Tissue Responses of the Monkey Retina: Tuning and Dependence on Inner Layer Integrity

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Recent technical and conceptual advances have made it possible to experiment with models of local human inner retinal disease and changes in very small, tissue-specific signals. Local retrograde degeneration of the ganglion cells was induced in four rhesus monkeys by 160° microdiathermy fiber layer burns at the nasal or temporal edges of the optic disc. There were no abnormalities of the classical electroretinograms (ERGs) during the following 210 days. With nasal lesions, pattern-evoked retinal (PERR) and cortical responses over a range of grating contrasts and spatial frequencies were largely normal. The authors found a cortical spatial tuning peak near 0.5 cycles/deg (cpd) and a retinal peak at 0.25–0.3 cpd. With temporal lesions, the retinal signals to high frequency stimuli (>1.0 cpd) approached zero between 20–60 days. The cortical evoked signal declined with a course similar to the retinal components. Histological evidence was found for extensive loss of ganglion cells and fibers in a central 30–40° temporal area, including the macula, 210 days after the temporal lesions. This is strong evidence that local ganglion cell-dependent electrical potentials, bearing little relation to the ERG, can be measured in response to selected stimuli. Invest Ophthalmol Vis Sci 27:734–745, 1986

During this century, research on the electrical action potential recorded from the vertebrate cornea in response to retinal stimulation (electroretinogram, ERG) has produced a body of literature which probably establishes this as one of the most thoroughly studied of all bioelectric signals. Much of the basic effort has been devoted to components and tissue origins of the signal, typified by Granit’s1 pioneering investigations of the signal changes accompanying physiological and chemical impairment of particular retinal cell classes. Early clinical research correlated tissue-specific retinal pathology to associated ERG abnormalities, as typified by Karpe’s2 reports from this period. The progression of this research has been traced in recent reviews.3 The resultant body of information on the cellular origins of the ERG, including more recent intra- and extracellular microelectrode studies,4-7 allows an understanding of retinal neurophysiology unparalleled by that of any comparable neural tissue. A feature of this impressive body of evidence and theory is the assignment of the traditional ERG to specific classes of glial and outer-retinal cells and insensitivity to inner-retinal, spatio-temporal neural processing and/or inner-retinal pathology. This generally and firmly held concept of inner-retinal independence probably influenced early interpretation of pattern-evoked corneal potentials as ERGs of unusually small amplitude due to reduced intraocular light scatter and/or photopic adaptation levels, both features of this stimulus configuration.8,9 Against this very structured background, Maffei and Fiorentini10 reported loss of pattern-evoked responses at the cornea, but normal flash-evoked ERGs, following induced optic atrophy in cats. Dawson, Maida, and Rubin1 said similar findings from a human patient with unilateral optic nerve section. In this, as in all clinical research on this subject, the selectivity of the lesions was assumed. Subsequently, research from both clinical (~90% of total) and basic science laboratories has demonstrated interrelationships between pattern-evoked retinal signals and inner-retinal pathology, spatial, and temporal stimulus properties (tuning) and independence of outer-retinal disease.12-17

However, not all findings support the association of PERR with inner retina and there is controversy on this subject. Normal PERR production in the presence of clinically diagnosed inner-retinal lesions has been reported.18 Depth recordings have not indicated an inner-retinal origin for pattern elicited potentials.19 Also, there have been theoretical arguments for outer-retinal...
origins of these signals. Clearly, these issues, inner-retinal dependence and cellular origin, remain unresolved, while many other questions have yet to be posed. For example, there are no data on effects of histologically verified, characterized, local, inner-retinal lesions in species having primate macular specializations, on central retinal/macular-specific lesions and responses, or on differentiation of components of the PERR. In order to address some of these problems, we have recorded macular PERRs and ERGs from the corneas of rhesus monkeys (Macaca mulatta) after microdiathermy lesions to a 160° arc along the temporal margin of the optic papilla (experimental), similar lesions on the nasal side (operated control) and no lesion (normal control), with histological verification of selective atrophy of the central retinal/macular ganglion cell population in the experimental group.

Materials and Methods

Five juvenile (aged 2-4 yr) rhesus monkeys (Macaca mulatta) from the Caribbean Primate Research Center were shipped to the AAALAC accredited facility at the University of Florida where they were housed in individual cages. All animal use in the research was consistent with the ARVO Resolution on Use of Animals in Research. The animals were clinically screened by ophthalmoscopy, under mydriasis and cycloplegia. Clinical electrophysiology was applied to detect any early degenerative outer retinal disease. All monkeys had clinically normal eyes.

Prior to electrical recording, each animal was fitted with a scleral ERG contact lens similar to that of Riggs. Special attention was given to the optical quality of the front surface so that normal resolution could be attained with corrections of no more than 2 diopters. There was a 4 mm artificial pupil. The cornea was anesthetized with topical proparacaine drops (Ophthaine; Squibb), cycloplegia and mydriasis was achieved and, under ketamine-xylazine anesthesia, the trachea was intubated. Atropine was administered IM to reduce secretions and a patent IV drip was established for fluid supplementation. Subsequent to the initial ketamine-xylazine anesthesia, tranquilization was produced with diazepam and muscular relaxation was achieved with pancuronium bromide. Small quantities of the ketamine-xylazine mixture were administered periodically to insure stable analgesia as indicated by EEG records. Respiration was assisted with constant monitoring to maintain end-tidal CO2 between 3.8 and 4.4%. Eye signals were recorded between the active corneal electrode and an indifferent electrode placed immediately to the eye at the lateral canthus. Signals could not be recorded at the right (OD) eye when the left (OS) eye was stimulated. Visual cortical signals were recorded by an active silver-silver chloride disc electrode attached with conductive paste to the scalp surface above the lunate gyrus. The cortical reference electrode was on the adjacent earlobe. A ground lead was attached to the forehead. After ophthalmoscopy, streak retinoscopy and the addition of corrective lenses, stimuli (2.5 Hz square wave, optically counterphased grating or 0.25 Hz flash) were presented to each eye on a 30° tangent screen at 1 meter. The square wave gratings had an integrated luminance of 1.4 log foot Lamberts (fL) with contrast adjustable from 17-52%. The flash stimulus originated from the diffused output of a Grass PS22 Xenon flash tube (Grass; Quincy, MA). Flash-integrated luminance of the tangent screen measured by a UDT photometer was 20 fL · sec. The tangent screen was 1/2 meter before a diffusely illuminated (~ 1.4 log fL) rectangular white curtain that subtended 100°. Eyes were aligned with the screen by centration of the reflex. Stimulation, electrical signal recording, and processing were otherwise as described earlier. Passband was 0.2-300 Hz (3db points) except as specified in Figure 1.

Peripapillary lesions were made in the fiber layer. Under sterile conditions and deep anesthesia a stele
rotomy was made at the pars plana. A bipolar diathermy electrode (Clinitex; Beverly, MA) was inserted under operating microscope control and microdiathermy lesions were made without touching the retina. Five or six white round spots about 0.2 disc diameters were made in a partial crescent to be confluent at the disc margin. Blood vessels were not involved in the lesions. The production of these lesions, their discrete nature, and the resulting nerve fiber bundle defects have been fully described.23

As described in Table 1, three monkeys had lesions placed over a 160–170° area at the temporal margin of the disc. One had a 160° lesion placed along the nasal margin of the disc and one remained as an unoperated control. The left eye of B-860 (nasal lesion) and the right eye of B-46 (temporal lesion) were enucleated after 210–220 days. The two eyes were fixed immediately following enucleation with the slow intravitreal injection of Karnovski’s solution. After 5 min the anterior segment was removed and the eye cups and 3-mm sections of the optic nerves were immersed in cold Karnovski’s solution. The flat mounted retina was embedded in Epon–Araldite and subsequently 1-2 μm, stained with toluidine blue, and examined by interference contrast microscopy. All monkeys were returned to the Caribbean Primate Research Center.

### Results

All eyes responded similarly to the local microdiathermy treatment. Animal B-41 and A-3 developed mild vitritis that was expressed primarily as a vitreal clouding which persisted for about 10 days and cleared completely. All animals showed ophthalmoscopic evidence of edema within 1 disc diameter of the lesioned area for approximately 20 days. In one (B-41) this was followed by very local gliosis in the region of the fiber layer up to half a disc diameter from the lesion. After about 30 days, in the temporally lesioned eyes there were changes in coloration of the arcuate area extending from the lesion margins toward, superior and inferior to, the macular area. These were interpreted clinically as indicative of changes in the fiber layer. These changes were not as evident on the nasal side (B-860), but the other sequelae were present. In B-46, B-41, and A-3 there was a clinical loss in “reflectivity” of the fovea during the final 50 days of the study. No retina or pigment epithelium changes were ever identified at any other retinal sites.

The electrophysiological record bandwidth is important in the resolution of the primate retinal response to pattern stimulation (PERR). The signals in Figure 1 were recorded with a lower frequency limit (digital filtering, exponential rolloff) at 0.2 Hz. Using the fast Fourier analysis and inverse transform it is possible to remove specific frequency domain information without altering phase. Repeated digital filtration (with due attention to sampling limits and artifacts) of the wideband (0.2–1 KHz) retinal signal (upper trace) yields a family of waveforms (lower traces) temporally related to the visual stimulus. The character of the wideband PERR (upper trace) provides a rationale for amplitude analysis of two components, P1 and N1. However, amplitude measures require subjective identification of peaks and, as inspection of this trace demonstrates, N1 amplitude may not be independent of P1 amplitude changes. Inspection of the lower five waveforms in Figure 1 illustrates that P1 is virtually eliminated if frequency information above 15 Hz is excluded, whereas little N1 information is lost if only frequencies from 15 Hz and below are considered. Thus, power spectral density offers a means for objective quantification of the signal and eliminating judgmental errors in peak detection with small signals. Isolation of the two components in the frequency domain, avoids the problem of amplitude dependence, allowing for meaningful component analysis. The wide band signals (upper trace) in these eyes typically show the small negative deflection (implicit time = 20 msec) preceding P1 and the small component (circled, Fig. 1) on the descending phase of N1. Modal implicit times for P1 and N1 are about 37 and 70 msec, respectively. All components were observed to vary with stimulus spatial frequency, contrast, focus, and luminance.

Figure 2 provides evidence for spatial selectivity in the rhesus eye. These are signals from B-46 before lesioning. Amplitudes (A) and power spectral density (B) of the cortical signal and retinal P1 and N1 are plotted against spatial frequency. Cortical signal amplitude was measured peak-to-peak, and P1 and N1 amplitudes were measured as described above. In the frequency domain, more than 80% of the total power was at the stimulus frequency harmonics, allowing use of a ‘total power’ measure with less intrinsic bias. In (B), total cortical power includes all power from 0.2–50 Hz, whereas retinal power was divided into totals in two bands, 2–11 Hz and 12–50 Hz. The smooth curves were ‘best fit’ (all standard deviations < 1.0, most < 0.5, scale units) by nonlinear regression analysis and all

### Table 1. Eye treatment—lesion status

<table>
<thead>
<tr>
<th>Animal number</th>
<th>OD</th>
<th>OS</th>
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<tbody>
<tr>
<td>B46</td>
<td>Temporal 160°</td>
<td>Normal</td>
</tr>
<tr>
<td>B860</td>
<td>Normal</td>
<td>Nasal 160°</td>
</tr>
<tr>
<td>B41</td>
<td>Normal</td>
<td>*Temporal 160°</td>
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<td>A3</td>
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<td>*Temporal 160°</td>
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<td>B42</td>
<td>Normal</td>
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* Post surgical vitritis.
functions are of the form \( y = A_1 + A_2 X + A_3 X^2 \). The total power measure in the 2–11 Hz band, roughly corresponding to N1, shows improved tuning relative to the N1 amplitude function and more nearly approximates that of the cortical signal. The P1 and 12–50 Hz tuning functions are generally less similar to the cortical functions than are those of N1 and the 2–11 Hz band. Although not this clear in all eyes under our stimulus and recording conditions, the presence of spatial tuning in all functions in Figure 2 establishes that this important property of the PERR is found in the rhesus eye. Spatial frequency tuning is a well-established characteristic of inner retinal function in many species, including man.

Typical retinal and cortical signals in response to a series of patterns (grating bar width = 0.3–3.4 degs) recorded over an extended pre- and post-lesion period for a lesioned-control (Nasal) animal are shown in the upper set of records of Figure 3. These do not differ significantly from the potentials from the normal control eyes. Day-to-day variations may be due to anesthetic level, image quality, and electrode placement. These are more pronounced in the cortical signals. A particularly good set of cortical records were obtained from B-860 (Nasal lesion) at +120 days. The peak positive signal here has an implicit time between 80 and 90 msec while the preceding negative trough occurred between 55 and 65 msec. These values parallel retinal counterparts described above (Fig. 1).

The differential effects of lesion site and duration on retinal and cortical signals are illustrated in Figure 3 by comparing data from experimental animal B-46 (Temporal) to lesion-control animal B-860 (Nasal). Retinal and cortical signals, particularly for the smaller gratings, are sharply reduced or eliminated by 120 days by lesions along the temporal margin of the optic papilla. Very large gratings (ie, 1–3.4°) with high (33% and 52%) contrast continue to produce PERRs after 210 days. But these responses were not recordable at lower contrast levels. Other features of this figure, consistent across all temporally lesioned animals (B-41, B-46, A-3), are that the P1 amplitude is usually smaller than the N1 amplitude, and there is a trend toward early, post-lesion, selective enlargement of N1. Polarity reversal in the cortical signal can occur from day to day, as a consequence of dipole “straddling” and small changes in electrode position.

Power spectral density was not routinely utilized to evaluate effects of lesions over time because the increased sampling requirements (large numbers of individual records) lengthened the recording sessions to a degree inconsistent with the animals’ welfare. However, other parameters emerging from the presentations in Figures 1 and 2, P1 and N1 amplitudes at spatial frequencies, change over time after temporal lesions.

Fig. 2. Tuning of PERR and cortical signals of the rhesus monkey. Grating stimuli counterphased at 2.5 Hz, 33% contrast. A, component analysis by amplitude is identified (P1, N1) in Figure 1. B, Analysis of (A) data in the frequency domain by power spectral density. Ordinate is total power in the bands 2–11 Hz or 12–50 Hz (retina), and 2–50 Hz (cortex). Cortical absolute value is scaled \( \times 0.5 \). Curves are fitted by nonlinear regression methods.
Fig. 3. Simultaneously recorded PERR (R) and cortical (C) signals from the rhesus monkey, before and after nasal (B-860) and temporal (B-46) retina lesions at the disc margin. Days are numbered relative to surgery. Grating stimuli were 0.3° (3.33 cpd) to 3.4° (0.29 cpd) in subtense with a 2.5 Hz counterphase rate and 33% contrast. Calibrations (temporal-10 days) refer to all signals.

Figure 4 presents mean signal ratios (lesion/control eye) for P1 (A), N1 (B), and cortical signals (C) from B-46 in response to 52% contrast gratings for the 210 days following surgery. Since the data in Figure 3 suggest that signal loss may vary with stimulus spatial frequency, mean ratios (n = 4) for low (<1 cycle/degree) and high (>1 cycle/degree) frequency gratings were plotted separately. Some SD limits have been drawn to indicate variance. Large variances (eg, A, day 40, low frequency) result from zero values in the sample. All data points are relative to the −10 day (pre-surgery) value, which was set to one. Lines are estimates of best fit. Where temporal lesions were present (B-41, B-46, A-3) trends were the same; decline—except N1—on the day of surgery (while under residual anesthesia) followed by relative hyperresponsiveness with rapid subsequent decline. Important specific points in this figure are that responses to high spatial frequency stimuli decay more rapidly than those to low frequencies, while the latter are generally more resistant to effects of temporal lesions, and that P1 and cortical responses to high frequencies vary in nearly identical fashion, while N1 lags slightly. Notably, there is poor correspondence between the behavior of the cortical re-
sponse and P1 and N1 under the low frequency stimulus conditions.

All temporally lesioned eyes produced significantly lower (P < 0.01) responses (stimuli 52% contrast and >1 cycle/degree) by 120 days. Normal animal (B-42) and nasal-lesion animal (B-860) showed only random variation of the various response ratios (lesion/control) at all contrasts during a similar 220-day period (not illustrated). At 33% contrast all temporal-lesion animals gave measurable 210-day responses (eye or cortex) only to low frequency stimuli. At 17% contrast and +120 days there were no responses to any pattern. Flash-elicited ERGs were always normal, but could have been contributed by nonlesioned retinal areas stimulated by intraocular light scatter. To confirm that outer retina can support normal ERGs when stimuli are confined to the area having inner retinal lesions, we increased the luminance (2.0 log fL) of the surround to differentially light-adapted peripheral retina and masked the stimulator to confine the flash (<1.0 fL \( \cdot \) sec) to the 30° central tangent screen (1.0 log fL). Under these conditions, the normal (OD) and temporally lesioned (OS) eyes (A-3) produced normal light-adapted ERGs of virtually identical amplitude, although no cortical signal was detected with stimulation of OS. When the stimulus flash was presented in the high luminance surround, with the central 30° screen masked, no ERGs or cortical responses were detectable on stimulation of either eye, whereas normal ERGs and cortical responses (both eyes) were recorded under this condition with reduction of the surround luminance to 1.0 log fL. The surround adaptation, therefore, effectively eliminated ERG production by the peripheral retina indicating that the ERGs recorded (OS) on central stimulation were from the same central area which was incapable of PERR production in response to high frequency and/or low contrast stimuli.

At the end of the 210-day period, and following tissue preparation, the plastic-embedded, flat-mounted retinas were sampled in the same way. Two or three samples for examination were taken from three sites: peripapilla, periphery (site of lesions), and intermediate (midway) between these two points. The samples were 3-mm diameter retinal buttons removed by motorized cutter from the plastic flatmount. Adjacent buttons were immediately superior to, centered on, and inferior to the horizontal meridian at each site. Figure 5, from the intermediate sample site of the temporal-lesion retina, shows a section from the most superior portion of the superior button, one from the middle of the central button and one from the most inferior portion of the inferior button. A few scattered cell bodies (G) appear to indicate ganglion cells in the most distal portions of the inner layer in the superior and inferior section. Elsewhere there are no ganglion cells or fiber layer.

'Cystic-like' (C) spaces occur only in the inner-nuclear layer of the central sections. These are presumed to have been the sites occupied by the large displaced ganglion cells described in the rhesus retina.24 Outer retinal layers, receptor outer segments, and pigment epithelium appear normal.

The only transretinal pathology occurred at the sites of the microdiathermy burns (not illustrated) where gliosis and fibrosis extended through the retinal thickness to the pigment epithelium. The radii of the burns extended 300–600 \( \mu \)m, where normal outer retinal layers began. Samples from the same positions in the nasal-lesion retina (lesion-control) showed no evidence...
Fig. 5. Retinal sections taken at the extremes and center of a 9-mm vertical segment (3 buttons) centered between the disc and fovea of monkey B-46, lesioned (temporal disc edge) eye. G and C indicate ganglion cell and "cystic-like" space, respectively. Toluidine blue stain, Epon-Araldite embedment, 2-μm section.

of abnormality. There was no evidence of pathological detachment in any tissue. Foveal sections from B-46 (Temporal lesion, A) and B-860 (Nasal lesion, B) are shown in Figure 6. A full complement of receptors, outer nuclear and inner nuclear layer cells, may be seen. The ganglion cell layer is 5–6 cells thick in the region immediately adjacent to the foveal pit of B-860 (B). In B-46 (A) the prominent parafoveal mound is missing with preservation of the inner plexiform layer, while a few scattered cells remain in the ganglion cell layer. Results at the intermediate sample sites were consistent with those in Figure 6 (central site). Samples from B-860 were normal whereas the fiber and ganglion cell layers in B-46 were absent.

Optic nerve sections confirm the retinal inner layer histopathology. Figure 7A shows a relatively local area (region N-N, 20–30%) with the fasciculated, normal optic nerve axons remaining in the section from B-46 (Temporal lesion). Elsewhere there are no fasciculated axons but moderately active gliosis is present. The results from B-860 (Fig. 7B) are almost the inverse. The area of gliosis and extensive destruction covers approximately 20–30% of the sample. The margins of the abnormal areas fade gradually into the regions where the normal, fasciculated axons appear. Direct spatial comparison of the two nerve samples is difficult. There is extensive atrophy of the B-46 nerve and consequentially a lower overall area.

Discussion

In these experiments we have created two types of local retinal lesions, each directly involving approximately the same amount of retinal tissue but very different areas of influence and degrees of inner-retinal layer involvement\(^\text{25}\); we then evaluated PERRs under each condition. We chose the rhesus monkey because of its similarity to human retinal structure, its fovea, its cone distribution, and the extensive elaboration of macular ganglion cell and fiber layer.\(^\text{26}\) The recent international activity in research on the PERR has been reviewed by Lawwill.\(^\text{27}\) Previously PERRs have only been recorded from humans, dogs, cats, and pigeons.\(^\text{8,21,22,28}\) Current fundamental and clinical interest in the inner and macular retina suggest the need for a model offering, in addition to the necessary structures, a good signal/noise ratio and spatial frequency sensitivity characteristics.

Our results from the rhesus eye establish that its PERR has electrical properties similar to those inferred from human data from this laboratory.\(^\text{11}\) Rhesus wide band signals contain complexities and small components (cf, Fig. 1) absent, with two notable exceptions,\(^\text{17,29}\) in published PERR waveforms, because of upper frequency constraints usually imposed to improve signal-to-noise ratios. Sharp band limitations can be very useful to isolate electrical components. But information may be lost. Waveform distortion and phase shifts can be introduced by active filters.\(^\text{30}\) We find that the rhesus eye offers excellent signal-to-noise ratios relative to human, without extensive filtering, as well as excellent spatial frequency sensitivity (see Figs. 1, 2). These species characteristics, when added to those noted above, identify special advantages for those interested in the tissue aspects of inner retinal physiology.

Some early reports on the PERR do not show strong tuning.\(^\text{31-34}\) Recently however, evidence of spatial processing similar to Figure 2 has become more common.\(^\text{17,35-37}\) Dawson\(^\text{22}\) describes contrast and rate-dependent tuning of inhibition of the PERR by windmill-like objects moving within the grating-stimulated field. Ringo et al\(^\text{38}\) did not find tuning of a pattern-elicited retinal signal in cat. Schuurmans and Berninger,\(^\text{39}\) conversely, found clear tuning functions in the perfused cat eye and a "striking similarity" of pattern ERGs and optic nerve responses (from 42 eyes). This deserves special notice since the traditional relationship between the flash stimulated ERG and optic nerve response has been very poor.\(^\text{40}\)

The human psychophysical contrast sensitivity maximum, at modest adaptation levels (~111 candles/
Fig. 6. Sequential sections of the rhesus parafovea. A, 210 days after temporal 160° microdiathermy disc-edge lesions. B, nasal lesions otherwise as A, one approximately mid-fovea, six approximately inferior rim. Sections are approximately 35 μm apart and 2 μm thick. Interference contrast microscopy, toluidine blue stain, Epon-Araldite embedding.
Fig. 7. Rhesus optic nerve sections taken approximately 4 mm from the globe. A, two hundred ten days after 160° lesions of the inner retina at the temporal margin of the disc. B, two hundred ten days after nasal lesions (otherwise as A). Regions where normal (N) and atrophic tissue merge are indicated. Interference contrast microscopy, 3-μm sections, Epon–Araldite embedment, toluidine blue stain, A and B, equal magnification.

All of our temporal-lesion animals showed initial retinal and cortical hyperresponsiveness followed by decline beginning the second week post-lesion. Arden et al. found a similar hyperresponse-depression sequence in early active human optic neuritis. Our results further indicate different decay rates for the major PERR components, differential effects of stimulus spatial frequency, and contrast on decay and differences in similarity of P1 and N1 decays to that of the cortical response. The observation (Fig. 4) that for low frequency/high contrast stimuli, the cortical response decays more rapidly and completely than either PERR component suggests that PERRs to low frequency/high contrast stimuli are less ganglion cell dependent than their high frequency/low contrast counterparts. Of course, not all ganglion cells were eliminated by our lesions, as indicated by the retinal and optic nerve histopathology. Surviving cells/axons in the lesioned area may account for a significant portion of the residual function apparent when very low spatial frequency, high contrast stimuli are presented. Differences in P1 and N1 post-lesion behavior and spatial frequency tuning may suggest different generators, but current understanding of this complex signal is inadequate to support more than speculation on this question or on the significance of the interesting small components seen in the wide band response.

The delayed effects of the lesions, even in transmission to the visual cortex, are surprising. This suggests a fiber population damaged but not immediately destroyed and that axon transmission failure may be a graded process that proceeds for at least 2 wk. This agrees well with the temporal decay of the high spatial frequency P1 component. Sommer et al provide clinical evidence for up to 5-yr delays in field loss in the presence of nerve fiber layer defects. James cut the optic nerve in rabbits intraorbitaly and found that most ganglion cells showed some chromatolysis at ten days. By the twentieth day only a few nuclear and cell body fragments could be found in the ganglion cell layer. By 30–60 days very large ganglion cells could only be seen rarely. These had disappeared by 120 days. Radius and Anderson reported that the ganglion cells and nerve fiber layer did not change noticeably during the first 2 wk after photocoagulation of the peripapillary axons of the monkey. By the end of 3 wk there was some decrease in ganglion cell counts, especially in the perimacula. After 4 wk the ganglion cell population had decreased significantly, and by 6 wk the degeneration had reached a plateau and was highly significant statistically. This time course appears to be consistent with the decay of the PERRs and cortical responses in our data. Overall, the results support the notion that ganglion cell body function may not cease immediately following damage to its axon, with the first effects appearing between 2–4 wk.

Microscopic examination of the lesioned retinas disclosed no multi-layer pathology involving outer retina or pigment epithelium, except immediately at the microdiathermy burn sites. Except for effects directly attributable to retrograde degeneration of the fiber layer...
and ganglion cells, all retina other than the burn sites appeared completely normal after 210 days. This evidence of outer retinal integrity in the lesioned eye was confirmed by the consistently normal flash (local and diffuse) ERGs in the lesioned eyes. Neither ERGs nor serial color fundus photographs gave evidence of ischemia, although the photographs showed large arcuate areas of “highlight loss” interpreted clinically as fiber bundle defects. Because of the optimal pigmentation of the rhesus fundus no special fundus photographic techniques were needed.

We did not find these spaces in nasal-lesion retinas. The only detectable effect of these lesions on outer retina was some distortion (not cell pathology) of a 100-μm region of the foveal outer nuclear layer (cf, Fig. 6A). Presumably, this was a mechanical effect of redistribution of inner plexiform tissue, Henle fibers and/or photoreceptor cell bodies subsequent to degeneration of inner retinal tissue (ganglion cells/fibers), although intermittent processing artifact cannot be ruled out. These observations clearly establish that our temporal peripapillary diathermy burns produced extensive fiber layer defects and elimination of the ganglion cell layer over the majority of the central retina, including the macula and fovea, with no significant effect on outer retinal structure. This conclusion is consistent with our understanding of fiber layer organization.

The inner layer pathology may indirectly affect the fundus appearance. As the lesions developed our ophthalmoscopic data indicated progressive loss of foveal reflexes in the temporal-lesion retinas. The primate medial parafoveal mound, prominent in the naso-lesion retinas, (cf., Fig. 6B), appears to be composed mainly of Henle fiber elaboration and, to some extent, inner nuclear layer tissue. According to Fine and Yanoff, the obliquely oriented Henle fibers (the foveal cone receptor axons) and the plexiform layer just distal to the primate inner nuclear layer form the outer plexiform layer. They do not describe a foveal mound in their rhesus material. However, Van Buren shows several examples of a medial mound in his human tissue (A57-261, A56-1, NA-25-51) but does not discuss it. The atrophy of the mound, with loss of its shadowing effect and loss of most of the foveal pit undoubtedly accounts for the loss of the foveal “reflex” during the post-temporal-lesion (+60 days) period.

In spite of the size and completeness of the inner retinal temporal lesions, the local ERG recordings establish the ability of the rhesus outer retina to produce normal signals in areas where the inner retina is atrophic. This is entirely consistent with current ERG theory (as discussed below) and suggests that major damage to the glial network is absent. Additionally, important relationships are established between our local lesions, PERRs, ERGs, and cortical signals initiated in the primate central retina.

The prime origin of the term electroretinogram is obscure. We have not found it used before the 1924 paper “Das Elektroretinogramm” by Kahn and Löwenstein. Magiot referred to the retinas “courant d’action” in 1922. And in America, Sheard and McPeek applied the term “electrical response of the eye” in 1919, which was adopted by Hartline in 1925 and as late as 1930 by Chaffee and Sutliff. Each of these authors clearly identified their signal with the retinal response to diffuse illumination. Until the first use of patterned stimuli in Riggs’ laboratory, there had been no deviation from this convention. It is not yet established that the signals recorded by Riggs and discussed in this paper have any close relation to the classical “ERG.” Indeed, the gathering evidence presented by authors using the “ERG” terminology to describe responses to patterns seems to argue against the relationship. The high precision of current vision research calls for a brief examination of this practice.

No alterations of the ERG have been found in patients with profound disease of the inner retina and optic nerve. Following pioneer findings of Karpe and many others, subsequent influential clinical volumes by Krill, Deutman, and recently Fishman do not discuss inner retinal implications of the ERG a- and b-waves, for it is well established that there are none. In the last 10 years there have been a few papers of clinical interest where ERG and inner retina are related. These involve the small ERG components called “minor components,” “oscillations” or “fast potentials” in stark contrast, during the last 3 years there have been numerous papers relating the pattern-evoked retinal response to diseases or abnormalities of the inner retina. A small sample includes amblyopia, optic nerve disease, glaucoma, multiple sclerosis, and traumatic optic atrophy.

The basic science background that has so strongly fused the conceptual linkage between the ERG and the outer retina has been described in full detail in chapters by Riggs, Tomita, and Granit in a recent volume. Riggs’ contribution to this volume was written in 1982; at that time, he did not discriminate between the ERG and the pattern-evoked retinal signal (which was first recorded in his laboratory). Another major contributor to the firm conceptual fusion between the “ERG” and the outer retina was provided in the now classic paper on potential distributions by K. T. Brown. Together with the elegant cellular proofs offered by Werblin and Dowling and by Miller and Dowling there seemed little remaining to spark controversy about the cellular origins of the ERG. But, Tomita and Yanagida provide more detail on the identification of additional...
current sinks provided by Müller cells and stimulated by potassium discharge from nearby retinal neurons. Intraretinal techniques similar to those used by Brown and Newman, Frambah, and Odette provide impressive evidence for the preeminence of the Müller cell endfoot for clearing of potassium. K+ injection there can cause large potentials in mid-retina distal to the site of injection. Together these form a promising potential mechanism for the involvement of the Müller cells in the consequences of processing of pattern information by the neurons of the inner retina.

Upon this basis, it is possible to develop a testable hypothesis that may be used to reconcile the distribution of the pattern-elicited potential in mid-retina with the inner retinal cell, pattern-signal interdependence. It is consistent to propose a mid-retinal potential change that is driven indirectly by inner-retinal neurons. In a process analogous to the interaction between the photoreceptors and Müller fiber elements of the outer retina, ganglion cells (and/or other inner retinal elements) may depolarize Müller cells indirectly by liberating potassium near their endfeet. This mechanism does not eliminate a possibility of direct contribution of the inner-retinal neurons to the "PERR" but encourages the consideration of a composite potential of summed neural and glial activity. In this way the PERR may share mechanisms with the ERG but arise from different origin(s). The PERR may be a complex sum of these (glial and neuronal) processes, whose regional balance and excitability is dependent upon both species and stimulus characteristics. A combination hypothesis involving both activated inner-retinal neuron, K+ extrusion, and secondary Müller cell potentials would serve to explain most of the existing data relating to PERR origin(s).

The disease sensitivities, stimulus characteristics and inner retinal cell viability associated with pattern-elicited retinal responses are very different from those traditionally associated with the ERG. The term used to describe these interesting action potentials is not important. But continued, indiscriminant use of the term "ERG" to describe pattern-evoked potentials may confuse students of retinal physiology for decades.

**Key words:** PERR, lesions, Macaca mulatta, retina, ganglion cells, macula, optic nerve, pattern, ERG, K+

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