Spatial differences in the human ERG

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Electronic computer techniques have been employed to enhance the recording of the ERG so that a sensitivity of 1 μv is attainable. A study of ERG profiles to 1 degree red and blue light stimulation of both normal and pathologic eyes indicates that: The normal ERG profile shows a high red sensitivity centrally that diminishes 15 degrees of either side of the horizontal meridian. The normal profiles to blue light show no significant spatial difference. At threshold the positive peak of the normal response to red light occurs at approximately 50 msec. The positive peak of the normal blue response is longer than 90 msec. even at amplitudes much greater than the red response. The former resembles the x-wave and the latter the b-wave of the higher amplitude ERG. Damage to the macula produces a lowering of the central response in proportion to the extent of the lesion and is more detectable with red light. Advanced retinopathies with markedly elevated ERG thresholds can be differentiated by spatial, temporal, and threshold differences in their summed low-level responses to chromatic stimulation.

The recent introduction of electronic computer techniques to the study of biologic information has opened new approaches to basic and clinical physiologic investigation. The detection of evoked electrical responses of the human nervous system with scalp electrodes and electrical enhancement methods is one example. Computers, termed evoked response detectors, employ the principle that when a number of responses, superimposed on random noise but "time-locked" to a stimulus, are algebraically summed only the response increases. The theoretical improvement in signal to noise discrimination varies directly with the square root of the number of summations, and results in a considerable increase in sensitivity. This technique has achieved its widest application in the study of evoked cortical potentials and it has not been until recently that Armington and associates have applied it to the study of the electroretinogram (ERG). The ERG is even more suited to this method than the evoked cortical or electroencephalographic (EEG) potentials since, occurring at a peripheral level in the nervous system, it is less dependent on the state of consciousness of the subject. The ERG is usually superimposed on considerable noise resulting predominantly from continuous extraocular muscle movements so that few conventional systems can detect responses less than 20 μv. By means of computer techniques, ERG responses of 1 μv are readily detectable.

This report shows how responses of this magnitude permit some spatial differentiation of the ERG of normal subjects. The ERG profiles of pathologic eyes with either normal or extinguished responses on conventional testing show deviations from those of normal subjects in a manner

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which reflects the location of the retinal pathology.

Methods

Conventional ERG, as well as computer techniques, were used simultaneously to study each subject. The signal to the computer was amplified 50 db by two preamplifiers in tandem with a bandwidth of 0.2 c.p.s. to 1 kc. The computer is a type of evoked response detector and is a modified version of the one originally described by Cox and Evarts. It employs a single operational amplifier connected sequentially across a series of condensers by electromagnetically driven glass reed relays. The ERG response is broken into small intervals, within which the signal is integrated by the operational amplifier and added to a storage condenser associated with that time interval. This process is repeated for a number of equal intervals successively following the stimulating flash. The process is repeated for each flash and a voltage, which reflects the temporal pattern of the ERG, is slowly built up on the storage condensers. The resolution of the response depends upon the number and the duration of the integrated periods. Theoretically, samples of any function limited to a bandwidth 0 to W c.p.s. can be completely described by a series of points \( \frac{1}{2W} \) second apart. In this system 3 msec. intervals were integrated every 6 msec. for a 90 msec. period following the stimulus, which affords good delineation of the s-wave at the 1 \( \mu \)v level and the rising phase of the b-wave at the 5 \( \mu \)v level at flicker rates of 4 c.p.s. The time constant of integration was 0.002 second. The build up of the response was continuously monitored on the tube face of an oscilloscope during each experimental session and photographs taken at 30 second intervals permitted an evaluation of the linearity of the response buildup. Responses which did not increase linearly were discarded and subjects who were consistently noisy were excluded from this study. A single test period lasted 2 minutes in which time the ERG responses to a 4 per second stimulus were summed. Calibrations were made by applying a known voltage at the input and summing for the duration of a test period. The system was quite linear within the response amplitudes measured. ERG amplitudes were measured from the initial negative to the subsequent positive peak of the response and profiles determined by comparing amplitudes at different locations of retinal stimulation.

A Grass stroboscopic stimulator (PS-1) with a specified maximum brightness of \( 6 \times 10^7 \) millilamberts and a flash duration of 10 \( \mu \)sec. was used. The diffuser on the stroboscopic face was occluded except for a circular area having a diameter of 2.4 cm. This test spot was placed in the center of an arc with a radius of 1 m, and its intensity varied either by switching the charging condensers of the instrument or interposing neutral density filters (Inconel). The red and blue absorption filters supplied with the Grass instrument were used routinely. The former transmitted little light less than 600 mp and the latter had a peak transmission at 450 mp, transmitting less than 1 per cent above 570 mp. A dim red light which could be shifted along the perimeter was used for fixation during stimulation of the more peripheral retina. The test light subtended 1 degree 20 minutes (referred to subsequently as 1 degree) and the fixation light 10 minutes. Routinely, three different retinal locations were stimulated along the central horizontal meridian, the fovea, and 15 degrees both nasally and temporally. No correction was made for the effective pupilary diameter which does not vary markedly within the relatively narrow central range studied.

A methyl methacrylate ring and metal electrode of our own design was routinely used in place of a contact lens electrode. It is light, fitted to the sclera and cornea, and has an outer diameter of 20 mm. and a circular corneal window 10 mm. in diameter. The electrode is a polished 4 sq. mm. silver surface contacting the lower nasal quadrant of the cornea about 2 mm. from the limbus. The corneal surface is moistened by blinks which the subject is requested to do between test periods. The reference electrode is a stainless steel button held firmly on the central forehead by a head strap. The left ear lobe was grounded. Ophthaine (proparacaine hydrochloride, 0.5 per cent) and methyl cellulose (0.5 per cent) were used with the corneal electrodes and Sanborn electrode paste with the skin electrodes. Noosynephrine (10 per cent) was used only for mydriasis in patients with markedly diminished responses.

The ERG profiles of seven normal adults were compared with those of patients with retinal pathology. The patients were all comprehensively studied by the Ophthalmological Service of the National Institutes of Health. All subjects were routinely tested a few minutes after turning off a room light of 40 foot-candles, first foveally, then extramacularly, and finally the central stimulation was repeated. This was done first with red and subsequently with blue light. The final stimulus was the central blue spot and occurred approximately 20 minutes after the room lights were extinguished. Because of adaptational changes noted, especially with blue light testing even after 20 minutes of relative darkness, only the last central response was compared with those of the periphery. The patient sat on a comfortable, rotatable chair with a head rest, and in the same plane as the test light. The chair was rotated in the direction of the fixation light during extra-
macular stimulation to eliminate shifts in the recording electrode.

Results

Normal ERG profiles. The typical oscilloscopic buildup of the responses of a normal subject to testing with 1 degree red and blue lights is shown in Fig. 1. The pattern of the responses and the linearity of the buildup are typical for these different testing conditions. The red response is triphasic, being successively negative, positive, negative, and the response from the central retina shows this most characteristically. The blue response is a slower, diphasic wave, initially negative and then positive, and the response sampled by the computer represents only 30 per cent of a response which is almost sinusoidal at the stimulus frequency of 4 c.p.s. The range of normal ERG profiles to 1 degree red and blue testing along the horizontal meridian is shown in Fig. 2, where the mean amplitude and standard deviations of the responses of seven normal adults are plotted.

The profiles obtained with red light show a maximum amplitude centrally (3 ± 0.9 \( \mu \text{V} \)) and a symmetrical, almost 50 per cent reduction both 15 degrees nasally (1.5 ± 0.8 \( \mu \text{V} \)) and 15 degrees temporally (1.6 ± 0.4 \( \mu \text{V} \)). The difference is significant (\( P > 0.01 \)) and indicates objectively that the central retina has a relatively high sensitivity to red light. There is no significant difference between the responses of the extramacular retina with this technique al-

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**Fig. 1.** Oscillograms of the summation of normal responses to 1 degree red (R) and blue (B) light stimuli at 4 c.p.s. The subscripts T, C, and N signify 15 degrees temporal, central, and 15 degrees nasal field stimulation, respectively. The upper trace is the summed response of the computer, and the lower the response to single flashes. A number of traces are superimposed in each record. A blink artefact is apparent in Bo, 90 sec. Bo, demonstrates the large buildup to a stimulus 4 times threshold. The calibration (CAL.) shows the buildup of 1 \( \mu \text{V} \). The trace durations are 100 msec.

**Fig. 2.** ERG profiles to 1 degree red and blue lights. The ordinates in microvolts (\( \mu \text{V} \)) are each related to a fixed intensity of light stimulation. The hatched area indicates one standard deviation above and below the mean values of seven normals. The code for the abnormal profiles is O, • central uveitis; \( \Delta \), • retinitis pigmentosa; \( \nabla \), V congenital nyctalopia; □, ■ chloroquine retinopathy.
though the temporal field stimulus is in the area of the optic disc.

The ERG sensitivity to blue light in contrast to the red continues to increase even 20 minutes after the subject has been in a room, dark except for the dim intermittent 1 degree stimulation. The blue profiles are flatter and show no significant difference with the area of stimulation (Fig. 2).

At threshold, the latency of the peak amplitude of the positive response to red light is approximately 50 msec. and resembles the x-wave of the higher amplitude photopic response (Fig. 3). The peak latency of the positive response to blue light is 90 msec. (Fig. 3) or longer, even at amplitudes much greater than the red response, and resembles the scotopic b-wave.

Macular degeneration. Both hereditary macular degeneration and central uveitis have been studied. In the former, the ERG profile to 1 degree red light is lower and flatter than normal and in advanced cases is undetectable. In central uveitis, the red profile is also lower, but, if the lesion is localized, an inversion of the profile may occur so that the extramacular responses are as large as, or larger than, those to central stimulation. The ERG profile to 1 degree blue light is closer to normal in both these conditions, although abnormalities may be found, especially with central stimulation.

The ERG profiles of a patient with a central uveitis are plotted in Fig. 2 (○, ●). This lesion was well demarcated and computed from photographic measurements to involve 13 sq. mm. of central retina. Tangent screen perimetry with a test object 10 mm. in diameter demonstrated a symmetrical central scotoma extending 11 degrees from the center of vision at its widest margin. The ERG profiles to both 1 degree red and blue light are reduced centrally with a slight inversion of the red profile apparent. The implicit times of the positive threshold responses are normal (Fig. 3).

Retinitis pigmentosa. This retinopathy is characterized by a markedly diminished ERG with a close correlation existing between the ERG sensitivity and the amount of functioning retina. Typically, the thresholds for both blue and red ERG profiles are elevated with the greatest deviations from normal occurring with extramacular testing.

The ERG profiles of a patient with advanced retinitis pigmentosa are plotted in Fig. 2 (▵, ▲). This patient had a central island of vision with a visual acuity of 20/20. Tangent screen perimetry with a test object 10 mm. in diameter demonstrated a central field limited to 14 degrees from fixation at its widest extent. Goldmann perimetry indicated no peripheral vision with a test object of 4 sq. mm. There was an elevated monophasic dark adaptation curve and a subjective retinal profile with high thresholds to blue light peripherally. Ophthalmoscopic examination revealed bone corpuscular pigmentation and attenuated retinal vessels. The ERG profile to 1 degree blue light was markedly elevated and the profiles to both chromatic stimuli were peaked centrally.
The implicit times of the positive responses at threshold to both chromatic stimuli were simultaneous at 50 msec, in contrast to the differences of normal responses (Fig. 3).

There is a similarity between the ERG profiles of this patient and those of a congenital nyctalope also plotted in Fig. 2 (\( \triangleleft, \nabla \)). This patient exhibited a high ERG threshold to blue light, with central peaking in the ERG profiles but not as pronounced as those of the patient with retinitis pigmentosa. The congenital nyctalope has no scotoma demonstrable by perimetric testing. The implicit times of the threshold positive responses to both chromatic stimuli were also simultaneous at 50 msec (Fig. 3).

**Chloroquine retinopathy.** This retinopathy has been reported in patients who have prolonged treatment with chloroquine and is characterized clinically by attenuation of the visual fields with early macular involvement. Recent ERG findings show a marked diminution in the x- and b-waves and a slight increase in the a-wave. In this study there is, correspondingly, an overall elevation of the thresholds of the positive responses, and, in contrast to retinitis pigmentosa, it is more marked for red than for blue light.

The ERG profiles of a patient with chloroquine retinopathy are plotted in Fig. 2 (\( \square, \cdot \)). This patient had an extremely small central field with an acuity of 20/30. Tangent screen perimetry with a test object 3 mm. in diameter demonstrated a 1 degree central field and a nasal island approximately 10 degrees from the fixation point. Goldmann perimetry with a 64 sq. mm. test object showed peripheral constriction of the visual fields with bitemporal scotomas. Ophthalmoscopic examination revealed some attenuation of the retinal vessels. The dark adaptation curve was normal and subjective retinal profiles were difficult to obtain. The ERG profiles showed an elevated threshold to both red and blue light. The response to 1 degree red light was markedly reduced at all retinal areas, whereas that to blue light was most reduced with temporal field stimulation (Fig. 2). The implicit times of the positive responses at threshold to both chromatic stimuli were greater than 90 msec (Fig. 3).

**Discussion**

This study indicates that the increased sensitivity afforded by computer techniques allows some spatial differentiation of both the normal and pathologic ERG. Threshold responses to 1 degree red light are localized to the central retina and have a relatively short implicit time or peak latency. Such localization has been obtained recently by Armington and associates using similar electronic techniques and stimulating with 1 degree orange light at 20 c.p.s. in a Maxwellian viewing system. The present study shows that the localization is detectable with longer wavelengths at flicker rates as low as 4 c.p.s. and with the simpler non-Maxwellian system. The high red sensitivity of the central retina confirms other objective measurements of human photopigments by reflection densitometry. This low-level response to red light is closely related to the x-wave or photopic response of higher amplitude ERG because of its relatively short implicit time and long wavelength sensitivity. To date, the evidence which links the x-wave with the cones has been its relatively high red sensitivity and its association with photopic vision. Although there was an earlier report showing that a slight area difference in the x-wave was detectable at the 25 \( \mu V \) level in trained observers, the recent marked spatial differences of this wave at lower response levels indicates more clearly its close relationship to the distribution of cones in the retina.

The ERG to 1 degree blue light is a slower, less localized response which is more sensitive to the level of adaptation and undoubtedly represents the b-wave of larger amplitude ERG's. Since the central blue response is always measured last during a time when dark adaptation is still
progressing but is, nevertheless, never larger in amplitude than the more peripheral responses (Fig. 2), this suggests that it either adapts more slowly or that the central retina has a lower sensitivity to blue light. Such spatial differences may become more distinct with prolonged dark adaptation and greater sensitivity in response detection. An increase in the blue sensitivity of the present system can be obtained by prolonging the sampling time beyond 90 msec to include the implicit time of the threshold blue response.

The poor localization obtainable with blue light may be partly due to factors other than the sensitivity of the present system in detecting low amplitude b-wave responses. There is greater physical scattering of blue light which would tend to stimulate areas of retina other than those tested.14 In addition, scattered and reflected light would be more effective in stimulating the rods than the cones because of the Stiles-Crawford effect. The gradients in cone density across the retina are sharper than those of the rods16 so that spatial differences might be more easily detectable when the former system is predominantly responsible for the ERG response.

The fact that the optic disc was not detectable with either 1 degree red or blue mapping indicates the limitations in the resolution of the present technique. The red response diminishes so much 10 degrees from the fovea that comparisons between the responses of the blind spot area and those of the corresponding temporal retina are difficult. There are factors, however, other than the optic disc which tend to distort the symmetry of the ERG profiles. The effective pupil size is larger for temporal than for nasal field stimulation at 15 degrees.8 There is evidence that a reference electrode on the central forehead favors the detection of responses from the nasal retina.13 There is also an asymmetrical distribution of photoreceptors along the horizontal meridian with a higher cone density extending further in the nasal direction,16 and the highest rod densities surrounding the optic disc. In addition, the high reflectance of the disc itself may produce responses in nonfocal areas of the retina as the tapetum of some nocturnal vertebrates.

The utilization of this technique to study pathologic maculas widens the scope of the ERG as a clinical tool. Although there are reports that ERG detection of macular degeneration is possible with diffuse light stimulation,10,17 the abnormality may be more discernable with electronic averaging. The results of this study indicate that a central retinal lesion of approximately 13 sq. mm. may now be detected. The contrast between these cases of retinitis pigmentosa and chloroquine retinopathy, both of which had markedly diminished ERG’s, demonstrates the increased dynamic range of this method.

There are some limitations to this technique, however, which were particularly impressed upon the experimenters. The response, representing an average, may not always resemble those to single stimuli, especially if changes occur in both the latency and implicit times of the response as summing progresses. Either dark or light adaptation can produce such changes. As the intensity of stimulation is increased to elicit response from abnormal retinas, a noticeable degree of light adaptation may occur during the summing period. This effect has been particularly obvious in cases with high ERG thresholds and a disproportionate preservation of peripheral retina.

Although the signal to noise enhancement theoretically increases with the square root of the number of responses summed, the absolute sensitivity depends upon the actual signal to noise ratio. It is difficult to quantitate the noise of a subject. The means used in this study were both to monitor raw records continuously on an ink writer and also to ascertain the linearity of the response buildup by taking serial photographs of the computed response. These measures could be replaced by a separate computer channel programed to determine the standard deviation of the
average response. It is noteworthy in this respect that, even in pathologic conditions of retinas, the average wave form appears similar enough to the large amplitude photopic and scotopic responses that any marked deviations from this pattern must be interpreted cautiously, whereas similarities suggest reliability.

The duration of the test period is important since subjects are requested to fixate and subdue blinks during this time. There was an obvious increase in noise during the latter part of the 2 minute test periods and any longer durations might be expected to be correspondingly less useful. Increasing the rate of stimulation could shorten the summing time, but then attenuation of response would occur, especially in the case of the slow scotopic response.

In a number of cases of particularly quiet subjects with apparently well-maintained fixation, a rhythmic nystagmus is often detected in the continuous unsummed ink writer recordings. In all cases this movement has a frequency of approximately 1 c.p.s., and, although producing no apparent change in the summed ERG responses to 4 c.p.s., stimulation indicates that eye movements may produce voltages that are closely linked to either the rate or a submultiple of the rate of photic stimulation. Such artefacts are more difficult to eliminate than random noise and may become more obvious as greater increases in sensitivity are sought.

Despite some of the limitations associated with this technique, however, the results of this study indicate that it should eventually prove to be an important adjunct to clinical ERG laboratories.

REFERENCES