RETROSPECTIVE STUDY OF HYPERABNORMAL (SUPRANORMAL) ELECTRORETINOGRAPHIC RESPONSES IN 104 PATIENTS*

BY *John R. Heckenlively,* MD, *Troy Tanji,* MD (BY INVITATION), AND (BY INVITATION) *Sangeeta Logani,* MD

INTRODUCTION

THE ELECTRORETINOGRAM (ERG) IS A WELL-KNOWN TEST USED COMmonly in ophthalmology to diagnose or to assist in the understanding of a number of retinal disorders. The standardized protocol for testing involves performing a light-adapted photopic (cone-isolated) ERG, and after dark-adapting the patient for at least 30 minutes, using a dim flash to stimulate a rod ERG and a bright stimulus to stimulate a mixed cone and rod response.[1] A flicker stimulus at 30 Hz is commonly used to further assess cone function.

Diagnostic patterns of dysfunction may be seen that can greatly assist in understanding a patient's problem[2]; common examples are generalized poor responses in retinitis pigmentosa, negative wave forms in congenital stationary night blindness and X-linked juvenile retinoschisis, and poor photopic but normal scotopic responses in cone dystrophies. The ERG is commonly ordered when there are signs of retinal degeneration that lead the clinician to believe the test may help to clarify the diagnosis. The interpretation of the ERG generally involves looking for below normal or poor responses, and for the most part, responses larger than normal have been ignored and treated as "normal" or a normal variant.

The concept of what is "normal" may be more difficult to establish than might be realized; does one randomly recruit 100 people from the street and do ERGs to establish normal values, or is it better to inspect the eye first to

**From the Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles.

avoid performing the test on any subject who shows any ocular abnormality? The latter approach is generally preferred by most visual physiology laboratories, yet it is still possible to miss identifying retinal disorders that are microscopic in nature or that may involve intracellular dysfunction without discernible changes on ophthalmoscopy.

To establish normal values, most laboratories run a set of subjects with normal eye examinations, recording the amplitudes and implicit times of the a- and b-waves for each test parameter (rod ERGs do not have measurable a-waves). These values are subjected to analysis to ensure that there is a bell-shaped distribution curve common to physiologic measurements, and values two standard deviations above and below the mean are taken to be abnormal. Because normal ERG studies have demonstrated some amplitude and implicit time changes with age, age-adjusted values are commonly used.[3,4]

In this retrospective study, we evaluated cases referred to the UCLA Visual Physiology Laboratory who had large ERG responses that fell at or above the two standard deviation mark to see what type of ocular problems they had that might account for or be associated with their abnormally large responses. As part of this review, we were interested in whether hyperabnormal (supranormal) ERG responses should be interpreted as normal.

PATIENTS AND METHODS

As an essential component of this study, we reexamined our normal control data. These ERG values consisted initially of normal subjects who were recruited for establishing normal laboratory values, but then as there were referrals of patients who had ERGs that were normal by these initial standards, or patients with one good eye that was used as a control against a bad eye, these cases were added to the database only if they had a normal ophthalmoscopic examination. While these additions did not provide as rigorous normal control data as is ideal, they provided reasonably normal data and this practice commonly was used by large numbers of universities around the world during this period.

A total of 242 normal subjects were analyzed; distribution curves, means, normal ranges, and standard deviations were calculated for the group and by gender. Ranges and maximum values were established for b-wave amplitudes which were equal or greater than 2 standard deviations by age-group (Table I, Fig 1). The maximum value can be identified on the righthand side of each range for b-wave amplitudes. As examples, an 18-year-old man would have to show a photopic b-wave amplitude $\geq$ 244 μV, or a 43-year-old woman would need a bright flash dark-adapted b-wave amplitude $\geq$ 666 μV to be included in the study.

TABLE I: ERG NORMAL RANGE*
(DETERMINED BY NORMAL ± 2 SD OF EACH PARAMETER)

Photopic a-wave amplitude

Age	Male	Female
0-20	30-94	36-109
21-40	33-91	37-94
41-60	29-78	33-89
61+	19-105	30-78

Photopic b-wave amplitude

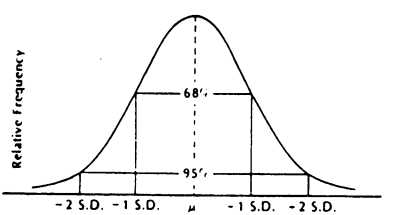
Age	Male	Female
0-20	96-244	95-282
21-40	85-223	95-225
41-60	86-186	85-212
61+	75-217	109-178

Photopic a-wave implicit time

Age	implicit time
0-20	12.2-14.3
21-40	12.0-14.8
41-60	12.7-14.9
61+	12.7-15.4

Photopic b-wave implicit time

Age	implicit time
0-20	28.8-34.4
21-40	28.9-33.5
41-60	29.6-35.6
61+	29.6-37.2



Scotopic b-wave amplitude

Age	Male	Female
0-20	213-515	240-512
21-40	205-463	232-575
41-60	187-449	220-565
61+	156-432	181-443

Scotopic b-wave implicit time

Age	implicit time
0-20	63.0-86.9
21-40	61.5-96.6
41-60.	69.3-97.5
61+	71.1-100.9

Bright flash a-wave amplitude

Age	Male	Female
0-20	156-336	176-387
21-40	160-369	160-358
41-60	164-330	148-368
61+	118-340	132-327

Bright flash b-wave amplitude

Age	Male	Female
0-20	276-756	419-698
21-40	355-639	338-717
41-60	255-655	339-666
61+	303-612	321-617

Bright flash a-wave implicit time

Age	Male	Female
0-20	20.0-22.9	19.7-23.2
21-40	20.7-23.1	19.9-21.0
41-60·	20.4-23.4	19.6-23.3
61+	21.5-24.4	20.6-24.3

Bright flash b-wave implicit time

Age	Male	Female
0-20	39.8-52.5	41.1-58.3
21-40	39.6-55.2	40.7-56.2
41-60	42.3-51.8	47.0-58.6
61+	46.8-53.7	46.8-58.9

*Normal electroretinographic ranges for control male and females divided by age groups. Highest amplitude for each gender and age group was used as the cut-off value for inclusion in this study. On the left center is a standard bell-shaped distribution curve illustrating the concept of 95% of the population would be considered normal, while those outside the two standard deviation would be abnormal.

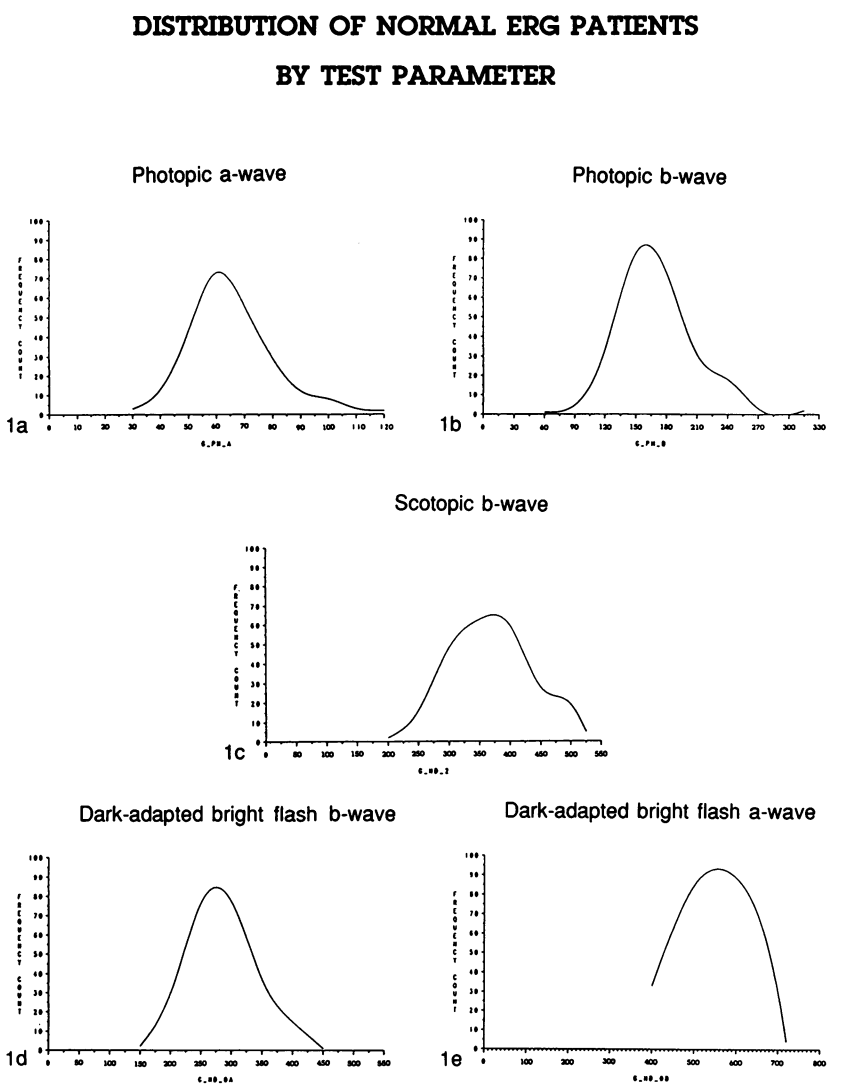


FIGURE 1

A-E: Distribution curves for 241 normal control patients evaluating their photopic a- and b-waves, scotopic b-wave, and dark-adapted bright flash a- and b-wave amplitudes. Normal population distribution curves were generally seen (see Results).

Between 1979 and 1993, over 5,000 ERGs were performed on patients referred to the UCLA Visual Physiology Laboratory. These ERGs were screened by gender and age bracket for patients who had hyperabnormal b-wave amplitudes that were ≥ 2 SD. The photopic, scotopic rod–isolated, and dark-adapted bright flash ERGs were all included as parameters; the minimum qualification for patient selection was a single amplitude in one eye that was hyperabnormal (≥ 2 SD). Once identified, patient records were evaluated to assured that there was adequate information, including fundus photographs, for the retrospective analysis.

Charts were examined to identify aspects of the history or clinical findings that could be related to the associated finding of a hyperabnormal response. The pertinent findings were categorized by the most prominent feature. In particular, the fundus photographs and fluorescein angiogram were carefully evaluated for pathology.

CASE REPORTS

CASE 1

A 55-year-old Hispanic man presented with complaints of decreasing visual acuity. History revealed an alcohol consumption of seven scotches a day for about 20 years. On examination his best-corrected visual acuity was 20/70 OU. Fundus examination revealed multiple round yellow-white deposits at the level of the retinal pigment epithelium in the foveas OU (Fig 2A). The fluorescein angiogram demonstrated numerous basilar deposits in the posterior pole as well as foveal edema (Fig 2B). On late phases both nerveheads had a sliver of intense temporal disc staining. His ERG demonstrated hyperabnormal scotopic b-wave amplitudes and dark-adapted bright flash a- and b-wave amplitudes (Fig 3 composite). The diagnosis was macular degeneration with basilar laminar drusen OU.

CASE 2

A 25-year-old college student complained of intermittent blurry vision. Family history was negative for any other affected person. On examination her visual acuity was 20/25- in each eye. Ophthalmoscopy demonstrated focal areas of dropout in the perifoveal regions with some flecklike deposits. The fluorescein angiogram showed the dark choroid effect, window defects in the perifoveal regions, and on late phases an intense staining of the temporal optic nervehead (Fig 4). Her ERG showed hyperabnormal scotopic and bright flash dark-adapted b-wave amplitudes (Fig 3). Although the ERG was not typical of most cases, fundus findings were consistent with Stargardt's disease.

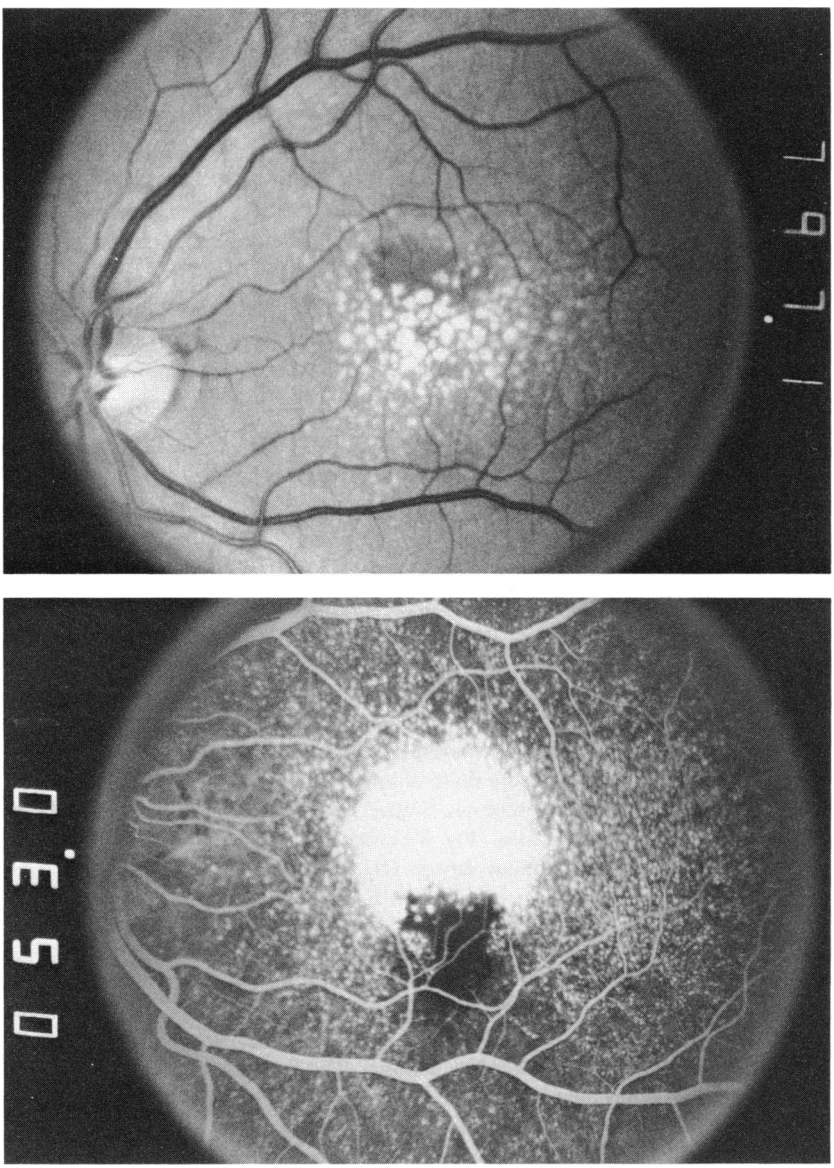
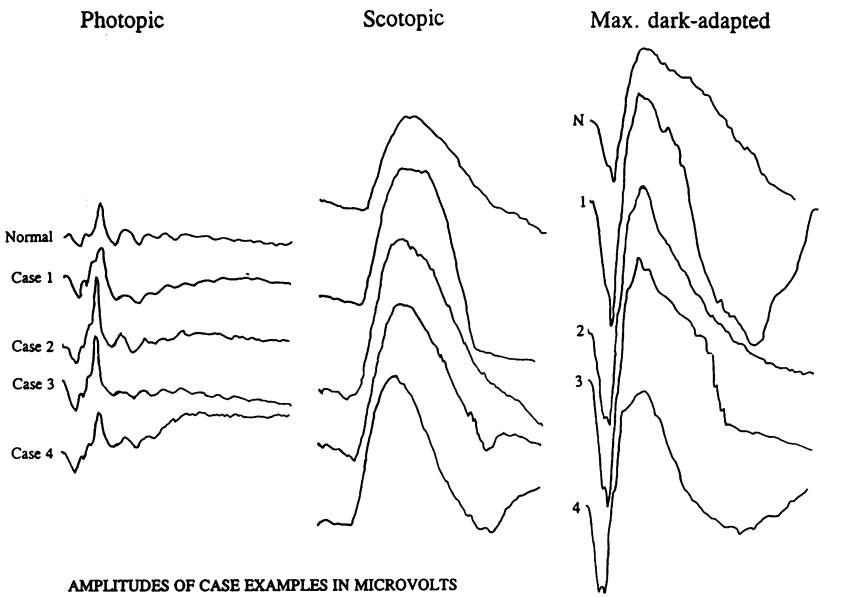


FIGURE 2
Case 1. Fundus photograph (A) and fluorescein angiogram (B) of left eye of 55-year-old man with macular degeneration and basilar laminar drusen in posterior pole. Late phases (not shown) demonstrated intense staining of temporal nerve head.



AMPLITUDES OF CASE EXAMPLES IN MICROVOLTS

Case	Photopic a-wave	Photopic b-wave	Scotopic b-wave	Max. dark-adapted a-wave	Max. dark-adapted b-wave
Normal	51	141	385	207	422
Case 1	74	164	450	402	753
Case 2	57	271	496	308	773
Case 3	94	230	527	414	809
Case 4	62	191	476	253	648

Out of 2 standard deviation range (age-matched) values are underlined.

FIGURE 3
Composite illustration of normal and four case examples of hyperabnormal electroretinograms from one eye. Amplitude values are listed below waveforms.

CASE 3

A 27-year-old woman had a 1½-year history of blurred vision. She had a history of headaches and photosensitivity. On examination the visual acuity was 20/200 in each eye. Fundus examination revealed a blond fundus and optic pallor OU. There were some granular changes and atrophy in the foveas OU (Fig 5A), and the fluorescein angiogram showed minor window defects in the maculae and an intense late staining of the temporal optic nervehead OU (Fig 5B). The ERG demonstrated hyperabnormal photopic, scotopic, and bright flash dark-adapted responses (Fig 3).

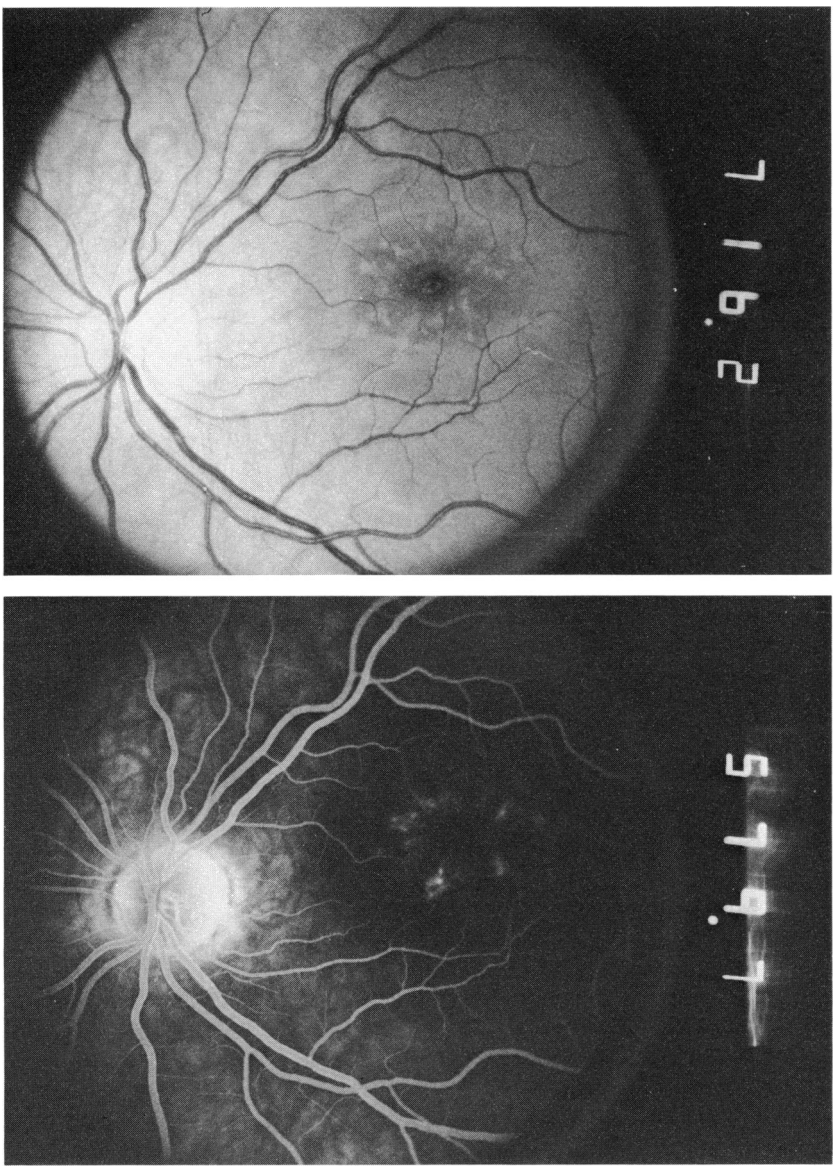


FIGURE 4

Case 2. Fundus photograph (A) and fluorescein angiogram (B) of right eye of 25-year-old woman with Stargardt's disease. Patient had flecklike lesions in perifoveal region and on fluorescein angiogram, dark choroid effect and minor window defects in region with flecks. Notable was intense late staining of temporal optic nerveheads OU.

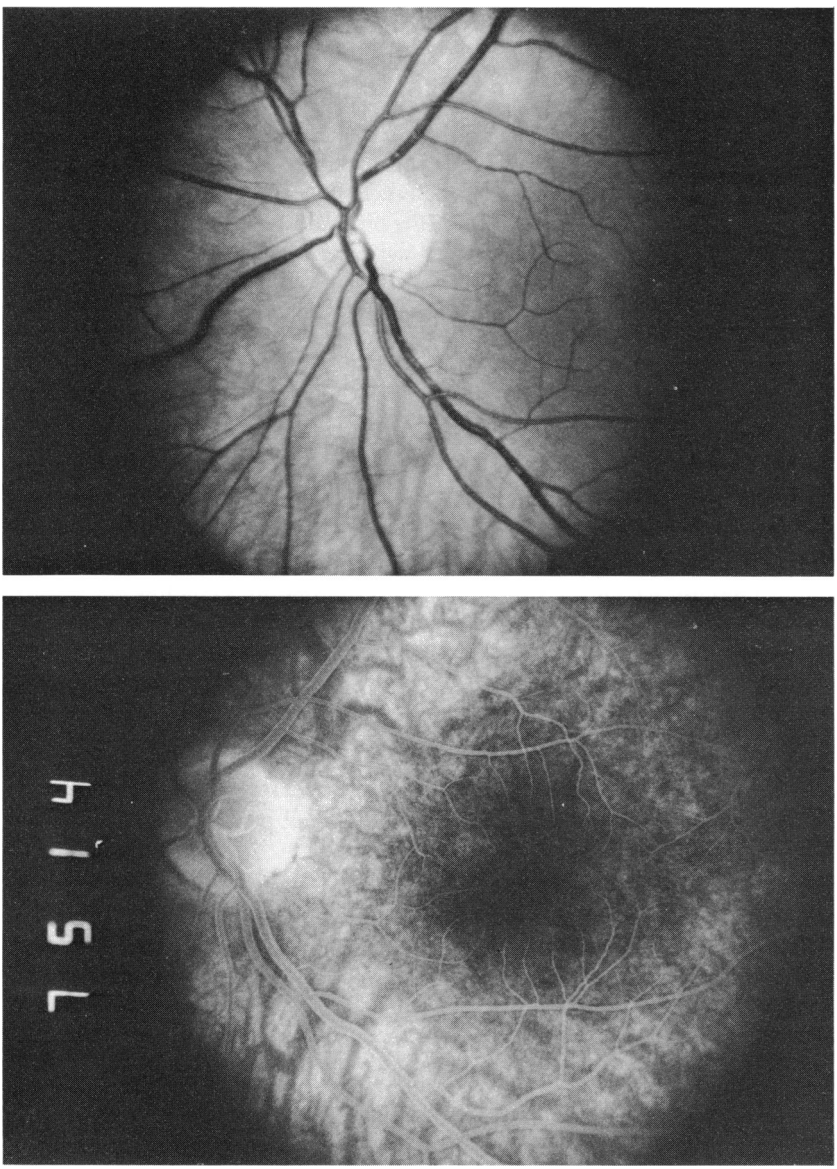


FIGURE 5
Case 3. Fundus photograph (A) and fluorescein angiogram (B) of left eye of 27-year-old woman with optic neuropathy with history of headaches and photosensitivity. Optic pallor was evident on funduscopy, while on late phases of fluorescein angiogram intense temporal staining was seen in optic nerve head.

CASE 4

A 72-year-old woman with atrophic macular degeneration had been followed routinely for 8 years. At the time of her ERG, visual acuity was 20/20 in both eyes owing to intact foveal islands. Fundus examination showed scalloped loss of the retinal pigment epithelium in the perifoveal region and hyperpigmented intact fovealar tissue, with scattered crystalline-like drusen in the posterior pole (Fig 6A). The fluorescein angiogram showed window defects in the perifoveal region and an edge of temporal staining of each optic nerve (Fig 6B). An ERG was ordered because of the symmetric foveal central involvement and some complaints of photosensitivity. The ERG demonstrated hyperabnormal photopic, scotopic, and bright flash dark-adapted b-waves (Fig 3), an unexpected finding in an elderly woman with atrophic macular degeneration.

RESULTS

The 242 normal controls were plotted on frequency distribution curves, and all had reasonably normal bell-shaped distributions (Fig 1A through E). There were 139 females and 103 males. The photopic and rod scotopic b-wave distribution appeared to be slightly bimodal (Fig 1B and C), with higher-amplitude values represented more frequently. The photopic a-wave distribution has a long tail on the high end; both these latter findings suggest that some patients were marked as normal but had hyperabnormal responses that were not appreciated at the time of testing. If true, this occurrence would only move the cut-off point lower for determining the 2 SD cut-off for hyperabnormal. The normal ranges for the amplitudes and implicit times by gender and age are listed in Table I for the photopic, scotopic, and bright flash dark-adapted ERGs, all performed on the same equipment using a standard protocol.

In searching our records, 381 patients were found to have a response > 2 SD in at least one ERG parameter. Because we are a referral laboratory for testing, the number of complete charts available for examination was limited; however, 104 patients with hyperabnormal responses were found to have adequate information to allow a full review of their clinical findings. In classifying their ophthalmologic findings the following categories and numbers of patients were found (Table II): maculopathies, 22 (22%) of all types, including 4 patients with Best's disease; optic neuropathies, 19 (19%); retinitis pigmentosa suspect or carriers, 20 (20%), including 5 who were known carriers and 2 patients with family histories of retinitis pigmentosa; panretinal degenerations (other than maculopathy), 7 (7%); color blindness or cone dysfunction, 6 (6%); drug toxicity, 6 (6%); neurologic referrals of ataxic patients, 3 (3%); posttrauma, 5 (5%); aniridia, 3 (3%); and miscellaneous findings, 13 (13%) including 2 patients with congenital nystagmus.

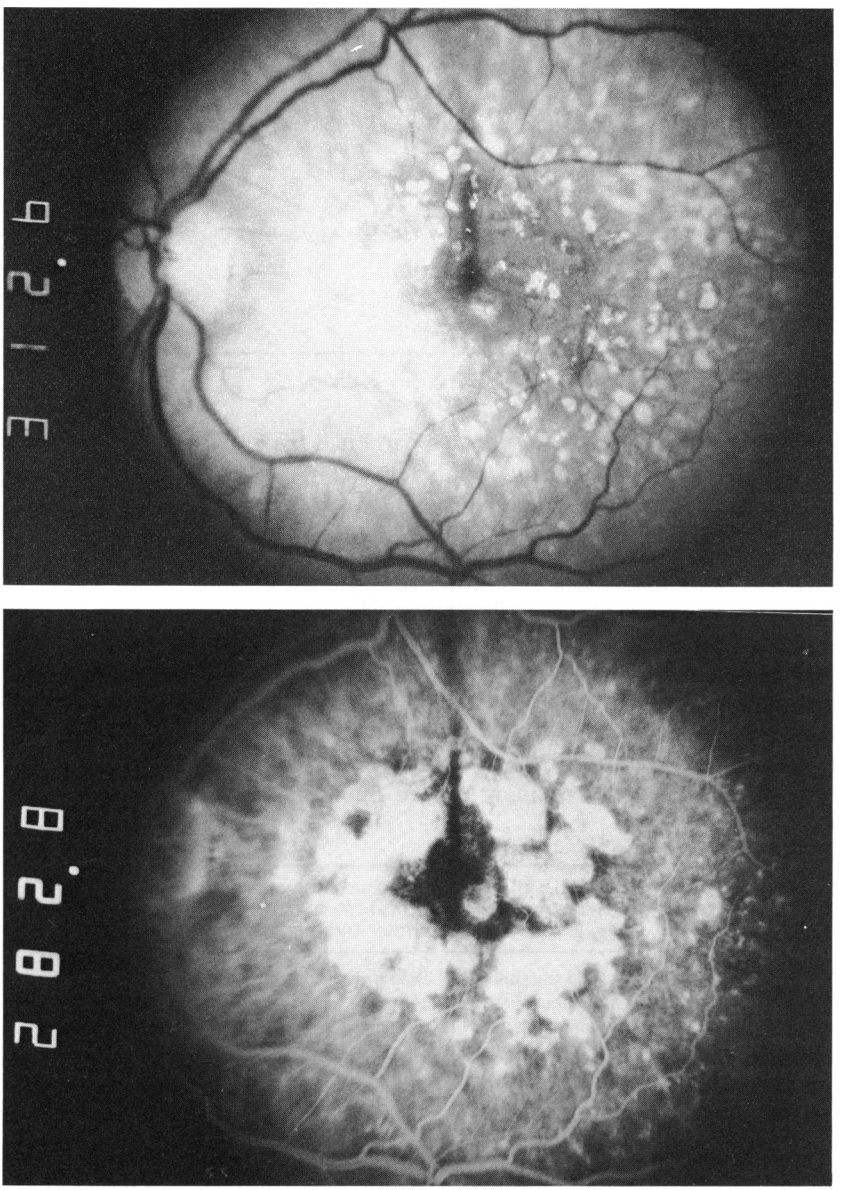


FIGURE 6

Case 4. Fundus photograph (A) and fluorescein angiogram (B) of left eye of 72-year-old woman with atrophic macular degeneration with crystallike drusen scattered in posterior pole (A). On late phases of fluorescein angiogram there was distinct edge of temporal disc staining OU. Her hyperabnormal photopic ERG was particularly surprising in light of macular atrophy.

TABLE II: DISTRIBUTION OF HYPERABNORMAL RESPONSES BY CATEGORY*

CATEGORY	NO	PHOTOPIC	SCOTOPIC	BRIGHT FLASH
Maculopathy	22	15	6	11
Optic neuropathy	19	12	1	9
RP suspect/carrier	20	14	6	12
RPE/retinal degeneration	7	1	2	4
Cone dysfunction	6	1	2	4
Drug toxicity	6	5	0	2
Neurology referral	3	1	2	2
Posttrauma	5	2	0	4
Aniridia	3	2	0	2
Miscellaneous	13	3	3	10

*Number of patients, no ERG category excludes another.

When looking at the categories, no particular hyperabnormal component of the ERG was predominant. Optic neuropathy and maculopathy patients had representation from hyperabnormal photopic, scotopic, and bright flash dark-adapted ERGs, although there was only one patient with optic neuropathy and a hyperabnormal rod response; this response was also underrepresented in the drug toxicity and trauma categories.

In reviewing the fluorescein angiograms, 14 patients had bright temporal disc staining on late phases (Figs 4B and 5B), which was not easily explained, since the majority (10) were in cases of maculopathy or retinal degeneration (Table III). While this temporal staining was found in only 14% of cases, it was distinctive and suggests that there may be an association between temporal disc staining on the fluorescein and a hyperabnormal ERG.

TABLE III: DIAGNOSES IN HYPERABNORMAL ERG PATIENTS WITH TEMPORAL DISC STAINING ON LATE PHASES OF FLUORESCEIN ANGIOGRAM

Retinal pigment epitheliopathy
Optic neuropathy
Chronic macular edema and degeneration
Macular degeneration
Idiopathic foveal dysfunction
Fundus flavimaculatus
Suspected retinitis pigmentosa (mother had)
Macular degeneration
Optic neuropathy
Optic neuritis
Behr's syndrome (optic atrophy)
Early macular degeneration
Macular degeneration
Macular degeneration

DISCUSSION

Less than normal ERG responses have been useful in diagnosing a large number of clinical disorders, but hyperabnormal (supranormal) responses have generally been considered "normal," or oddities that were classed as normal. Amplitudes greater than normal, sometimes called "hypernormal," have been recognized from the early days of electroretinography.

A number of known clinical states have been associated with hyperabnormal ERGs in past reports; these include metallosis,[5,6] albinism,[7] atypical cone dystrophies,[8-10] optic nerve sectioning,[11,12] optic neuropathies (eg, hypoplasia, optic atrophy),[13-15] vascular occlusions and ischemia,[16-20] uveitis,[21,22] cortical steroids,[23] low-dose barbiturates,[24] and carbon disulphide poisoning.[25,26] In some of these examples, it is easy to intuitively comprehend that metallosis, chronic inflammation, and ischemia are physiologically irritating to the retina and may result in larger-than-normal responses. Likewise, in our cases of aniridia and albinism, more light is reaching the photoreceptors and larger responses are expected.

The mechanism for higher electroretinographic amplitudes in optic neuropathies is unknown, and it can only be speculated that inhibitory components within the retina may be affected during the course of transsynaptic degeneration, resulting in higher ERG amplitudes. It can be speculated that the temporal optic atrophy and straining seen in some of the patients with hyperabnormal responses may be related to degeneration of inhibitory nerve fibers.

Perhaps the most puzzling group of patients in this study was that of the patients with macular degeneration and hyperabnormal responses. Generally, any patient exhibiting retinal degeneration, whether in the posterior pole or more diffusely, would be expected to have a reduced ERG. Yet in the macular degeneration patients with hyperabnormal responses, there were 13 hyperabnormal photopic and 11 with dark-bright flash hyperabnormal responses (some eyes had both). This finding might imply that these eyes are experiencing a panretinal dysfunctional process in which the visual sign is macular degeneration. Certainly, it appears that the ERG may be more useful than previously thought in differentiating types of macular degeneration.

In this retrospective study, patient selection was on the basis of their having a hyperabnormal response, and then a clinical correlation was performed. Since the vast majority of the cases had obvious pathology or reasons associated with the hyperabnormal ERG, we would conclude that hyperabnormal responses should not be automatically treated as a normal variant but that they are likely indicative of a disease process. While there was no specific association between the presence of a hyperabnormal ERG

and one or two diseases, the finding of a hyperabnormal ERG should emphasize the need for further investigation of the case.

Identification of hyperabnormal ERGs is contingent on each electrophysiology laboratory having carefully maintained standardized testing and normal control values. Inherent in this methodology are the use of Ganzfeld stimulation and a Burian-Allen style contact lens electrode for recording, and the maintenance of careful background light and flash calibration.

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DISCUSSION

DR RONALD C. PRUETT. I was pleased to have been asked to open discussion of this paper. As I am a retina surgeon and not a retinal electrophysiologist, perhaps my impressions and questions after hearing it will be similar to those of the majority of Society members.

The authors devote space in their manuscript to describing the difficulties involved in developing a normal electroretinogram (ERG) database. This requires that measurements be made on patients who are asymptomatic, have no immediate family history of a genetic disorder known to affect the ERG, and have normal findings on examination. The authors mention that both age and sex alter the response to a standardized light stimulus under controlled conditions. But so also do refraction and ocular pigmentation and even the time of day the recording is made (*Principles and Practice of Ophthalmology, Clinical Practice*. Philadelphia, WB Saunders, 1994, vol 2, pp 1193-1213). So "normal" is not a number; it is a bracketed range of values from a selected population gathered usually by an individual laboratory.

The authors remark that an ERG is usually obtained by a clinician when a retinal degeneration of some type is suspected, and it is hoped that the results will help to clarify the diagnosis. The interpreter generally looks for below-normal responses to detect disease, and there is a tendency to ignore or treat lightly responses that are above normal values. I agree with the authors that both "infra" and "supra" normal ERG responses contain clues to diagnosis, and neither should be disregarded. Semantics may be a silent contributor to this problem. If "normal" is good, isn't "supranormal" better? For purposes of defining a "supranormal" ERG, the authors selected those with at least one amplitude of one curve of one eye that was ≥ 2 SD above normal. If we consider a patient whose weight is 2 SD above normal for his age and height, would we consider him "supranormal?" He probably would be better called obese. It is too bad that common usage has combined the word "normal" with "supra." Clearly, individuals with hyperreactive ERG responses are "ab" normal. The question is why.

In his classic 1961 monograph on clinical electroretinopathy, Dr Jerry Jacobson described a number of situations in which the ERG had been found abnormally high (*Clinical Electrophysiology*. Springfield, IL, Charles C Thomas, 1961, pp 25-34).

Included among these were traumatic optic atrophy, optic neuritis, following retrobulbar anesthetic injection, and after prechiasmal optic nerve transsection. The speculation here is that the retina has been released from the influence of a central centrifugal inhibitory effect. Drugs also can cause hyperreactivity, possibly by altering blood flow and oxygenation. Hypertension, hyperventilation, variations in blood sugar, intraocular metallic foreign bodies, and many other factors can produce the same effect. Dr Heckenlively and his group have noted some of these, plus added others that may be "physiologically irritating" to the retina and result in an abnormally large response.

How to explain this? I have not heard a clear answer from the podium, nor can I offer one, even for the simple query "Why is the ERG response of women greater than that of men of similar age?" What does gender have to do with it anyway? The problem is that the ERG is a recording of a mass electrophysiologic event, the size, configuration, and time course of which are influenced by multiple factors, some of which are uncontrolled or unknown. It is somewhat like listening to a recording of the applause, cheers, and jeers at a football game without the benefit of seeing the action or getting a play-by-play description. Even with digitized computer-aided analysis, it is difficult to sort out the contributions of various retinal cellular elements in their response to a light stimulus, a response that itself is modulated by intraretinal and central nervous system interactions.

I thank the authors for drawing our attention to the supranormal ERG response and for stimulating the search for a better understanding of this end of the ERG spectrum. In closing I would pose two questions to Dr Heckenlively: 1. Have you had an opportunity to follow the 12 patients with temporal disc staining on fluorescein angiography? Is there any long-term evidence that an optic neuropathy of some type might be present, perhaps in those also with macular degeneration? 2. You might wish to comment further on those cases with a unilateral supranormal response. Are there any clues apparent when comparing the two eyes?

DR PAUL SIEVING. I wanted to add a note of thanks to Dr Heckenlively for pointing out that bigger is not always better. As Dr Pruett has aptly pointed out ERG contains a lot of complexity that we really haven't yet wrestled with. Although a Nobel prize was given for the ERG some three or four decades ago, we still really don't understand what drives the various wave components, and I certainly don't either. I would like to add one comment on the possible mechanism, however. For several years at the University of Michigan I have been recording monkey ERGs, both at the cornea and with microelectrodes inserted into the retina through a cannula inserted at the pars plana. The point of this was to study the origins of ERG components and particularly to ask a question, "what are hyperpolarizing bipolar cells doing in the primate retina?" I realize that even I as a medical retinal clinician don't spend much time thinking about hyperpolarizing bipolar cells. However, they constitute approximately one quarter to one third of the bipolar cells in the retina, and they are there for some reason. Yet for three decades they have been ignored in the ERG. One can begin to get clues as to their contribution to the ERG by applying drugs which will block the transmission from photoreceptors to the HBCs. We have been doing this,

and we have found some very interesting things, one of which is pertinent to Dr Heckenlively's observation. On putting in a drug to block activity of hyperpolarizing bipolar cells when the light is flashed, one finds that the dark adapted b-wave is clearly twice the normal size. This is relevant to the second of Dr Heckenlively's hypothetical mechanisms, that there may be an inhibitory component that normally holds in check the normal amplitude of the b-wave. It is possible that when the hyperpolarizing bipolar cells are subjected to a retinal insult that the normal b-wave can become super normal. I find it intriguing that Dr Heckenlively points out that one can't afford to ignore those larger than normal b-waves because they may be telling us something of worth about the pathway of physiologic mechanisms of retinal disease.

DR ROBERT DREWS. This was a very stimulating paper. It is always interesting to have people pay attention to things that we normally ignore. There are two questions in my mind though. If people with macular trouble for instance can have both subnormal and supernormal responses, that must mean that a normal response in these people doesn't rule out disease. Secondly, since about 2% to 3% of normal people have supernormal responses, what percentage of people with things like macular degeneration have supernormal, and is this simply part of the normal bell shaped curve in these patients rather than an abnormal response?

To explain supernormal responses in people with aniridia or albinism on the basis that there is more light getting to the retina, is also troublesome: the same extra light gets to the retina in patients with aniridia or albinism who have normal responses.

DR JOHN R. HECKENLIVELY. I would like to thank the discussants for their comments and I would like to respond to some of the questions. In answering the last question on macular degeneration patients with supranormal responses, or even subnormal responses, they are still included in the criteria for normality set by the bell-shaped curve. We ran controls for a project involving senior citizens several years ago; when we looked at this data, the values fell within the bell shaped curve, so people that fall off at either end are abnormal. When we looked at just the issue of what happens to the photopic ERG when there is a macular lesion, it turns out that it is reduced only 10% to 15%, and in this study we were showing patients with macular lesions with ERGs that were double normal, suggesting that there is a physiologic effect going on in these cases.

The cases that have optic nervehead staining and maculopathy are perhaps the most puzzling. I have followed a number of these cases over the last few years. The character of the lesions has remained constant. It has been my thought that the temporal disc staining may be due to transsynaptic degeneration related to the maculopathy, but until we have a histopathologic correlation, the etiology will likely remain unknown.