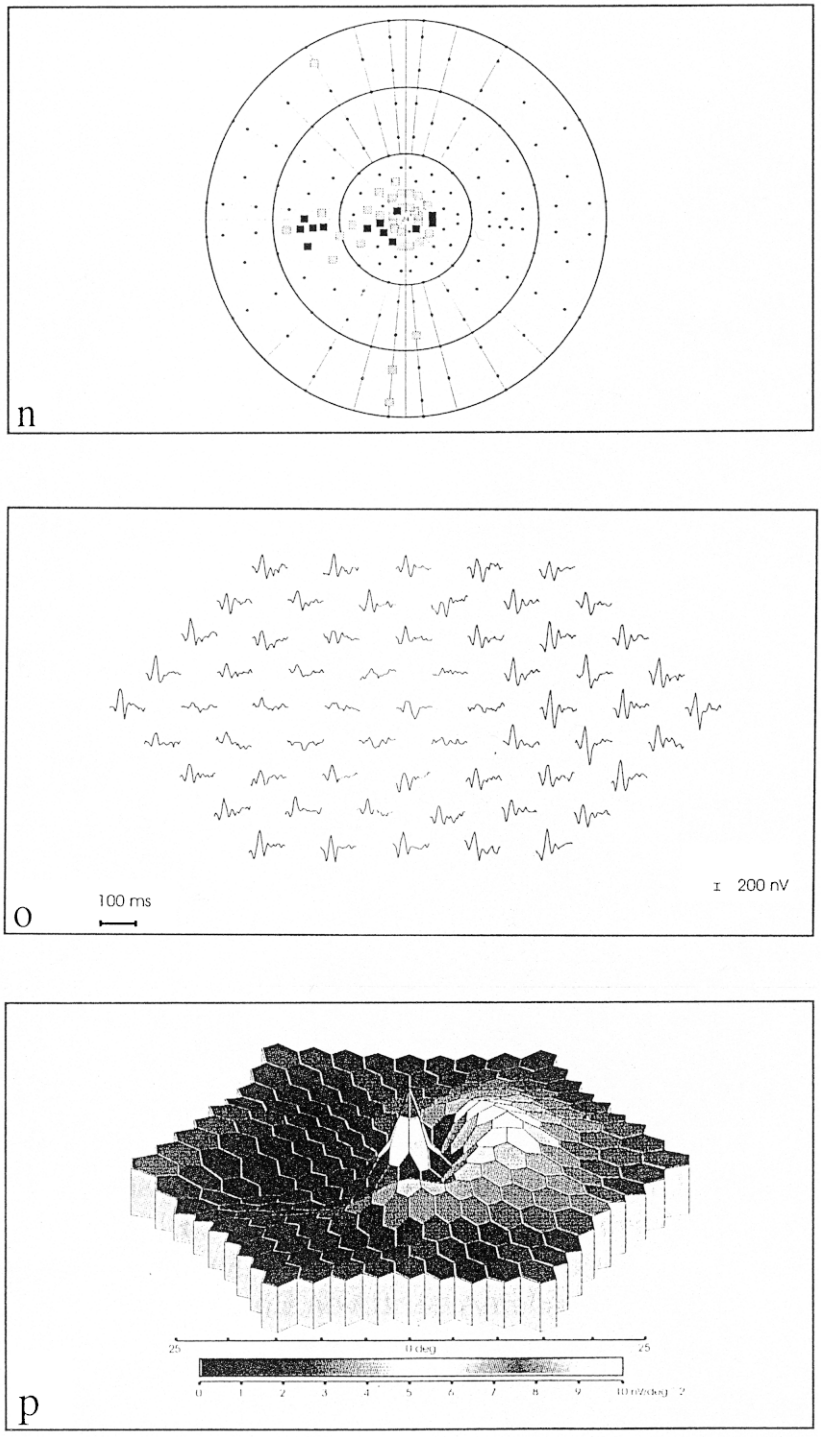

Fig. 10. Perimetric and multifocal ERG results of the left eye of a 22-year-old woman with idiopathic central serous chorioretinopathy. (n) Static perimetric results (Tübingen Automated Perimeter 30°). (o) Trace array of 61 first-order kernel ERG waves from the same eye. (p) Response density plot of the same eye calculated as scalar product. (Reprinted from Kretschmann U et al[75] with permission of Klin Monatsbl Augenheilkd.)

lung,[116] but also with other types of neoplasia[66,117] (for review, see Thirkill[115]). Vision abnormalities are frequently the first sign of illness, which prompts the patient to seek medical help. Complaints of flashing lights, loss of color vision, and night blindness are the most common early signs leading to subsequent clinical examinations and tests that identify the causal cancer. The underlying mechanism involves inhibition of photoreceptor function with subsequent decay probably caused by an immune response to retinal-specific proteins.[115] CAR is characterized by clinical, histopathologic, and electrophysiologic evidence of degeneration and loss of both rod and cone photoreceptors, with ERG a-waves and b-waves reduced markedly in amplitude.[55,103] However, by means of the scotopic and photopic ERG, another

type of dysfunction was found that selectively causes cone dysfunction leaving the rods unaffected.[24,79]

MELANOMA-ASSOCIATED RETINOPATHY

Retinal dysfunction associated with malignant melanoma (MAR), which is similar to that observed in congenital stationary night blindness (CSNB), was first described by Ripps and coworkers.[99] Because the patient received vincristine chemotherapy, it was reasonable to assume that vincristine contributed to the development of the retinal dysfunctions. However, the findings could be reproduced in patients with cutaneous malignant melanoma who had not received vincristine chemotherapy.[11,65]

Alexander and coworkers reported a patient with melanoma who had ERG changes similar to those observed in the patients with CSNB, suggesting a common underlying defect.[2] The dark-adapted rod ERG responses showed a selective reduction in the amplitude of the b-wave and an absence of OPs compared with the normal response. Both the a-wave amplitude and the a-wave implicit time were normal. The light-adapted cone ERG responses showed a selective reduction in b-wave amplitude and a diminuation of the OPs compared with the normal response. A-wave amplitude and a-wave implicit time were normal. To separate ON-components from OFF-components, the investigators administered longer flash durations. They obtained a severely reduced initial positive ON-component of the cone-ERG from their patient; the later positive component, representing a response to flash offset, was similar in both the patient and a representative normal subject (Fig. 11).

As we know from the experiments of Bush and Sieving with selective blockade of either the ON- or the OFF-pathway, the depolarizing bipolar cells (DBCs) drive the ON-pathway and the hyperpolarizing bipolar cells (HBCs) drive the OFF-pathway.[21] The DBCs appear to be the only type of bipolar cell that subserves the mammalian rod pathway.[26,106] A selective reduction in the ON-response component could be explained by a postsynaptic defect in the DBCs, which could cause such defects. The same site of defect is suspected in CSNB.[109]

CONCLUSIONS FOR CLINICAL APPLICATION

The EOG might be useful in the diagnosis of choroidal melanoma. The association of cancer with compromised retinal function highlights the importance of searching for occult malignancies in patients with acquired visual problems and abnormal electroretinographic findings who have no other ocular explanation for their symptoms. It can be difficult to differentiate cancer-associated retinal dysfunction from the effects of chemotherapy.

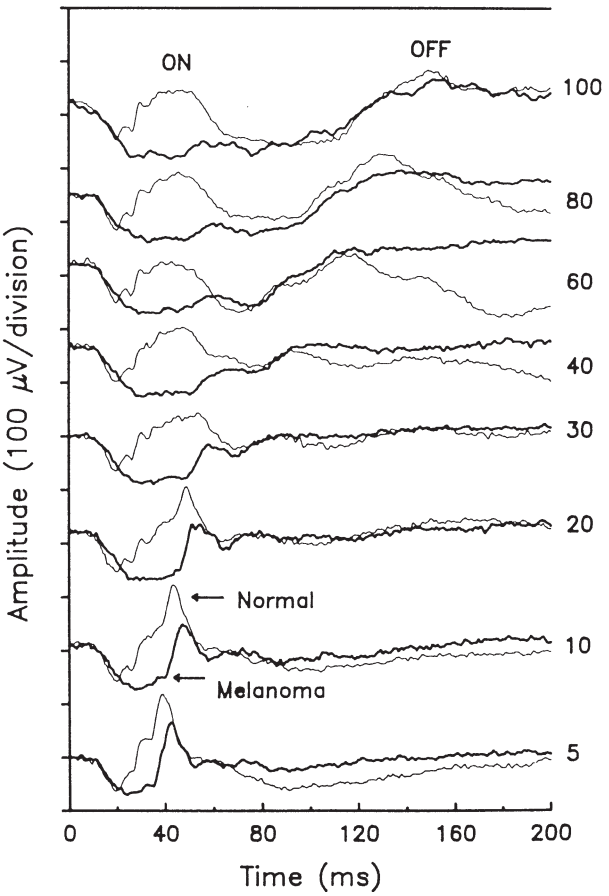

Fig. 11. ERG responses (UIC) to flashes of a constant luminance (3.7 log cd/m^2) but of different durations in a melanoma patient (thick tracings) and a representative normal subject (thin tracings). Responses of the two subjects are positioned vertically such that they coincide at time of flash onset. Flash durations in milliseconds are indicated at the right of each pair of waveforms. Responses were obtained against a rod-desensitizing adapting field of 2.1 log cd/m^2. (Reprinted from Alexander KR et al[2] with permission of *Invest Ophthalmol Vis Sci.*)

Vitamin A Deficiency

ERG AMPLITUDE DECREASE DUE TO REDUCED RETINOL BLOOD LEVELS

Any condition that interferes with ingestion, absorption, storage, or transport of vitamin A (e.g., dietary deficiency, liver disease, intestinal malabsorption caused by abetalipoproteinemia[42]) can lead to a deficiency in target tissues. As soon as the blood level of retinol falls, the level of rod visual pigment (rhodopsin) also falls, and reciprocally, the visual threshold rises, thus leading to night blindness.[30] Electroretinographic findings show reduced rod and cone responses with normal implicit times,[92] with the rod ERG affected before the cone ERG.[41] After starting vitamin A supplementation there is a complete recovery in the electroretinographic findings.[92]

In a study of chronic alcohol-abusive patients with liver cirrhosis, a reduction of ERG amplitudes was observed without an increase of latencies. This was mainly ascribed to vitamin A deficiency and was reversed within 1 month by vitamin A substitution.[102]

DEFECTIVE RETINOL-BINDING PROTEIN SYNTHESIS

Most of the body's retinol is stored in the liver in esterized form. The release from the hepatocytes requires the association of retinol with retinol binding protein (RBP). Seeliger and coworkers report the phenotype of two sisters with a compound heterozygous mutation in the gene for serum RBP.[105] Both exhibited extinguished rod ERGs with either normal or reduced cone ERGs. Since acne was the only symptom besides night vision problems, the markedly abnormal ERG led to the diagnosis.

CONCLUSIONS FOR CLINICAL APPLICATION

The rod ERG is indicated when any form of vitamin A deficiency is suspected. The effect of treatment (e.g., vitamin A supplementation) on retinal function can be monitored by the (scotopic) ERG.

Photochemical Damage

It is generally accepted that there are three different mechanisms of light damage.[46] When the light is very intense, in the order of terawatts per square centimeter, it will cause an acoustic shock wave in the retina. This so-called mechanical damage can be caused only by very strong lasers, such as the YAG laser, which is commonly used in ophthalmology. Lower intensities, down to about 10 watts per square centimeter, cause thermal damage, in which the temperature of the retina rises to the point at which proteins denaturate and the tissue cannot properly function. At lower intensities, photochemical damages can occur. Damage assessed by means of funduscopy and densitometry is most extensive 2 days after light exposure.[74] The intensity of transition between thermal and photochemical damages depends on several factors, the most important ones being the wavelength of the light and the size of the exposed area. The transition between thermal and photochemical damage is often not sharp, however, since photochemical damages are enhanced by temperature rises. In photochemical damage, the light is absorbed by a pigment, which starts a chain of chemical reactions presumably through radicals eventually leading to breakdown of retinal structures.[73]

PHOTOCHEMICAL DAMAGE TO DIFFERENT PHOTORECEPTOR TYPES

Kremers employed the intraretinal (local) ERG to establish the threshold for changes in the ERG shortly after exposure to intense white lights in macaque monkeys.[73] With use of the local ERG, it was possible to limit the damage to small retinal patches, and with the use of selective chromatic adaptation and dark adaptation it was possible to assess

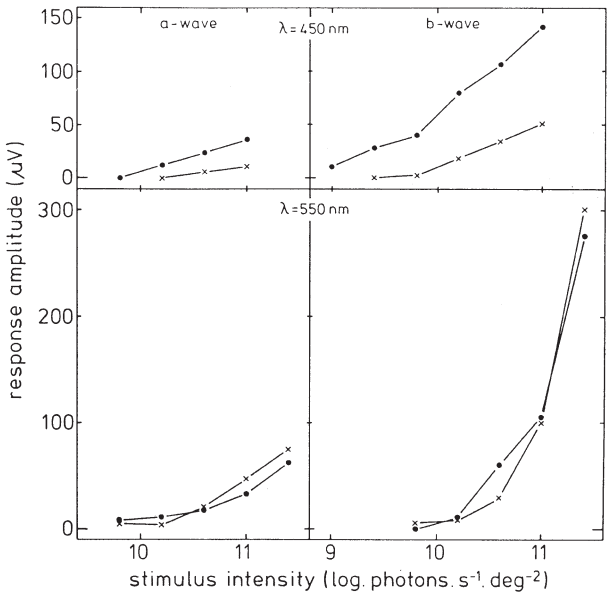

Fig. 12. Response amplitudes as a function of stimulus intensities for S-cone a- and b-waves (stimulus wavelength 450 nm) and for L-M–cone a- and b-waves (550 nm). Response amplitudes were measured before (●) and after (✕) a 600 sec, 87 W/cm^2 exposure. The exposure decreased only the S-cone response amplitudes. (Reprinted from Kremers J[73] with permission.)

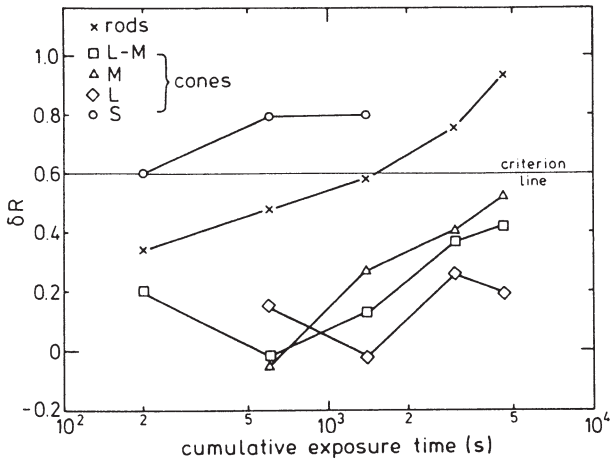

Fig. 13. Relative response decrease ($d_R = (R_{pre} - R_{post}) / R_{pre}$) of the different photoreceptor systems as function of the cumulative exposure time to exposures of 87 W/cm^2. The data originate from the same experiment described in Fig. 12. All systems show decreasing responses when exposure time increases. ERG responses of the S-cones were most vulnerable to the exposures, followed by those of the rods. The L- and M-cones were least vulnerable. (Reprinted from Kremers J[73] with permission.)

the relative vulnerability of different photoreceptor systems. The amplitude decrease was about 20% for the S-cones and virtually zero for the L-M–cones (Fig. 12).

Kremers also studied ERG responses after several exposures. Fig. 13 shows the response amplitude decrease as a function of the cumulative exposure time. After the first exposure of 200 seconds, the S-cone system showed considerably reduced responses (60%); the amplitudes of the rod responses were also reduced (35%) and the L-M–cone system showed a marginal reduction of 20%. After an additional exposure of 400 seconds, cone and rod responses were further reduced, but L-M–cone responses were back to baseline level. With additional exposures, further reduction in S-cone and rod responses occurred. Until after the fourth exposure, S-cone responses were no longer recordable. L-M–cone response also showed a tendency to be reduced, but these systems did not reach the reduction criterion.

Several aspects of the ERG changes resemble the psychophysical observations made by Kitahara and coworkers,[68] including the ERG changes directly after exposure to bright white light, the vulnerability of the S-cones, and the total reversibility after limited exposure time, but only partial recovery after extended exposures. These early ERG changes are possibly the electrophysiologic equivalent of psychophysical detectable disturbances which occur directly after exposure to bright light.[23,48,119]

CONSEQUENCES FOR OPHTHALMIC SURGERY: PHOTOCHEMICAL DAMAGE BY THE OPERATING MICROSCOPE

Lessel and coworkers[77] performed an electrophysiologic study on a series of 30 patients 6 months after cataract surgery. In 15 patients, extracapsular extraction (ECCE) was performed with light intensities during surgery of 3.4–7.3 milliwatts per square centimeter. Fifteen patients underwent intracapsular (ICCE), during which the light intensities were substantially lower (0.8–3.7 microwatts per square centimeter). Significantly reduced amplitudes of the photopic ERG b-waves and significantly reduced L/D ratios of the EOG were found in the ECCE-group, whereas there was no such change in the ICCE-group. These findings indicate light-induced damage by the operating microscope, which is probably caused by reduced number of functioning cones and a deterioration of the RPE.

Summary

We have presented a brief review of electrophysiologic findings in acquired retinal disorders, including diabetic retinopathy, glaucoma, inflammation, vitamin A deficiency, cancer, photochemical damage, hepatic retinopathy, and damage caused by chronic lead exposure. Information obtained by administration of ERG and EOG can assist in the evaluation of disorders at presentation and in the follow-up during and after treatment. We conclude our discussion of each entity with a section on the clinical usefulness of testing in that disorder.

Method of Literature Search

The literature search was performed using the Silver Platter MEDLINE database from 1966 to 1999. Primary search terms were *electrophysiology* OR *electroretinography* OR *electroretinogram* OR *ERG* OR *electrooculography* OR *electro-oculography* OR *electrooculogram* OR *electro-oculogram* OR *EOG* in combination with the subheadings *aging* AND *retin*, diabetic* OR *diabetes* AND *retinopathy, glaucoma, lead, hepatic* AND *retinopathy, chorioretinitis, cancer* AND *retinopathy, vitamin* AND *retin*, light and damage*. Major current journals in ophthalmology, vision research, and neuroscience were used for additional information. The references contained in these articles were also reviewed and were selected if they included important electrophysiologic findings. English abstracts from non-English and non-German articles were used. Materials from current conferences and symposia on electrophysiology of vision were also used. Two books covered a broad range of the discussed topics: *Principles and Practice of Clinical Electrophysiology of Vision* (Heckenlively JR, Arden GB, eds) and *Electrophysiological Testing in Disorders of the Retina, Optic Nerve, and Visual Pathway* (Fishman GA and Sokol S, eds.). Given the broad scope of the topic, however, from the initial set of citations, the references used as sources for this review were chosen for inclusion or exclusion based on primary focus of the report on electrophysiological (patho-) mechanisms, clinical relevance and originality.

References

1. Adams A: The normal electro-oculogram (E. O. G.). Acta Ophthalmol (Copenh) 51:551–61, 1973
2. Alexander KR, Fishman GA, Peachey NS, et al: 'On' response defect in paraneoplastic night blindness with cutaneous malignant melanoma. Invest Ophthalmol Vis Sci 33: 477–83, 1992
3. Arden GB, Barrada A: Analysis of the electrooculograms of a series of normal subjects. Br J Ophthalmol 46:468–82, 1962
4. Arden GB, Hamilton AM, Wilson HJ, et al: Pattern electroretinograms become abnormal when background diabetic retinopathy deteriorates to a preproliferative stage: possible use as a screening test. Br J Ophthalmol 70:330–5, 1986
5. Arndt CF, Derambure P, Defoort DS, Hache JC: Outer retinal dysfunction in patients treated with vigabatrin. Neurology 52:1201–5, 1999
6. Bach M, Funk J: Pattern electroretinogram and computerized optic nerve-head analysis in glaucoma suspects. Ger J Ophthalmol 2:178–81, 1993

7. Bach M, Hiss P, Rover J: Check-size specific changes of pattern electroretinogram in patients with early open-angle glaucoma. Doc Ophthalmol 69:315–22, 1988
8. Bach M, Sulimma F, Gerling J: Little correlation of the pattern electroretinogram (PERG) and visual field measures in early glaucoma. Doc Ophthalmol 94:253–63, 1997
9. Berninger TA, Arden GB: The pattern electroretinogram. Eye 2 (Suppl):S257–83, 1988
10. Berson EL, Gouras P, Hoff M: Temporal aspects of the electroretinogram. Arch Ophthalmol 81:207–14, 1969
11. Berson EL, Lessell S: Paraneoplastic night blindness with malignant melanoma. Am J Ophthalmol 106:307–11, 1988
12. Birch DG, Anderson JL: Standardized full-field electroretinography. Normal values and their variation with age. Arch Ophthalmol 110:1571–6, 1992
13. Birch DG, Fish GE: Rod ERGs in retinitis pigmentosa and cone-rod degeneration. Invest Ophthalmol Vis Sci 28:140–50, 1987
14. Bohar A, Farkas A: Comparative electrophysiologic observations of intraocular tumors and retinal detachment. Doc Ophthalmol Proc Ser 10:399–403, 1976
15. Bresnick GH: Diabetic Retinopathy, in Heckenlively JR, Arden GB (eds): Principles and Practice of Clinical Electrophysiology of Vision. St. Louis, Mosby Year Book, 1991, pp 619–35
16. Bresnick GH, Condit RS, Palta M, et al: Association of hue discrimination loss and diabetic retinopathy. Arch Ophthalmol 103:1317–24, 1985
17. Bresnick GH, Korth K, Groo A, Palta M: Electroretinographic oscillatory potentials predict progression of diabetic retinopathy. Preliminary report. Arch Ophthalmol 102:1307–11, 1984
18. Bresnick GH, Palta M: Oscillatory potential amplitudes. Relation to severity of diabetic retinopathy. Arch Ophthalmol 105:929–33, 1987
19. Bresnick GH, Palta M: Predicting progression to severe proliferative diabetic retinopathy. Arch Ophthalmol 105: 810–4, 1987
20. Bresnick GH, Palta M: Temporal aspects of the electroretinogram in diabetic retinopathy. Arch Ophthalmol 105: 660–4, 1987
21. Bush RA, Sieving PA: Inner retinal contributions to the primate photopic fast flicker electroretinogram. J Opt Soc Am A 13:557–65, 1996
22. Butterworth RF, Giguere JF, Michaud J, et al: Ammonia: key factor in the pathogenesis of hepatic encephalopathy. Neurochem Pathol 6:1–12, 1987
23. Cellini M, Profazio V, Fantaguzzi P, et al: Photic maculopathy by arc welding. A case report. Int Ophthalmol 10:157–9, 1987
24. Cogan DG, Kuwabara T, Currie J, Kattah J: Paraneoplastische Retinopathie unter dem klinischen Bild einer Zapfendystrophie mit Achromatopsie. Klin Monatsbl Augenheilkd 197:156–8, 1990
25. Daneshvar H, Racette L, Coupland SG, et al: Symptomatic and asymptomatic visual loss in patients taking vigabatrin. Ophthalmology 106:1792–8, 1999
26. Daw NW, Jensen RJ, Brunken WJ: Rod pathways in mammalian retinae. Trends Neurosci 13:110–5, 1990
27. Dawson WW: Malignant melanoma, in Heckenlively JR, Arden GB (eds): Principles and Practice of Clinical Electrophysiology of Vision. St. Louis, Mosby Year Book, 1991, pp 643–5
28. De RA, Kayembe D: A clinical procedure for the simultaneous recording of fast and slow EOG oscillations. Int Ophthalmol 3:179–89, 1981
29. Dorey CK, Wu G, Ebenstein D, et al: Cell loss in the aging retina. Relationship to lipofuscin accumulation and macular degeneration. Invest Ophthalmol Vis Sci 30:1691–9, 1989
30. Dowling JE, Wald G: The biologic formation of vitamin A acid. Proc Natl Acad Sci USA 46:587–608, 1960
31. Eckstein AK, Reichenbach A, Jacobi P, et al: Hepatic retinopathy. Changes in retinal function. Vision Res 37:1699–706, 1997
32. Elsner AE, Berk L, Burns SA, Rosenberg PR: Aging and human cone photopigments. J Opt Soc Am A 5:2106–12, 1988
33. Entenmann B: Elektrookulographie. Physiologische Grundlagen, Durchführung, Normwerte, Fehlerquellen und klinische Anwendung. (1996). Univ. Diss. Tübingen.
34. Fishman GA: Retinal toxicity with the use of chloroquine and hydrochloroquine, in Heckenlively JR, Arden GB, (eds): Principles and Practice of Clinical Electrophysiology of Vision. St. Louis, Mosby Year Book, 1991, pp 594–9
35. Fishman GA, Sokol S. Electrophysiological testing in disorders of the retina, optic nerve, and visual pathway (whole book). San Francisco, American Academy of Ophthalmology (Ophthalmology monographs; 2): 1990.
36. Foulds W: Ocular melanoma. Pigment Cell 6:127–49, 1983
37. Fox DA, Katz LM: Developmental lead exposure selectively alters the scotopic ERG component of dark and light adaptation and increases rod calcium content. Vision Res 32: 249–55, 1992
38. Frishman LJ, Shen FF, Du L, et al: The scotopic electroretinogram of macaque after retinal ganglion cell loss from experimental glaucoma. Invest Ophthalmol Vis Sci 37:125–41, 1996
39. Fuerst DJ, Tessler HH, Fishman GA, et al: Birdshot retinochoroidopathy. Arch Ophthalmol 102:214–9, 1984
40. Gao H, Hollyfield JG: Aging of the human retina. Differential loss of neurons and retinal pigment epithelial cells. Invest Ophthalmol Vis Sci 33:1–17, 1992
41. Gouras P: Electroretinography, in Aminoff MJ (ed): Electrodiagnosis in Clinical Neurology. Edinburgh, Churchill Livingstone, 1999, pp 397–420
42. Gouras P, Carr RE, Gunkel RD: Retinitis pigmentosa in abetalipoproteinemia: Effects of vitamin A. Invest Ophthalmol 10:784–93, 1971
43. Gouras P, MacKay CJ: Electroretinographic responses of the short-wavelength-sensitive cones. Invest Ophthalmol Vis Sci 31:1203–1209, 1990
44. Grant WM, Schuman JS: Effects on the eyes and visual system from chemicals, drugs, metals and minerals, plants, toxins and venoms; also, systemic side effects from eye medications. Springfield, IL, Charles C. Thomas Publishers, 1993
45. Greenstein VC, Hood DC, Ritch R, et al: S (blue) cone pathway vulnerability in retinitis pigmentosa, diabetes and glaucoma. Invest Ophthalmol Vis Sci 30:1732–7, 1989
46. Ham WT, Ruffolo JJ, Mueller HA, Guerry D: The nature of retinal radiation damage: dependence on wavelength, poser level and exposure time. Vision Res 20:1105–11, 1980
47. Hammond PB, Dietrich KN: Lead exposure in early life: health consequences. Rev Environ Contam Toxicol 115: 91–124, 1990
48. Hansen E: The disturbance of colour vision after sunbathing, in Verriest G (ed): Colour Vision Deficiencies V. Bristol, England, Adam Hilger Ltd, 1979, pp 157–61
49. Harding GFA: Evaluation of ocular trauma, opaque media, in Heckenlively JR, Arden GB (eds): Principles and Practice of Clinical Electrophysiology of Vision. St. Louis, Mosby Year Book, 1991, pp 567–72
50. Holder GE: Significance of abnormal pattern electroretinography in anterior visual pathway dysfunction. Br J Ophthalmol 71:166–71, 1987
51. Holopigian K, Seiple W, Lorenzo M, Carr R: A comparison of photopic and scotopic electroretinographic changes in early diabetic retinopathy. Invest Ophthalmol Vis Sci 33: 2773–80, 1992
52. Iijima H: Distribution of ERG amplitudes, latencies, and implicit times, in Heckenlively JR, Arden GB (eds): Principles and Practices of Clinical Electrophysiology of Vision. St. Louis, Mosby Year Book, 1991, pp 289–90
53. Jacobi PC, Miliczek KD, Zrenner E: Experiences with the international standard for clinical electroretinography: normative values for clinical practice, interindividual and intraindividual variations and possible extensions. Doc Ophthalmol 85:95–114, 1993
54. Jacobi PC, Ruther K, Miliczek KD, et al: Klinische Elek-

troretinographie: Standardprotokoll und Normwerte. Klin Monatsbl Augenheilkd 202:27–42, 1993
55. Jacobson DM, Thirkill CE, Tipping SJ: A clinical triad to diagnose paraneoplastic retinopathy. Ann Neurol 28:162–7, 1990
56. Jampol LM, Sieving PA, Pugh D, et al: Multiple evanescent white dot syndrome. I. Clinical findings. Arch Ophthalmol 102:671–4, 1984
57. Jenkins TC, Cartwright JP: The electroretinogram in minimal diabetic retinopathy. Br J Ophthalmol 74:681–4, 1990
58. Johnson MA: Use of electroretinographic ratios in assessment of vascular occlusion and ischemia, in Heckenlively JR, Arden GB (eds): Principles and Practice of Clinical Electrophysiology of Vision. St. Louis, Mosby Year Book, 1991, pp 613–8
59. Jones RM, Klein R, De VG, Myers FL: Abnormal electrooculograms from eyes with a malignant melanoma of the choroid. Invest Ophthalmol Vis Sci 20:276–9, 1981
60. Juen S, Kieselbach GF: Electrophysiological changes in juvenile diabetics without retinopathy. Arch Ophthalmol 108:372–5, 1990
61. Kaplan HJ, Aaberg TM: Birdshot retinochoroidopathy. Am J Ophthalmol 90:773–82, 1980
62. Karpe G: Basis of clinical electroretinography. Acta Ophthalmol (Copenh) 24 (Suppl):1–118, 1945
63. Karpe G, Rendahl I: Clinical electroretinography in detachment of the retina. Acta Ophthalmol (Copenh) 47: 633–41, 1969
64. Karwoski CJ, Kawasaki K: Oscillatory potentials, in Heckenlively JR, Arden GB (eds): Principles and Practice of Clinical Electrophysiology of Vision. St. Louis, Mosby Year Book, 1991, pp 125–8
65. Kellner U, Bornfeld N, Foerster MH: Severe course of cutaneous melanoma associated paraneoplastic retinopathy. Br J Ophthalmol 79:746–52, 1995
66. Keltner JL, Roth AM, Chang RS: Photoreceptor degeneration. Possible autoimmune disorder. Arch Ophthalmol 101:564–9, 1983
67. Keunen JE, van Norren D, van Meel GJ: Density of foveal cone pigments at older age. Invest Ophthalmol Vis Sci 28: 985–91, 1987
68. Kitahara K, Tamaki R, Hibano H, Oyama T: A case of blue-yellow defect induced by intense blue light, in Verriest G (ed): Colour Vision Deficiencies VIII. Dordrecht, The Netherlands, Dr W Junk Publishers, 1987
69. Knave B: Electroretinography in eyes with retained intraocular metallic foreign bodies. Acta Ophthalmol (Copenh) 100(Suppl):1–63, 1969
70. Korth M, Nguyen NX, Horn F, Martus P: Scotopic threshold response and scotopic PII in glaucoma. Invest Ophthalmol Vis Sci 35:619–25, 1994
71. Kothe AC, Lovasik JV, Coupland SG: Variability in clinically measured photopic oscillatory potentials. Doc Ophthalmol 71:381–95, 1989
72. Krauss GL, Johnson MA, Miller NR: Vigabatrin-associated retinal cone system dysfunction: electroretinogram and ophthalmologic findings. Neurology 50:614–8, 1998
73. Kremers, J. Photochemical damage of the retina. (1989). University of Utrecht. Maastricht: Universitaire Pers Maastricht.
74. Kremers J, van Norren D: Retinal damage in macaque after white light exposures lasting ten minutes to twelve hours. Invest Ophthalmol Vis Sci 30:1032–9, 1989
75. Kretschmann U, Schlote T, Stübiger N, et al: Multifokale Elektroretinographie bei erworbenen Makulafunktionsstörungen. Klin Monatsbl Augenheilkd 212:93–100, 1998
76. Krogh E: Normal values in clinical electrooculography. IV. Analysis of two dimensionless EOG parameters and their relation to other variables. Acta Ophthalmol (Copenh) 55: 739–49, 1977
77. Lessel M, Thaler A, Heilig P, et al: Intraoperative retinal light damage reflected in electrophysiologic data. Doc Ophthalmol 76:323–33, 1991
78. Linsenmeier RA, Steinberg RH: Mechanisms of azide induced increases in the c-wave and standing potential of the intact cat eye. Vision Res 27:1–8, 1987
79. MacKay CJ, Gouras P, Roy M, et al: Paraneoplastic cone dystrophy (abstract). Invest Ophthalmol Vis Sci 35 (Suppl): 2119, 1994
80. Maffei L, Fiorentini A, Bisti S, Hollander H: Pattern ERG in the monkey after section of the optic nerve. Exp Brain Res 59:423–5, 1985
81. Markoff JI, Shaken E, Shields JA, Augsburger JJ: The electro-oculogram in eyes with choroidal melanoma. Ophthalmology 88:1122–5, 1981
82. Marmor MF: Retinal toxicity from thioridazine and other phenothiazines, in Heckenlively JR, Arden GB (eds): Principles and Practice of Clinical Electrophysiology of Vision. St. Louis, Mosby Year Book, 1991, pp 600–6
83. Marmor MF, Zrenner E: Standard for clinical electro-oculography. International Society for Clinical Electrophysiology of Vision. Arch Ophthalmol 111:601–4, 1993
84. Marmor MF, Zrenner E: Standard for clinical electroretinography (1994 update). Doc Ophthalmol 89:199–210, 1995
85. Miyake Y, Shiroyama N, Ota I, Horiguchi M: Local macular electroretinographic responses in idiopathic central serous chorioretinopathy. Am J Ophthalmol 106:546–50, 1988
86. Naarendorp F, Sieving PA: The scotopic threshold response of the cat ERG is suppressed selectively by GABA and glycine. Vision Res 31:1–15, 1991
87. Norenberg MD, Baker L, Norenberg LO, et al: Ammonia-induced astrocyte swelling in primary culture. Neurochem Res 16:833–6, 1991
88. Norenberg MD, Lapham LW: The astrocyte response in experimental portal-systemic encephalopathy: an electron microscopic study. J Neuropathol Exp Neurol 33:422–35, 1974
89. Ogden TE: The oscillatory waves of the primate electroretinogram. Vision Res 13:1059–74, 1973
90. Palmowski AM, Sutter EE, Bearse, MA Jr., Fung W: Mapping of retinal function in diabetic retinopathy using the multifocal electroretinogram. Invest Ophthalmol Vis Sci 38:2586–96, 1997
91. Pappas SC, Jones EA: Methods for assessing hepatic encephalopathy. Semin Liver Dis 3:298–307, 1983
92. Perlman I, Barzilai D, Haim T, Schramek A: Night vision in a case of vitamin A deficiency due to malabsorption. Br J Ophthalmol 67:37–42, 1983
93. Peterson H: The normal B-potential in the single-flash clinical electroretinogram. A computer technique study of the influence of sex and age. Acta Ophthalmol (Copenh) 99 (Suppl):1–77, 1968
94. Pfeiffer N, Tillmon B, Bach M: Predictive value of the pattern electroretinogram in high-risk ocular hypertension. Invest Ophthalmol Vis Sci 34:1710–5, 1993
95. Ponte F, Lauricella M: On the lack of correlation between the ERG and EOG alterations in malignant melanoma of the choroid. Doc Ophthalmol Proc Ser 13:87–92, 1976
96. Porciatti V, Burr DC, Morrone MC, Fiorentini A: The effects of aging on the pattern electroretinogram and visual evoked potential in humans. Vision Res 32:1199–209, 1992
97. Priem HA, Oosterhuis JA: Birdshot chorioretinopathy: clinical characteristics and evolution. Br J Ophthalmol 72:646–59, 1988
98. Pulfrich C: Die Stereoskopie im Dienste der isochromen und heterochromen Photometrie. Die Naturwissenschaften 10:553–69, 1923
99. Ripps H, Carr RE, Siegel IM, Greenstein VC: Functional abnormalities in vincristine-induced night blindness. Invest Ophthalmol Vis Sci 25:787–94, 1984
100. Ross J, Hogben JH: The Pulfrich effect and short-term memory in stereopsis (letter). Vision Res 15:1289–90, 1975
101. Ryan SJ, Maumenee AE: Birdshot retinochoroidopathy. Am J Ophthalmol 89:31–45, 1980
102. Sandberg MA, Rosen JB, Berson EL: Cone and rod function in vitamin A deficiency with chronic alcoholism and in retinitis pigmentosa. Am J Ophthalmol 84:658–65, 1977
103. Sawyer RA, Selhorst JB, Zimmerman LE, Hoyt WF: Blind-

ness caused by photoreceptor degeneration as a remote effect of cancer. Am J Ophthalmol 81:606–13, 1976
104. Schechner R, Miller B, Merksamer E, Perlman I: A long term follow up of ocular siderosis: quantitative assessment of the electroretinogram. Doc Ophthalmol 76:231–40, 1990
105. Seeliger MW, Biesalski HK, Wissinger B, et al: Phenotype in retinol deficiency due to a hereditary defect in retinol binding protein synthesis. Invest Ophthalmol Vis Sci 40:3–11, 1999
106. Sharpe LT, Stockman A: Rod pathways: the importance of seeing nothing. Trends Neurosci 22:497–504, 1999
107. Shields JA: Current approaches to the diagnosis and management of choroidal melanomas. Surv Ophthalmol 21: 443–63, 1977
108. Shirao Y, Kawasaki K: Electrical responses from diabetic retina. Prog Retin Eye Res 17:59–76, 1998
109. Sieving PA: Photopic on- and off-pathway abnormalities in retinal dystrophies. Trans Am Ophthalmol Soc 81:701–73, 1993
110. Sieving PA, Fishman GA, Jampol LM, Pugh D: Multiple evanescent white dot syndrome. II. Electrophysiology of the photoreceptors during retinal pigment epithelial disease. Arch Ophthalmol 102:675–9, 1984
111. Sieving PA, Frishman LJ, Steinberg RH: Scotopic threshold response of proximal retina in cat. J Neurophysiol 56:1049–61, 1986
112. Staman JA, Fitzgerald CR, Dawson WW, et al: The EOG and choroidal malignant melanomas. Doc Ophthalmol 49: 201–9, 1980
113. Sutter EE, Tran D: The field topography of ERG components in man-I. The photopic luminance response. Vision Res 32:433–46, 1992
114. Tanabe J, Shirao Y, Oda N, Kawasaki K: Evaluation of retinal integrity in eyes with retained intraocular metallic foreign body by ERG and EOG. Doc Ophthalmol 79:71–8, 1992
115. Thirkill CE: Cancer associated retinopathy. The CAR syndrome. Neuro-ophthalmology 14:297–323, 1994
116. Thirkill CE, Keltner JL, Tyler NK, Roth AM: Antibody reactions with retina and cancer-associated antigens in 10 patients with cancer-associated retinopathy. Arch Ophthalmol 111:931–7, 1993
117. Thirkill CE, Roth AM, Keltner JL: Cancer associated retinopathy. Arch Ophthalmol 105:372–5, 1987
118. Trick LR: Age-related alterations in retinal function. Doc Ophthalmol 65:35–43, 1987
119. Ts'o MO, Fine BS, Zimmerman LE: Photic maculopathy produced by the indirect ophthalmoscope. 1. Clinical and histopathologic study. Am J Ophthalmol 73:686–99, 1972
120. Tzekov R, Arden GB: The electroretinogram in diabetic retinopathy. Surv Ophthalmol 44:53–60, 1999
121. Wachtmeister L, Dowling JE: The oscillatory potentials of the mudpuppy retina. Invest Ophthalmol Vis Sci 17:1176–88, 1978
122. Wanger P, Persson HE: Early diagnosis of retinal changes in diabetes: a comparison between electroretinography and retinal biomicroscopy. Acta Ophthalmol (Copenh) 63: 716–20, 1985
123. Weale RA: Retinal senescense, in Osborne N, Chader GJ (eds): Progress in Retinal Research, Oxford, Pergamon Press, 1986, pp 53–73
124. Weiner A, Christopoulos VA, Gussler CH, et al: Foveal cone function in nonproliferative diabetic retinopathy and macular edema. Invest Ophthalmol Vis Sci 38:1443–9, 1997
125. Weleber RG: The effect of age on human cone and rod ganzfeld electroretinograms. Invest Ophthalmol Vis Sci 20: 392–9, 1981
126. Wu L, Massof RW, Starr SJ: Computer-assisted analysis of clinical electroretinographic intensity-response functions. Doc Ophthalmol Proc Ser 37:231–9, 1983
127. Yamamoto S, Kamiyama M, Nitta K, et al: Selective reduction of the S cone electroretinogram in diabetes. Br J Ophthalmol 80:973–5, 1996
128. Yonemura D, Kawasaki K: New approaches to ophthalmic electrodiagnosis by retinal oscillatory potential, drug-induced responses from retinal pigment epithelium and cone potential. Doc Ophthalmol 48:163–222, 1979
129. Zonneveldt A, van Lith G: The electrooculogram and its interindividual and intraindividual variability. Ophthalmologica 181:165–9, 1980
130. Zrenner E: The physiological basis of the pattern electroretinogram. Prog Retin Eye Res 9:427–64, 1990
131. Zrenner E: Tests of retinal function in drug toxicity, in Hockwin O, Green K, Rubin LF (eds): Manual of Oculotoxicity Testing Drugs. Stuttgart, Fischer Verlag, 1992, pp 331–61
132. Zrenner E, Ziegler R, Voss B: Clinical applications of pattern electroretinography: melanoma, retinal detachment and glaucoma. Doc Ophthalmol 68:283–92, 1988

The authors thank J. Kremers for discussion, G. Drasch for the contribution concerning lead toxicity, and R. Hofer for technical assistance.

This work was supported by fortüne-Grant 707-0-0 (Tübingen, Germany) to HS.

The authors have no commercial or proprietary interest in any product or concept discussed in this article.

Reprint address: Dr H. P. N. Scholl, Department of Pathophysiology of Vision and Neuro-Ophthalmology, University Eye Hospital, Schleichstrasse 12-16, 72076 Tübingen, Germany. E-mail: hendrik.scholl@uni-tuebingen.de