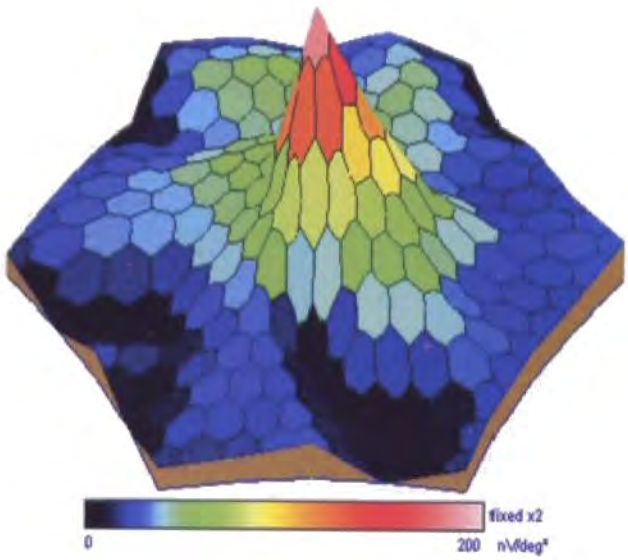
Visual electrophysiology in the Clinic: A basic guide to recording and interpretation



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(As part of CME programme)

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Foreword

Dear Colleagues,

In retinal practice, there are several times when the clinical findings need to be supported or confirmed with the help of electrodiagnostic tools. It is often necessary to follow up patients with the help of these modalities. It is therefore imperative that all ophthalmologists understand the basis of "Visual Electrophysiology" to enable its optimal use in the management of patients. I thank Dr. Subhadra Jalali for helping to make this CME Series.

I thank Dr. Chaitra Jayadev, the Editorial Manager for making it an international format.

I would like to thank the OBSC & ARC Committee Members of AIOS for their support. If members/readers have any suggestions, kindly e-mail: drsnatarajan@vsnl.net. The CME series is also available online at www.aios.org

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Preface

The electrical activity of the visual system is what converts the image of a beautiful picture into a meaningful signal for the brain to understand and for us to get the wonderful perception of 'seeing'. Often enough, as ophthalmologists we deal with the structure and function of the refractive aspects of the eye and the electrical phenomena escape our attention till we are confronted with situations of visual loss of unknown origin!

The electrical phenomena in the eye were first described back in the1800's but it took almost hundred years for this science to percolate from the laboratory scientists' interest to a clinically useful tool for assessing visual functions in the 1940's. Today, visual electrophysiology has come of age both because of fast computing and digital systems and also due to expert knowledge gained through numerous laboratory and clinical observations during the last century by dedicated groups of enthusiasts.

In India, traditionally, most of the visual electrophysiology has been conducted by neurologists, mostly visual evoked potentials and sometimes by ophthalmologists, but often confined only to flash electroretinograms. In the last decade we have seen a paradigm shift where ophthalmologists working in many major eye care centers in India have set up comprehensive clinical visual electrophysiology services that test various aspects of the visual function; the animal and cell-based visual electrophysiology still have to make a mark in India.

The International Society for Clinical Electrophysiology of Vision (ISCEV) publishes articles to set the international standards for these tests, starting in 1989 with updates every four years. The society is also actively involved in educational activities in the field. It is important that all electrophysiological tests conducted in India should meet these standards if we want to be at the cutting edge of scientific knowledge and practice.

Educational activity in this field has however remained slow. We conducted the first ever hands-on ophthalmic electrophysiology workshop in India in collaboration with the ISCEV in August 2004 at L V Prasad Eye Institute, Hyderabad to set the ball rolling. We also started a unique one month hands-on electrophysiology short term fellowship for skill enhancement. Following this, over the last five years, numerous educational activities in this field have been held by various eye institutes, in major cities as stand-alone CME's, or symposia during conferences. The membership of ISCEV from India has increased. We were also fortunate to bring to Indian ophthalmologists the first ever international educational activity in this field, by hosting the 45th Annual ISCEV Symposium at Hyderabad in August 2007 that allowed Indian experts to interact closely with their international friends. The information now needs to go around to all ophthalmologists so that they can utilize this beneficial technology in clinical care for their patients.

It gives us great pleasure to present some of this knowledge in a concise and crisp manner that can be of use to clinicians and vision scientists. While we have tried our best to avoid any mistakes and provide current information, we hope that any errors and omissions are brought to our notice for future corrections. The booklet describes various tests used in the clinic and gives basic information of their utility and interpretation. The Academic and Research Committee of the All India Ophthalmological Society has generously facilitated this effort by sponsoring the current CME booklet on '***Visual Electrophysiology***' having perceived the need in this area. We hope that this serves as a useful hand-guide to all readers and also kindles a keen interest amongst our young ophthalmologists in this fascinating field.

Subhadra Jalali, Hyderabad
L S Mohan Ram, Singapore

Graham E Holder, London
Vasumathy Vedantham, Chennai

Introduction

Dear Members,

The purpose of this CME Series is to give to the members a gist of the latest scientific material and practical tips on the concerned topic.

It is heartening to inform you that the AIOS CME series is getting more and more popular and is in great demand by our members.

CME Series No. 17 on **"Visual electrophysiology in the Clinic: A basic guide to recording and interpretation"** by Dr. Subhadra Jalali and team is in your hand.

I congratulate the author and Dr. S. Natarajan, Chairman, ARC for their efforts. Please go through it. I shall appreciate your feed back & suggestions.

With best wishes,

Yours sincerely,

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Introduction and Overview

The visual pathways start from the photoreceptor and retinal pigment epithelial (RPE) layers in the retina, proceeding through the inner retinal layers and the retinal ganglion cells. The two optic nerves meet at the optic chiasm where, in a normal, approximately 50% of the fibres project to the ipsilateral hemisphere of the brain and approximately 50% decussate to the contralateral hemisphere. From the optic chiasm the two optic tracts project to the lateral geniculate bodies of the thalami, and thence to the occipital cortex via the optic radiations. **Visual electrophysiology is an extremely powerful tool to assess the functional integrity of various levels of this visual system.**

The main tests available are the

- Electrooculogram (EOG) - which examines the function of the RPE and the interaction between the RPE and the photoreceptors
- Electroretinogram or ERG - the responses of the retina to full-field luminance stimulation that, through alterations in stimulus parameters and the adaptive state of the eye, enable the separation of the function of different retinal cell types and layers
- Pattern ERG (PERG) - which objectively assesses the macula and the central retinal ganglion cells
- Photopic negative response (PhNR) - which allows assessment of global ganglion cell function
- Multi-focal ERG (mfERG) - to demonstrate the spatial distribution of central macular cone function
- Visual evoked potential (VEP) - which provides information about integrity of visual pathways up to the occipital cortex.

A thorough understanding of the nature and limitations of each of these tests is a prerequisite to deciding which tests to perform, and thus to allow valid interpretation and diagnosis. Further, all test results need to be placed in clinical context, so a thorough clinical evaluation is mandatory prior to ordering or interpreting same.

Electrophysiological responses are strongly related to stimulus and recording parameters, and the adaptive state of the eye, and standardization is therefore mandatory for meaningful scientific and clinical communication between laboratories. The International Society for Clinical Electrophysiology of Vision (ISCEV, pronounced as *eyesev*) has published Standards and Guidelines for the main tests[1-6] and all practitioners are strongly urged to incorporate these standards in all routine test protocols. It should be remembered that the ISCEV Standards are intended to be minimum standards, and that in some clinical situations testing in excess of those standards will be necessary to make an accurate diagnosis. The ISCEV standards are available to all at www.iscev.org.

This document examines the basics of the available tests and presents some clinical cases to demonstrate their application. The recordings shown were taken using a variety of commercially available equipment, and the similarity of the waveforms demonstrates the value and importance of standardised recordings.

The Electroretinogram (ERG):

Recording Techniques

The flash ERG is the mass response of neural and non-neural retinal cells to full-field luminance stimulation. The initial action of light on the retina is to cause the photoisomerisation of rhodopsin. This sets up a chain of biochemical reactions within the photoreceptor, the phototransduction cascade, the result of which is hyperpolarisation of the retinal photoreceptors. The photoreceptors then signal to the bipolar cells, with rods and short wavelength cones (s-cones) being directly coupled to ON- (depolarising) bipolar cells (DBCs) and medium and long wavelength cones connecting both to cone ON cells (DBCs) and also OFF – bipolar cells (hyperpolarising). Different ERG components arise in relation to different structures and processes. From a clinical point of view there are many proteins involved either directly in the process of or

in the recovery from phototransduction. Retinal degenerations can arise as a consequence of mutations in these proteins.

Recording electrodes (Figure 1):

Clinical ERGs are obtained with an electrode placed at a distance from the retina. ERG recording should be performed with contact lens electrodes, or non-contact lens electrodes that are in contact with either the cornea or the bulbar conjunctiva. Skin electrodes should not be used for routine recording in adults, but may have a role in children or in adults in whom corneal electrodes cannot be used. Contact lens electrodes can be unipolar like the Jet-electrode and some of the Burian- Allen electrodes or bipolar like other Burian-Allen electrodes. They are centrally transparent with a large optical opening and may incorporate a speculum to hold the lids apart. Use of topical anesthesia and a non-viscous solution like 0.5% methylcellulose helps maintain good electrode contact. Contact lens electrodes provide the largest amplitudes but may need resurfacing periodically, are expensive, are uncomfortable and there is the rare possibility of corneal abrasion. Electrodes must be cleaned and sterilised after each use to prevent disease transmission. The non-contact lens varieties include gold foil, H-K loop, the DTL-fibre and the LVP-Zari electrodes. The latter are disposable, inexpensive electrodes made from locally available Zari-embroidery thread. They have a core of nylon covered with layers of silver, copper and gold, ensuring good conduction of electrical signals. Due to its nylon core, the movement of the fibre across the limbus is minimal, making the recordings reliable.[7] When comparing different recordings, always note the recording electrodes used.

The active electrode placement is in the lower fornix as close to the inferior limbus as possible or on the cornea as the case may be. The electrode should be stable, non-mobile and not injure the cornea. The reference electrode is placed at the outer canthus for unipolar electrodes. The positioning of the ground electrode is less critical; the forehead or ear lobe would be typical sites (Figure 2).

For all skin-electrodes used for ERG, EOG or VEP, good contact is essential with low impedance. To achieve this, the grease and dead cells on the skin are removed by rubbing with a gentle abrasive paste and use of an appropriate conductive paste or gel between the electrode and the skin. The impedance of the skin electrodes should be checked according to the individual manufacturers' recommendations. In general, surface electrode impedances should be equal and <5kΩ. Often, the electrodes are connected to a junction box and thence to the computerized amplifiers and recorders. The electrodes should be connected such that the negative a-wave of the ERG is recorded as a downward deflection and the positive b-wave an upwards deflection.

Recording equipment:

For ERG two types of illumination are under consideration, the background and the stimulus. For the background, a Ganzfeld bowl provides a uniform whole field illumination to the retina (Figure 3). The inside surface of the bowl has three to five light emitting diodes to enable accurate and constant fixation eye and also allow appropriate excursion of the eyes during EOG recordings. A chin rest allows proper positioning of the subject. The background in the Ganzfeld must be a steady and even white luminance of 17-34 candelas per meter squared across the full field. A stroboscope flash, or cathode ray tube or light emitting diodes provide the stimulus flash. The duration of each flash stimulus should be less than the integration time of any photoreceptors and so should not exceed five milliseconds. An ISCEV standard flash is one that produces 1.5 to 3.0 candela-seconds per meter squared of luminous energy at the surface of the Ganzfeld bowl. The system should be capable of attenuating the flash strength from standard flash over a range of at least three log units, either continuously or in steps of no more than 0.3 log unit attenuates. This attenuation should not change the wavelength. In addition, the most recent ISCEV standard added a "suggested" brighter flash of 11.0-12.0 cd.s/m^2 to allow better

assessment of the photoreceptor function. It is essential to calibrate the stimulus and background illumination periodically by integrated and non-integrated photometers to achieve standard test conditions. Using coloured background light and stimuli are specific for specialized tests.

The electrical signal generated by the retinal cells and received from the electrodes needs processing in such a manner that there is amplification of signal and filtration out of noise, but without artifactually modifying the actual signal response. The band pass of the amplifiers and preamplifiers should include at least the range of 0.3 to 300 Hertz and should be adjustable for oscillatory potential (OP) recordings and other more specialized requirements. Amplifiers are generally AC (alternating current) coupled. The patient should be electrically isolated according to local current standards of safety of clinical biologic recording systems. The recording equipment should be able to represent, without attenuation, the full amplifier band pass. The computer digitizers should sample responses at the rate of 1000 Hz or higher. The computerized digitizers also are usually capable of averaging multiple responses to increase the signal to noise ratio. The recordist should be able to monitor the displays for a high quality technical recording and to make any necessary adjustments to improve the recording quality, usually by the reduction of noise. Commercially available equipment should meet these requirements.

Recording Procedure:

The ERG is recorded after full pupillary dilatation so that all parts of retina are illuminated. The subjects, with properly placed electrodes, sit comfortably with their chin on the chin rest and their eyes open with their face inside the Ganzfeld bowl (Figure 2). It is common practice to insert the electrodes under dim red light after dark adaptation for 20-30 minutes has occurred. The height of the chin rest and the patient should be adjusted so that the neck and back muscles are relaxed. Some equipments have a connection box leading to the amplifiers which requires clipping to the patient; other equipment may have the junction box on a stand. Generally speaking, all leads from the patient to the junction box should go backwards from the patient, rather than in the direction of the Ganzfeld, and the lead taking the retinal signals from the junction box to the computer should be kept away from cables carrying the mains electricity. Very bright illumination of the retina, such as that used during fluorescein angiography, should be avoided prior to ERG recording.

ERG records:

ISCEV describes a minimum of *five* basic flash ERG response recordings, three in dark adapted (scotopic) conditions and two under light adaptation (photopic) (Figure 4 a-c show normal responses using different equipments). These five responses are, the "rod" response, obtained to a stimulus whereby the standard flash is attenuated by a factor of 2.5 log units (sometimes known as 25dB); the "mixed" response to a standard flash under dark adaptation; the oscillatory potentials (OPs;) the "30Hz" photopic flicker ERG; and the "photopic" ERG, the response of the light adapted retina to a standard flash. It should be emphasised that these recording are a *minimum* standard and in some disorders to make an accurate diagnosis will require more than just the ISCEV standard ERGs. The use of a brighter flash (the standard flash +0.6 LU) is recommended by ISCEV to enable better assessment of the photoreceptor function. Also, although not part of the ISCEV standard, photopic ON- and OFF- responses (from the long and medium wavelength cone systems) can be separated using a long duration stimulus (e.g. 200ms) superimposed upon a light adapting, rod-suppressing background. The responses of the short wavelength cone system can be assessed using a blue stimulus with an orange background to suppress the activity of the L-/M- cone systems

Once the patient has been fully dark adapted, and the pupils are dilated, it is standard practice to record the responses to low intensity stimulation first. To record the "rod" ERG, use a

dim-flash with intensity approximately 2.5 log units below the standard flash (25db flash). A blue stimulus may be used if equated to the white standard. At this low intensity level, the cones are insensitive to the stimulus, and the recordings only reflect activity of the rod system. The "rod" response consists only of a slowly rising, broad-peaked, b-wave. This b-wave arises in the rod ON- bipolar cells and gives a measure of rod system sensitivity but does not allow direct assessment of photoreceptor function. At this low luminance, there is insufficient phototransduction to record an a-wave. If computerised averaging is needed to improve the signal to noise ratio, there should be an interstimulus interval of at least 2 seconds to allow the retina to maintain its scotopic adaptive state. Progressive increase of flash stimulus shows increased responsiveness from rod photoreceptors with progressive increase in a- wave and b-wave responses. We can plot this as an intensity-response curve to study the rod-sensitivity pattern. As the intensity of the stimulus is increased, so must the interstimulus interval (ISI) be increased to avoid altering the adaptive state of the eye. With bright flashes an ISI of 20 seconds may be required.

A standard flash (no attenuation, duration less than five milliseconds), results in an electrical response arising in the photoreceptor and inner nuclear layers of the retina, which may be termed the mixed response; the mixed rod-cone response; the combined response; or, inappropriately, the maximal response. Perhaps the most appropriate term is the "Standard flash response (SFR)" The main components are the a- and b-waves (Figure 5). Both the cone and rod systems contribute to this response, which in a normal consists of a sharp negative a- wave and a larger, rapidly rising b-wave which returns to the baseline very slowly. Only the first 10 ms or so of the a-wave arises in the photoreceptors, so most of the a-wave evoked by the standard flash arises from post-receptoral structures. The b-wave is from the inner nuclear layer, arising in rod ON-bipolar cells and cone ON- and OFF- bipolar cells. The ISI for the standard flash response should be at least 10s. Measurements should include the amplitude and peak-time for each main component. The measurement of amplitude of the initial cornea negative a-wave is from baseline to the trough, while b-wave amplitude is from the trough of the a-wave to the peak of the cornea positive b-wave. Peak time measurement of each wave is from stimulus onset, marked by a vertical line across the baseline, to the peak of the response. For clarity, only one waveform of each response is shown, though ISCEV standard requires two reproducible waveforms.

Because much of the a-wave to the standard flash does not arise in the photoreceptors, ISCEV also "suggests" a brighter flash (approximately 0.6 log units brighter than the standard flash). The a-wave to that stimulus usually peaks in the region of 11.0 ms and thus largely arises in relation to photoreceptor function. The a-wave of this response is perhaps the best and most appropriate measure of the function of the photoreceptors. An ISI of 20s is required with this intensity of flash.

The OPs originate in the middle and inner retinal cell layers probably in relation to the amacrine cell activity. They are high frequency oscillations that occur on the ascending limb of the b-wave. Under scotopic condition and using standard flash intensity as a stimulus, resetting of the filters to a bandwidth of approximately 100-300Hz allows removal of other ERG activity and exposure of the OPs. They are best seen to the second of the two flashes with an ISI of 15 seconds.

To record the photopic responses from the cone system, the patient's retina is exposed to 10 minutes of rod-saturating light adaptation by switching on the background light in the Ganzfeld. Stimulation using the standard white flash with no attenuation provides the single flash photopic cone response, the "photopic" ERG. Inter-stimulus intervals should not be less than 0.5 seconds. This cone response is characterized by a small, less sharp a-wave and a very sharply rising b-wave that rapidly returns to the baseline. The a-wave reflects function both of the cone photoreceptor and a contribution from the off-bipolar cells.[8] The cone b-

wave reflects inner retinal post-photo transduction activity of the ON- and OFF- cone bipolar cells. Photopic OPs may be seen on the ascending limb of the photopic b-wave. Under the same light adapted state, a flicker ERG is recorded to repetitive standard flashes at a frequency of 30 per second (30Hz). Computerised signal averaging is usually used to improve the signal to noise ratio. In addition to the photopic background suppressing the rod system, the poor temporal resolution of the rods does not allow the rod system to respond at 30Hz. This response is perhaps the more sensitive measure of cone system dysfunction, but is generated at an inner retinal level.[9] Measurement of amplitude is from trough to peak of each response. The peak time is measured between the stimulus onset and the peak of the response usually occurring at 24-27ms. Some equipment will display a vertical line in the trace representing the onset of the stimulus. The normal responses are such that the peak of a given response falls before the stimulus onset for the next response. Hence, if the response peaks fall on the vertical stimulus line or immediately after the stimulus line, it depicts a delay in the responses.

ERG measurements include amplitude and implicit time for each component of the signals. For practical purposes, the variables most often measured are the b-wave amplitude of the isolated rod response, a- and b-wave amplitude and peak times of the SFR; the a- and b-wave amplitude and peak times of the photopic response; and the peak time and amplitude of the flicker ERG. The ERG report should include normative values for the laboratory and should show two representative waveforms of each response to demonstrate reproducibility.

Additional recordings:

Separation of the cone ON- (depolarizing bipolar cells, DBCs) and OFF- (hyperpolarizing bipolar cells, HBCs) sub-systems can be achieved using a long duration stimulus with a photopic background (Figure 4c).[10] A shutter system or light emitting diodes generate this type of stimulus. The photopic negative response (PhNR) is a negative-going wave that is particularly best seen using a red flash stimulus of 650nm on a rod-saturating blue background of 425-450nm.[11] The PhNR is presumed to arise in the retinal ganglion cells, and some disorders of retinal ganglion cell function have been shown to be associated with reduction in the PhNR. However, much further work is needed before this response can be routinely integrated into clinical practice, particularly in relation to sensitivity and specificity of this response in different disorders.

Since the flash ERG measures the mass responses of the retina, the ERG does not provide information about the function of the macular photoreceptors or ganglion cells and so cannot predict visual acuity. Despite the high photoreceptor density, an eye with a lesion confined to the macula has a normal flash ERG while an eye with generalised retinal dysfunction sparing the macula may have very abnormal ERGs but normal central visual acuity. Pattern and multifocal ERG recordings are newer techniques that can allow assessment of macular function.

The pattern electroretinogram (PERG):

The PERG is the response of central retina to an iso-luminant stimulus, usually a reversing black and white checkerboard. It allows both a measure of central retinal function, and an evaluation of retinal ganglion cell function. It is thus of great value in the electrophysiological differentiation between optic nerve and macular dysfunction (refer to Holder, 2001 for a comprehensive review).[12] PERG recording uses non-contact lens electrodes in contact with the cornea or bulbar conjunctiva to preserve the optics of the eye, and no mydriasis. The most common electrodes are the gold foil,[13] the DTL[14] and the H-K loop electrode.[15] LVP-electrodes also show comparable and reliable results.[16] Ipsilateral outer canthus reference electrodes are necessary to avoid contamination from the cortically generated VEP that results if forehead or ear reference electrodes are used.[17]

Recording Technique: At low stimulus frequencies, the PERG amplitude relates almost linearly to stimulus contrast. ISCEV recommends a high contrast black and white reversing checkerboard with ~40-minute checks in a 10-16 degree field. Optimal recording of the PERG uses an analysis time of 150 msec or greater with approximately 150 averages per trial. At 2-6 reversals per second (1-3 Hz), the result is a transient PERG response. It is a small response and stringent technical controls are important during recording. These are fully discussed elsewhere by Fishman et al.[18] Binocular stimulation and recording is usually preferred so the better eye can maintain fixation and accommodation, but if there is a history of squint it is necessary to use monocular recording. P50 is sensitive to optical blur, and accurate refraction is important.

PERG Waveforms (Figure 4C, 6): The transient PERG has two main components: A positive P50 component at approximately 50 msec and a larger negative N95 at 95 msec.[12] Measurement concentrates on the amplitude of P50, from the trough of the early negative N35 component; the latency of P50 measured to peak; and the amplitude of N95, measured to trough from the peak of P50. N95 is a contrast-related component in relation to the retinal ganglion cells. Approximately 70% of P50 appears to be generated in the ganglion cells, but the remainder is not related to spiking cell function and may be generated more distally.[19] The exact origins are yet to be ascertained. Although the PERG is generated in the inner retina, the P50 component reflects macular photoreceptor function, being "driven" by the macular photoreceptors.

Multifocal ERG

The multifocal electroretinogram (mfERG) is a relatively new technique, initially developed by Eric Sutter and colleagues, which attempts to measure the spatial distribution of the central retinal cone function.[22, 23] The technique provides valuable insight into macular pathology and is a valuable adjunct to conventional full field ERG. Herein, we provide an overview of the principles and basic clinical practice of mfERG. The patient *must* be able to maintain accurate fixation for mfERG data to be meaningful.

Recording Technique:

Pupillary dilatation is used for mfERG recording. The active, ground and reference electrode placement is similar to PERG. The stimulus sources include CRT (Cathode Ray Tube), LED (Light emitting diode), LCD projector and SLO (Scanning Laser Ophthalmoscope). The subject views a **black and white pattern of hexagonal elements each of which flashes on and off with its own pseudo-random binary sequence, known as an M-sequence. Cross correlations are then used to calculate the individual responses to each of the stimulus hexagons, and these resemble real ERGs. The screen is isoluminant over the whole time of the recording.** The hexagons increase in size with the distance from the centre (Figure 7). Typically, the sizes of the hexagons are scaled inversely with the gradient of cone density, in order to produce focal responses of approximately equal amplitude. The display usually contains either 61 or 103 or rarely 241 hexagons and subtends an angle of 50-60 degrees at the eye. The subject fixates centrally, and a continuous ERG recording is taken. Typically this lasts 4-8 minutes and is obtained in 15 - 30 second segments to make it easier for the subject to suppress eye movements and blinks. **Spatial resolution will improve with more hexagons but 61 hexagons generally provide a suitable compromise between the degree of spatial resolution and the time taken for testing – the test duration increases as the number of stimulus hexagons increases.** Technically, these responses are the first-order kernels of the cross correlation between the stimulation sequence and the continuously recorded ERG.

Response displays include the response density (voltage/unit area) and the summed response (total voltage). Because of the high density of cone receptors in the fovea and the high density of post-receptor cells to which they connect, the response to the central hexagon in a normal

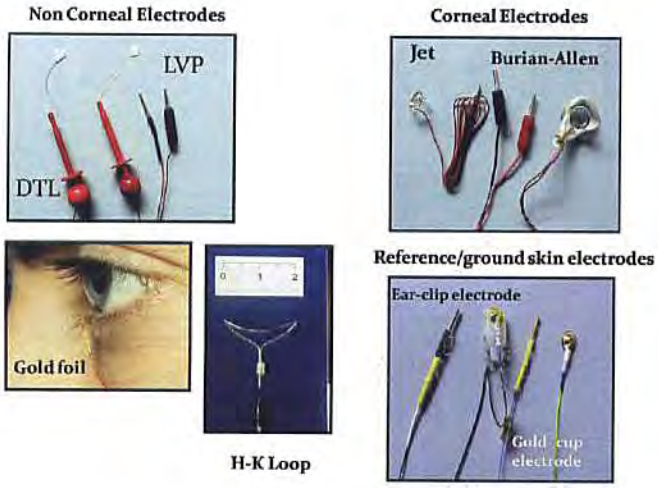


Figure 1. Electrodes used in visual electrophysiology

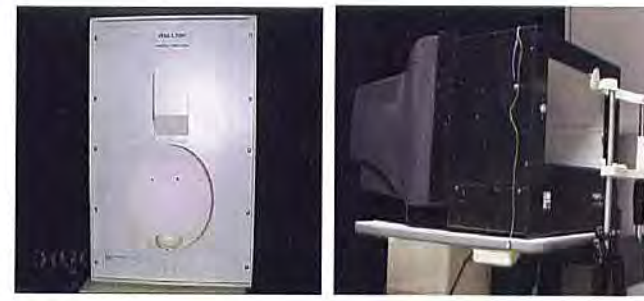


Figure 3. An integrated sphere called Ganzfeld, provides a uniform, whole field illumination to the retinal spherical surface. It provides both flash stimulation and a diffuse background light for photopic adaptation. The inside surface has three light emitting diodes as fixation targets for the eye and also for excursion of the eyes during EOG recordings. A chin rest allows proper positioning of the subject. Two prototypes are shown.

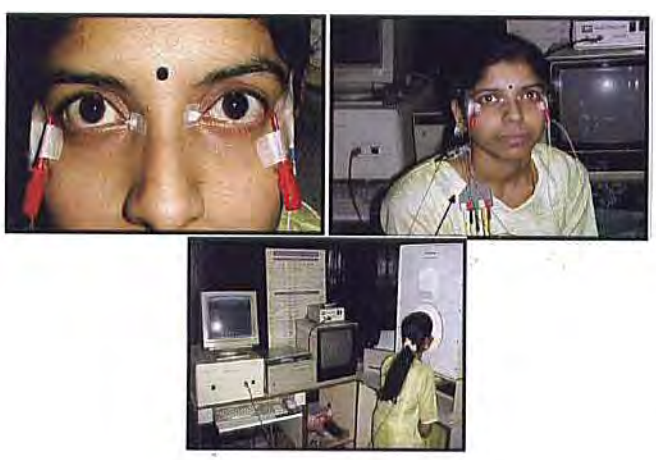


Figure 2. LVP Electrode placement (top left) and connections (top right) to junction box (arrow). ERG in progress (bottom)

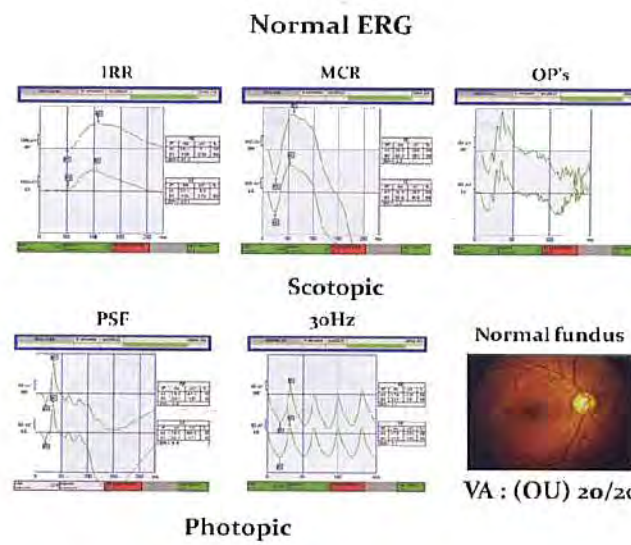


Figure 4a. Normal Flash ERG waveforms from a normal fundus using Metrovison machine. Under scotopic conditions, we can record the isolated rod response (IRR), the Maximal combined response (MCR), and the scotopic oscillatory potentials (OP's). The photopic responses include the single flash for cones (PSF) and the 30-Hertz flicker responses (30 Hz)

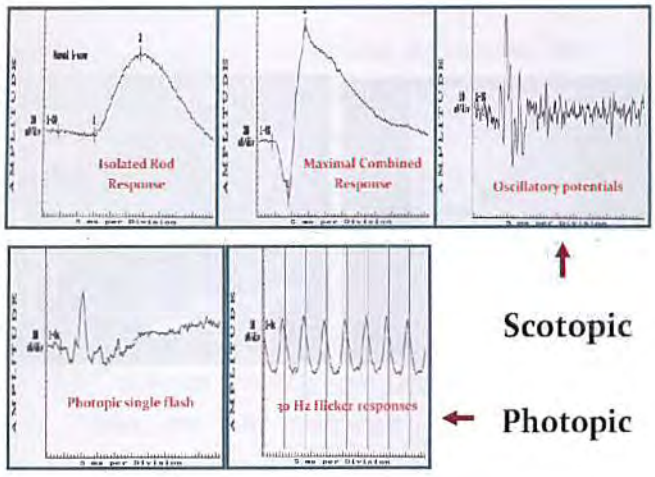


Figure 4b. Normal recordings on LKC UTAS 2000 machine

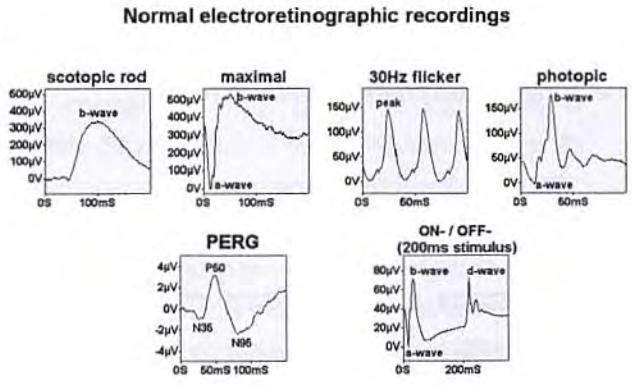


Figure 4c. Normal ERG recordings at Moorfields Eye Hospital

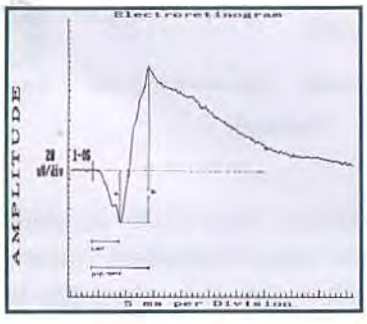
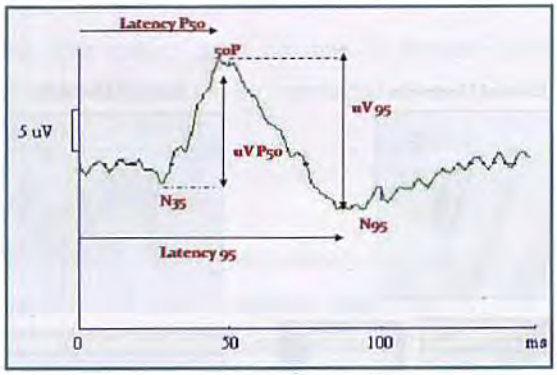


Figure 5. Methodology of Flash ERG amplitudes and latency measurements (see text for details)



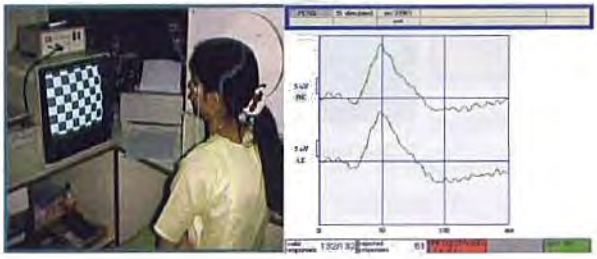


Figure 6. PERG measurements (top), PERG stimulus and recording in progress (below, left) and actual recording of PERG from two eyes (below, right)

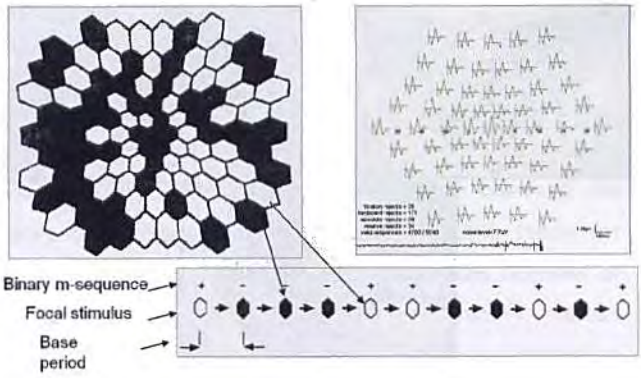


Figure 7.Top left, hexagonal stimulus array of 103 elements. Top right, sample trace arrays with 61 hexagons. Bottom, each hexagon follows a predetermined m-sequence that controls the order of flicker of the stimulus between light and dark.

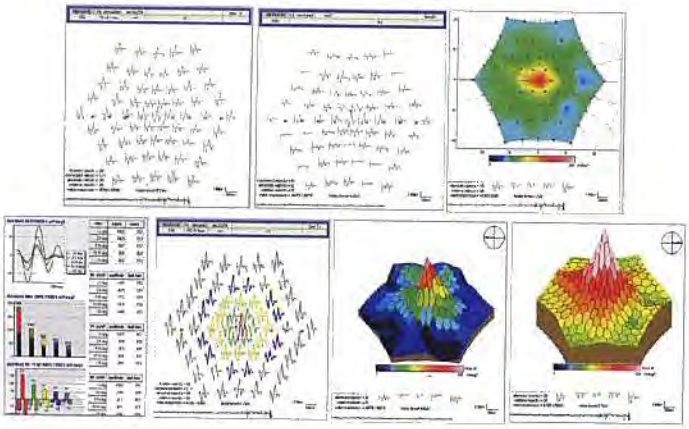


Figure 8. Various displays available for mfERG in a normal eye. Clockwise from top to bottom left trace arrays of two eyes, colored density plot, 3D scalar plot, scalar plot compared to normative data base, ring averages, average values of N1, P1 and P2.

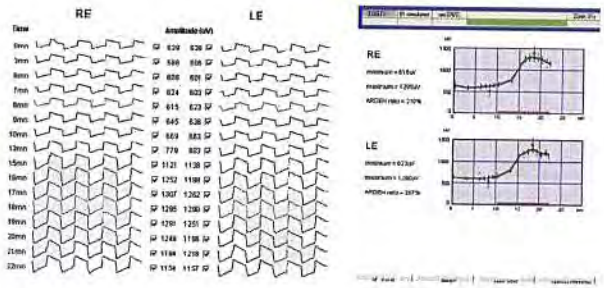


Figure 11 showing raw waveforms of the saccades (left) and the final EOG graph (right). Note the light rise and normal Arden ratio of >200% in each eye.

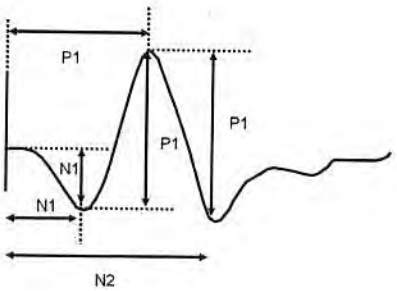


Figure 9. The mfERG response measurements of amplitude and implicit time (time-to-peak) for each deflection.

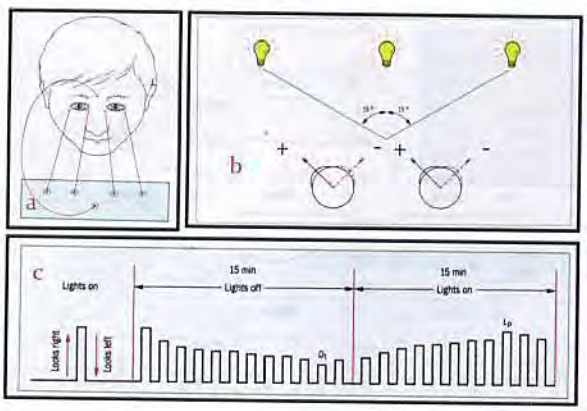
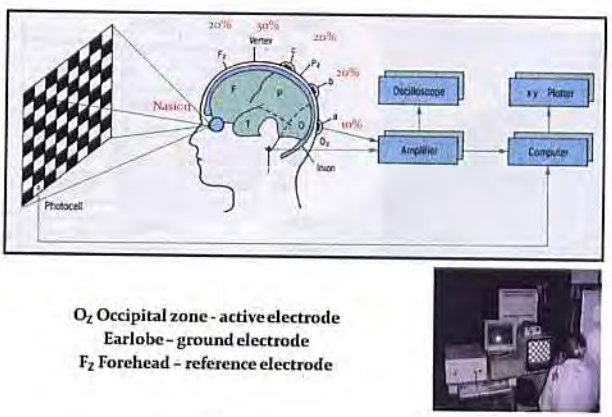


Figure 10. EOG recording procedure. a. Skin electrode placement. b. Ganzfeld Fixating lights (LED) 15 degrees apart, with 30° excursion from right to left. c. 16 to 20 sweeps per minute following a baseline recording of 6 minutes in white light. Recording is for 15 minutes in dark & 15 minutes in light



O_z Occipital zone - active electrode
Earlobe - ground electrode
F_z Forehead - reference electrode

Figure 12. The International 10/20 system of electrode placement for midline single channel VEP. Inset shows pattern VEP recording in progress.

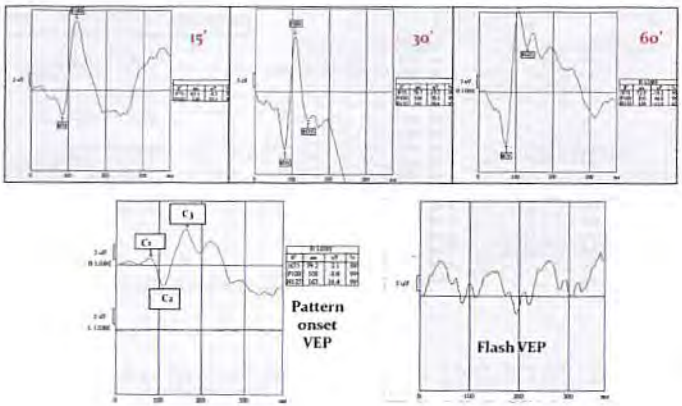


Figure 13. Normal pattern reversal to three different check sizes (top - 15, 30 and 60 minutes), Pattern-onset (bottom left) and Flash (bottom Right) VEP. Note changes in waveform and latency to different check sizes.

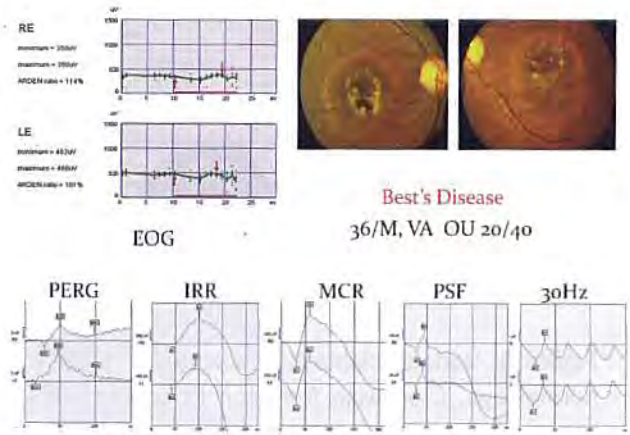


Figure 15. Shows poor light rise on EOG in a patient with subnormal vision and bilateral macular lesions. ERG recordings including macular photoreceptors (PERG) was normal as shown in ERG results.

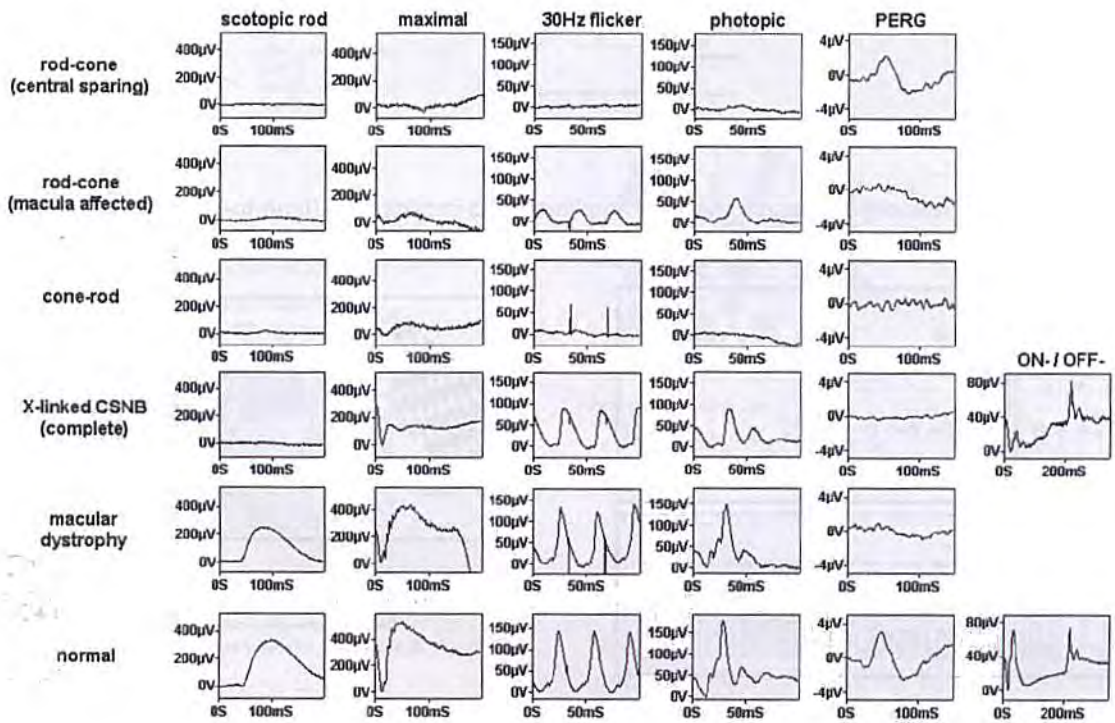


Figure 14. Representative waveforms of commonly seen retinal dystrophies in Moorfields Electrophysiology lab. Normal waveforms are at the bottom for comparison.

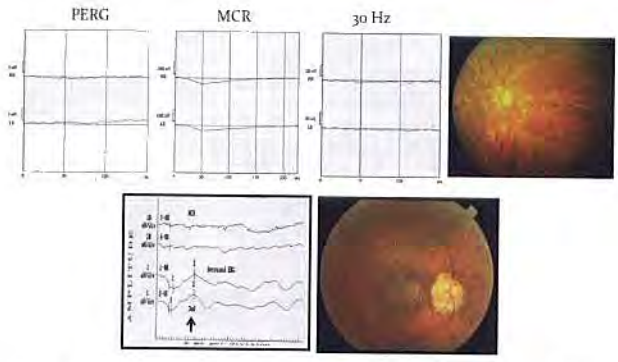


Figure 16. Top row. Unrecordable PERG and flash ERG in advanced retinitis pigmentosa depicting macular involvement. Bottom row. Extensive filtering and averaging of the maximal combined response to elicit a microvolt ERG (arrow, outside ISCEV standard) showing residual retinal function in patient of RP with visual acuity of 20/800 and macular atrophy.

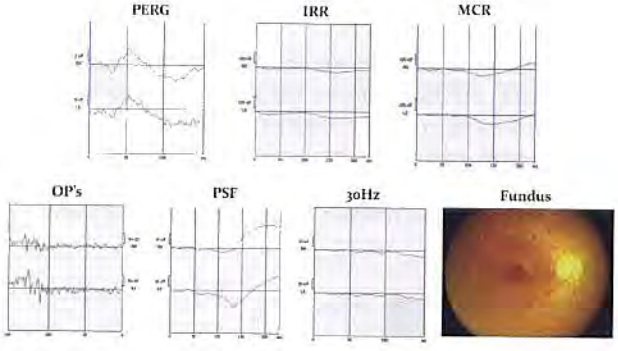


Figure 17. Preserved PERG in a patient of RP with extinguished flash ERG responses showing macular sparing. Visual acuity of the 25 year old male was 20/25 and visual fields showed central island of 10°.

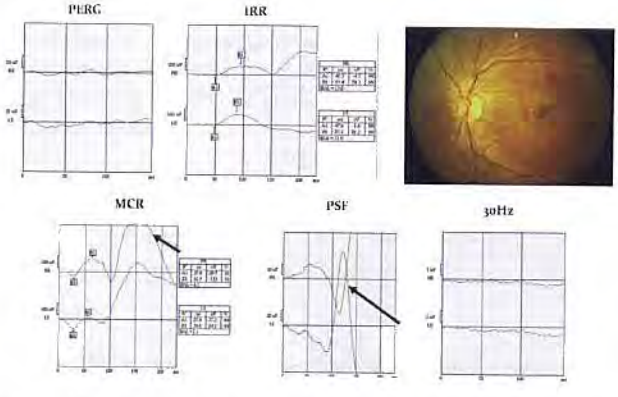


Figure 18. Cone-rod dystrophy. Retinal dystrophy with macular Bulls' eye lesion, mild arterial narrowing, peripheral RPE degeneration and disc pallor. ERG shows absent cone functions (PERG, PSF, 30 Hz) with subnormal but recordable rod response (IRR, MCR) suggestive of cone-rod dystrophy in 29 years patient with a VA of 20/80. Note large blink artifacts towards end of recordings (arrows) that are not uncommon due to photophobia in these subjects.

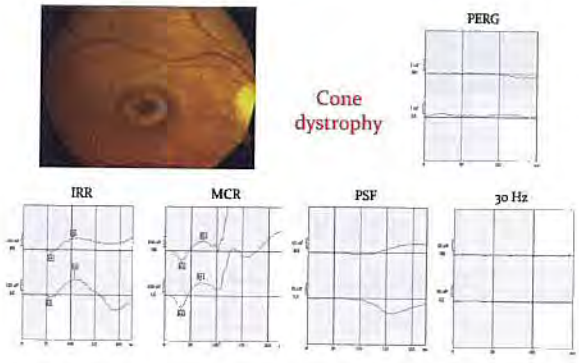


Figure 19. Bull's eye maculopathy in a 47 year old female with reduced vision of 20/100 since 15 years. ERG shows absent cone responses including PERG and reduced cone component in maximal combined response.

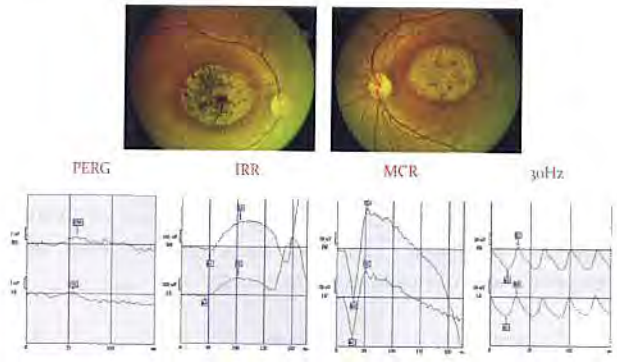


Figure 19 a. 36 male with a VA of 20/200, color vision loss and central scotoma. Localized macular cone dystrophy involving only macular photoreceptors as seen by severely reduced and delayed P50 in PERG. Other flash ERG responses are normal including photopic responses as the peripheral cones (that are more in numbers than macular cones) are uninvolved.

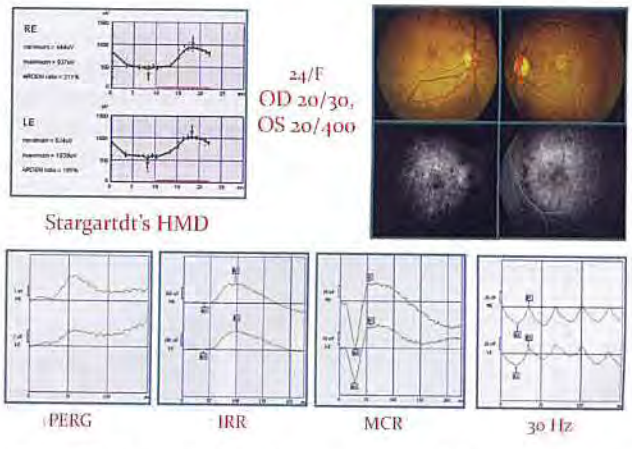


Figure 20. Normal EOG and normal Flash ERG in a 24 year old female with macular dystrophy. Silent choroid on FFA confirmed Stargardt's macular dystrophy. Pattern ERG affected in both eyes, left eye more than right eye with corresponding visual acuity loss.

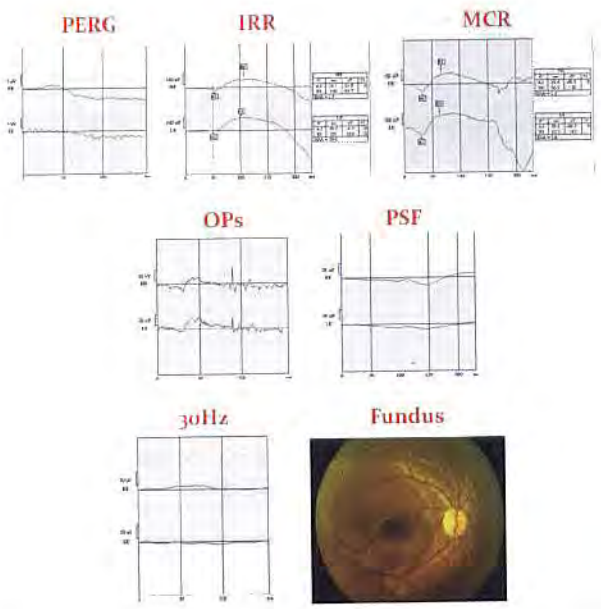


Figure 21. Rod Monochromatism. Showing poorly recordable PERG (due to nystagmus), and absent cone mediated responses (PSF, 30Hz) with normal scotopic rod mediated responses (IRR, MCR). Child of 8 years had a VA of 20/400, congenital nystagmus that had reduced with time and photophobia with complete achromatopsia.

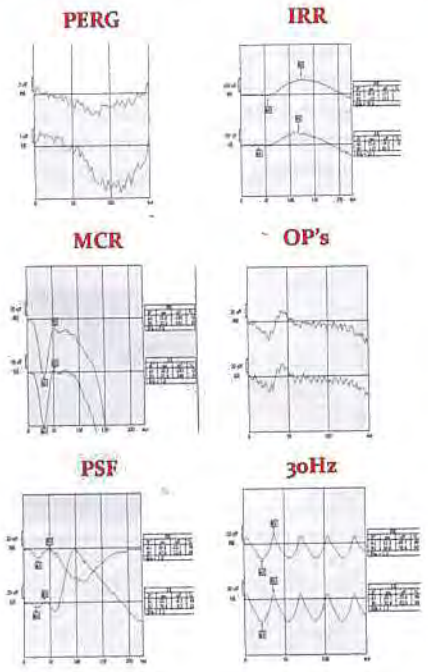


Figure 22. Negative ERG with preserved but delayed and subnormal isolated rod responses and photopic flash and flicker ERG suggestive of incomplete CSNB. Due to nystagmus commonly present in these eyes, pattern ERG recording is difficult and cannot be commented upon. See Figure 14 for Complete CSNB

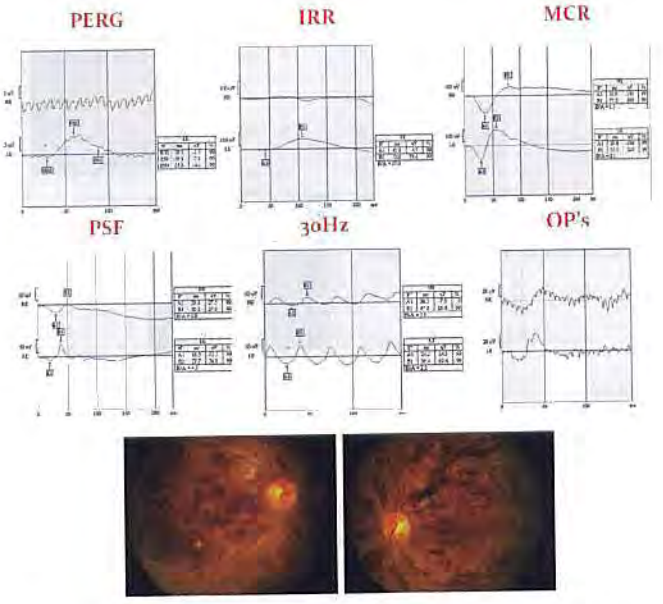


Figure 23. Ischemic CRVO in RE and non-ischemic in LE of a 40 year old male. RE has reduced b/a wave ratio and increased latency of b-wave in MCR; reduced amplitudes and delayed stimulus-to-peak time of 30 Hz flicker with absence of PERG, isolated Rod Response and oscillatory potentials. LE has no delays in responses but reduced amplitudes of all waveforms.

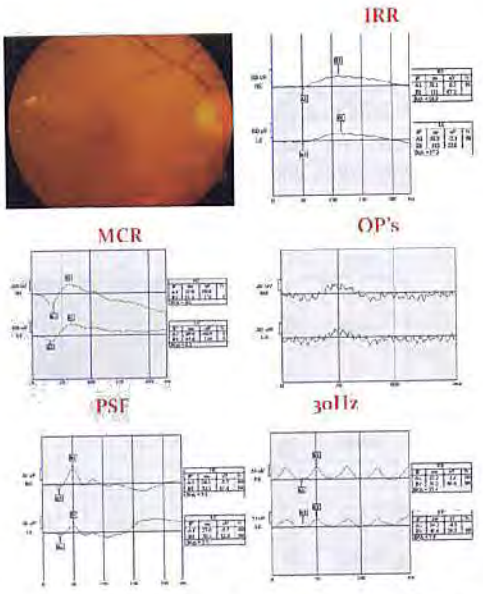


Figure 24. Ocular ischemic syndrome. 68 year old female with a VA of 20/50 and early cataract in each eye. Top: Fundus had features of NPDR, dilated veins and minimal disc pallor. ERG showed bilateral affliction. There was reduced amplitude of rod mediated inner retinal responses (IRR), and reduced b/a wave ratio in maximal combined response (MCR). The inner retinal ischemia was depicted by reduced amplitudes and poorly recordable OP, with delayed stimulus-to-peak time of 30-Hz flicker ERG. Carotid artery doppler (not shown) showed moderate atheromatous changes. Patient developed neovascular glaucoma six months later without worsening of retinopathy in the right eye and NVI in left eye after 8 months.

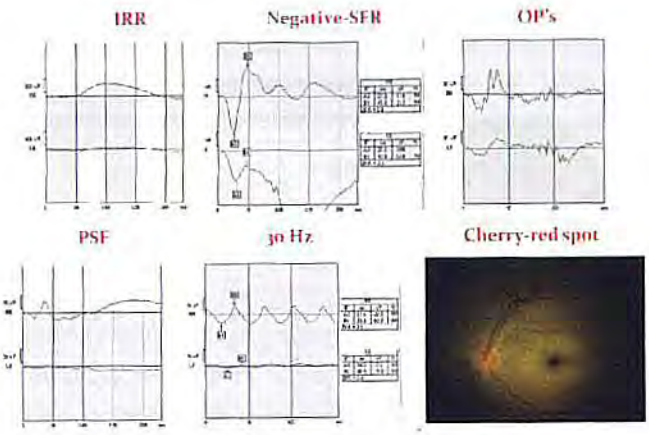


Figure 25. CRAO in left eye shows preserved a-wave and absent b-wave (negative ERG) in single flash response depicting preservation of outer retinal cell layers supplied by choroidal vasculature and ischemia in inner retinal layers supplied by central retinal artery. Right eye responses are normal.

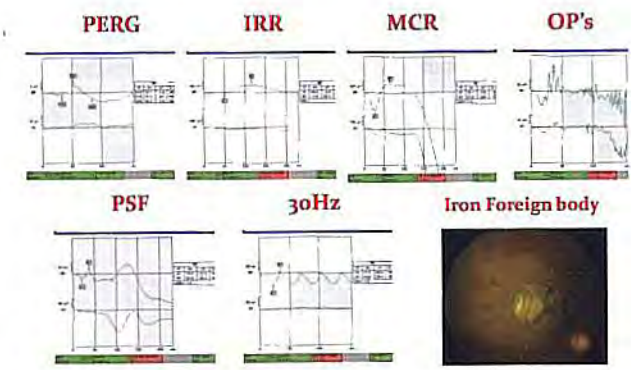


Figure 26. 34/M, defective Vision (OS) since last 2 yr. In advanced siderosis, retinal arterial narrowing and brown 'rust' pimentation is seen. ERG is extinguished except for a small a-wave in MCR. Removal of IOFB may not stop progressive visual loss and sometimes phthisis bulbi. Blink artifact is seen in the cone response.

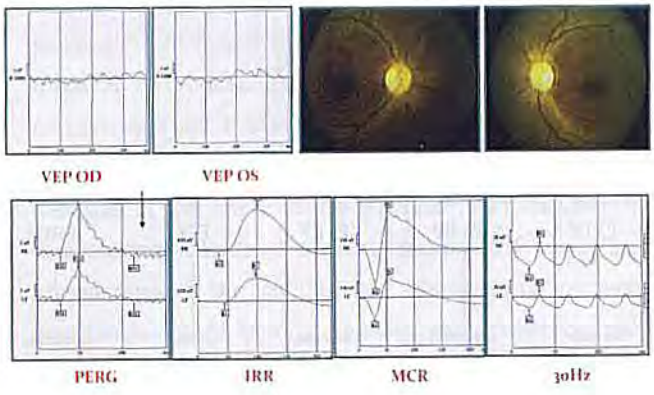


Figure 27. The pattern VEP is undetectable. Flash ERGs are normal. In PERG, the N 95 is absent (arrow) and P 50 is preserved confirming bilateral optic neuropathy. Visual fields showed central 7 degrees of scotoma in both eyes. History of antitubercular treatment in the past pointed to a diagnosis of possible ethambutol toxicity affecting the ganglion cell layer.

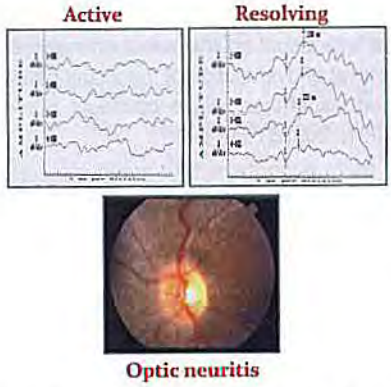


Figure 28. In acute optic neuritis, there is usually an unrecordable or poorly recordable pattern-VEP (PVEP) response. With recovery of vision, the waveforms of PVEP start appearing and over a period of time that may be up to 2-3 months the amplitude of PVEP may return to normal. However, the latency of P 100 remains prolonged for a long time and may never return to normal. The flash VEP is unrecordable in acute optic neuritis and may take longer to recover or may not recover at all. In eyes with abnormal VEP one should ensure that Pattern ERG P 50 is normal to exclude macular causes of abnormalities in VEP.

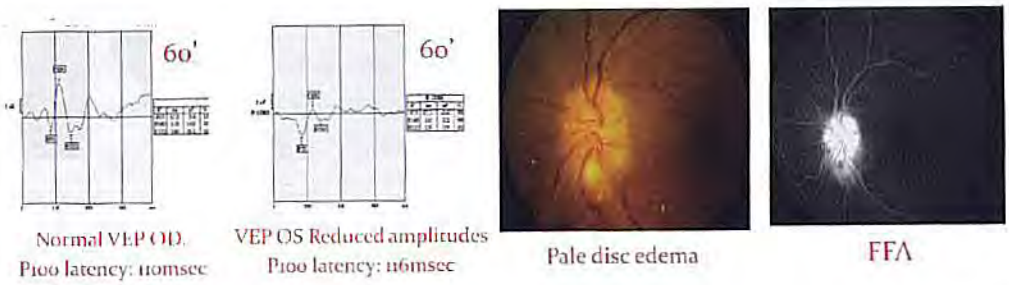
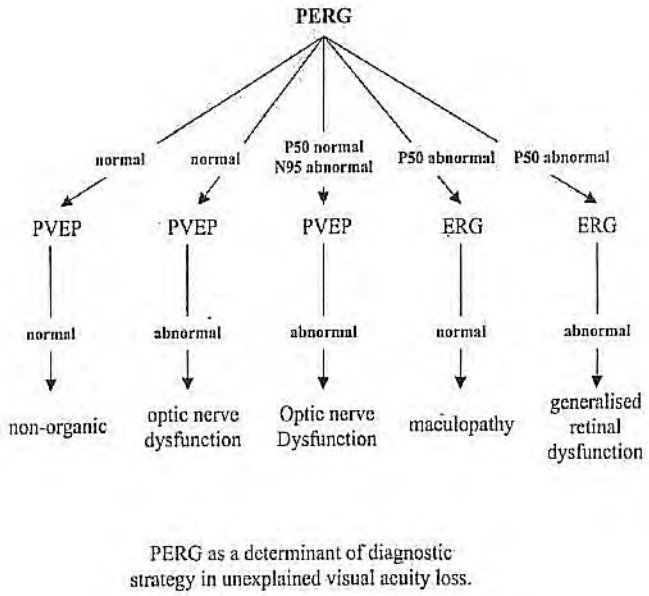


Figure 29. VEP in AION to 60 minute check size showed reproducible waveforms with reduced amplitude of P100.



PERG as a determinant of diagnostic strategy in unexplained visual acuity loss.

Figure 30. This slide shows a logarithm using pattern ERG as the first test, to proceed and interpret various electrophysiological tests in patients with visual acuity loss of unknown etiology. This helps to detect level of dysfunction of the visual pathways in eyes with unexplained visual loss. (Slide courtesy: Holder GE. Prog Ret Eye Res 2001; 20: 531-561)

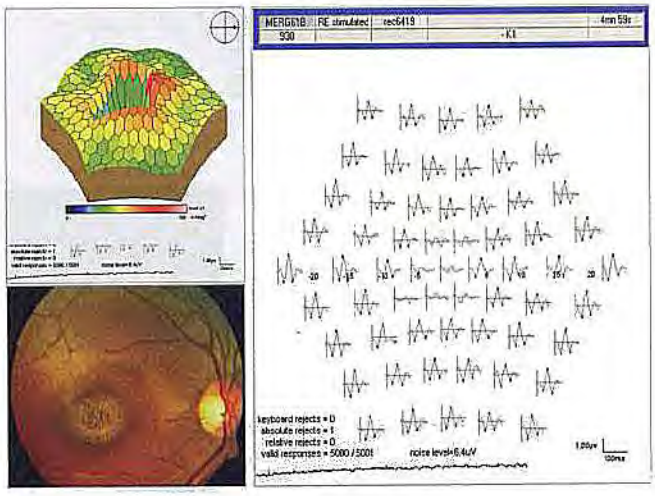


Figure 32. Multifocal ERG showing central retinal dysfunction and preserved paramacular function Stargardts' Heredomacular Degeneration

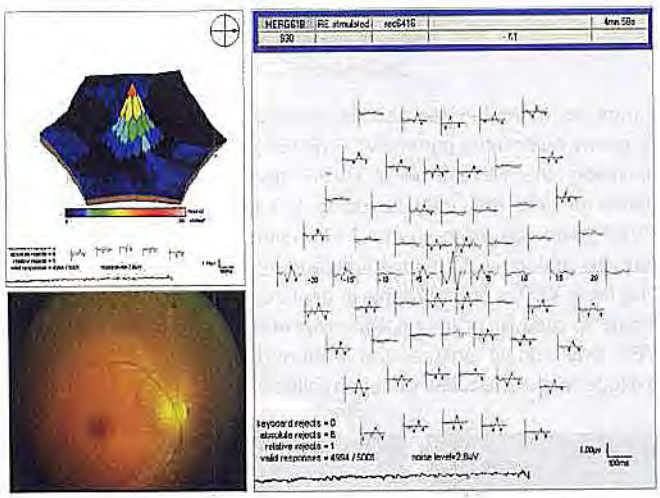


Figure 31. Macular sparing in retinitis pigmentosa seen on multifocal ERG

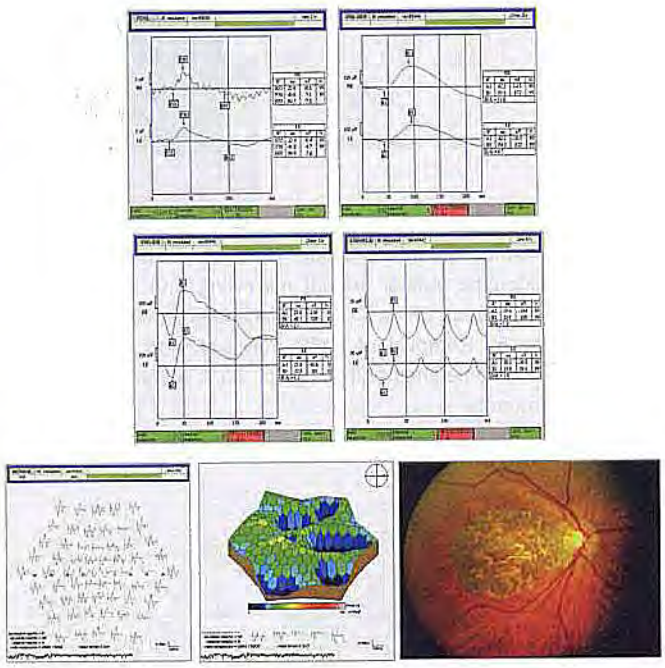


Figure 33: Normal flash and pattern ERG but abnormal, patchy changes in multifocal ERG could map out areas of relative functional sparing in an eye with central areolar atrophy

subject has the largest response density. The trace arrays are essential as they provide not only the actual data but also help to observe the reliability of the recording. In some cases, it is helpful to sum or average the responses within various regions of the display, such as within rings around fixation or as quadrants. Other displays include 3D scalar plot, with the peak representing the responses from the fovea and the trough the responses from the optic disc in a normal subject (Figure 8). Scalar plot images must never be shown in isolation; they must always be accompanied by the corresponding trace array.

Multifocal ERG waveform

Each focal trace response (Figure 9) typically consists of an initial negative wave (N1) followed by a positive peak (P1) and a later negative wave (N2), similar to a conventional photopic ERG. The origins of the components are still under research. The belief is that the cone-derived bipolar cell activity largely shapes the mfERG waveform, together with small contributions from the photoreceptor cells and inner (amacrine and ganglion) retinal cells.[24-26] The rods do not contribute except under very unusual circumstances.[27]

What are first and second order kernels?

The mfERG responses in Figure 9 are first-order kernels. The derivation of the first-order kernel for a given hexagon represents the response to the m-sequence. Mathematically, it can be obtained by adding all the records following the presentation of a flash in that hexagon (i.e. the presentation of a white hexagon), and subtracting all the records following a dark frame (black hexagon). This ensures that there is a build up of only the response to that hexagon, while elimination of the responses associated with all other hexagons. For a large majority of clinical conditions, first order responses are used.

Second order kernel (2K):

Sometimes a particular hexagon appeared white, a flash preceded it; the rest of the time a flash did not precede it. If the responses under the two conditions are the same, then there is no 2K response. If these two responses differ, then there is a 2K and it is the difference between the 1K responses. Thus, the presence of a 2K indicates that there is an effect of short-term adaptation on the final waveform because of the effect of the previous flash status. Hence, suggestions include that a diminished 2K indicates an abnormality in the circuits and connections involved in adaptation rather than a missing component or cellular response.[22, 23] There is only limited evidence that the 2nd order kernel responses have any clinical value, but one study showed that the reduction in 2K was more than the reduction in 1K in a patient with branch retinal artery occlusion.[28]

Electrooculogram (EOG)

The eye is in some ways like a battery with the standing potential of the eye resulting in the cornea being positive in relation to the retina. The standing potential, in the region of 6mV, varies according to the adaptive state of the eye and is dependant upon the function of the RPE. For example, retinal illumination by a steady light raises the level of the standing potential. The EOG is used to measure changes in the standing potential to light and dark conditions and is hence a measure of the photoreceptor-mediated RPE function. The development of a normal light peak requires normally functioning photoreceptors in contact with a normally functioning RPE, leading to progressive depolarization of the RPE basal membrane by mechanisms not fully understood. Clinically, EOG measures the standing potential indirectly with the patient making lateral eye movements with skin electrodes placed nasal and temporal to the eye, at the inner and outer canthi.[20] Changes in the standing potential can also be induced by chemicals, such as alcohol or acetazolamide, without the use of light.[21]

Recording Technique: (Figure 10)

Pupillary dilatation and a Ganzfeld dome are usually used. Standard silver-silver chloride or gold surface electrodes are placed at both inner and outer canthi, taking care that all

electrodes fall in the same horizontal plane to minimise artefact contamination from vertical eye movements which can occur when the patient blinks. The electrodes can be connected so that an eye movement to the right results in an upwards deflection on the screen. The ground electrode is typically placed on the forehead. The skin electrodes are applied using standard techniques to ensure that impedance is =5KΩ. Avoid too bright or dim illumination before EOG recording; the patient should be in room light for approximately 15 minutes before recording.

Consistent ocular saccades are induced by alternatively illuminating the fixation lights (LED) which are 30 degrees apart within the Ganzfeld dome, and asking the patient to follow the alternating targets from right to left, and then from left to right. The patient should be instructed to make sure that only the eyes move; the head should remain still throughout the procedure. Saccades are recorded for first 10-15 seconds of each minute, allowing 45-50 seconds rest. After a baseline adaptation in the Ganzfeld the lights are turned out, recordings take place for 20 minutes in the dark phase and 15 minutes after the Ganzfeld background is illuminated (the light phase). The EOG is quantified by calculating the ratio of the maximum amplitude in light (the light peak) to the minimum amplitude in darkness (the dark trough). It is usually expressed as a percentage, the Arden index. A normal EOG light rise will be >175% for most laboratories (Figure 11).

Only a normal functioning RPE will have a normal EOG light rise. However, as the EOG light rise also depends upon photoreceptor function, patients with abnormal rod ERGs will usually have reduction in the EOG light rise that mirrors the extent of rod photoreceptor disease. Any discrepancy, such that there is profound EOG light rise reduction, but relatively good rod function, then localises the dysfunction to the RPE. The classic use of EOG is in the diagnosis of Best's macular dystrophy, where the EOG light rise is virtually abolished in the presence of normal ERGs. Asymptomatic genetic carriers of the mutation show EOG abnormality, and if Best's disease is suspected in a young child who is not capable of doing the EOG, testing of both parents should be performed; as Best's disease is dominantly inherited, one of the parents must carry the mutation if the child is affected and will manifest the characteristic EOG abnormality.

Visual Evoked Potential (VEP)

The VEP is an evoked electrophysiological potential that can be extracted, using signal averaging, from the ongoing EEG (electroencephalographic activity) activity recorded at the scalp. The VEP is assumed largely to arise in the occipital cortices and allow assessment of the functional integrity of the visual pathways. Although of high importance in the assessment of the intracranial visual pathways, it should always be remembered that as a "downstream" response the VEP can be affected by a lesion anywhere in the visual path, including the eye, and that VEP abnormalities in themselves are often non-specific.

The ISCEV VEP standard[5] describes basic responses elicited by three commonly used stimulus conditions using a single midline channel. However, chiasmal and retrochiasmal disease can be missed using a single midline channel, and these can only be accurately identified using multichannel recording. The most commonly used stimulus is a black and white reversing checkerboard, such that the black and white squares interchange. It is important that there is no change in overall luminance at any stage, particularly during the pattern reversal. The pattern reversal VEP has the advantages that the waveform is very similar across a population, and the standard deviation for the peak time of the main components is low. Other commonly used stimulus types are pattern onset (pattern appearance) where the pattern emerges from a uniform gray background of identical overall mean luminance then to be replaced by the background; and diffuse flash. The latter is useful in patients where poor co-operation or optical factors make pattern stimulus inappropriate, including babies and young infants.

Recording Technique:

A black and white checkerboard pattern is most often used in diagnostic work. Definition of the pattern size is by the visual angle, in degrees and minutes of an arc, subtended at the eye by the side of a single check. Standard check sizes are 60 and 15 minutes and contrast should be more than 75%. There should be equal number of black and white squares. Luminance of the white areas should be at least 80 candelas per meter squared. Mean luminance variation between centre and periphery of the pattern should not be more than 30%. Background room light is subdued and no bright light surrounds the stimulus. Recording requires a stimulus field size of ~15 degrees and central fixation. The pattern reversal rate is often two reversals/second (1Hz) for a "transient" VEP. At higher reversal rates, the responses merge and become sinusoidal or "steady-state".

Standard surface EEG electrodes are applied to the scalp using standard techniques and ensuring that electrode impedances are equal and =5KΩ. The electrodes are position at Oz and Fz according to the International 10/20 system (Figure 12). The nasion is at the junction of the nasal bones to the frontal bone at the top of the nose. The inion is the bony protrusion at the back of the head in the midline. Using a measuring tape, one measures the distance between inion and nasion. A point midway between these two points (50%) marks the vertex (Cz). The point at 10% distance above the inion marks the Oz where the active positive recording electrode is placed. The reference electrode is placed at Fz, 70% of the distance between inion and nasion (30% from the nasion going towards the inion). A ground electrode is usually placed on the forehead, but an ear lobe is a suitable alternative.

Recording the VEP requires a natural size pupil. In case of any gross anisocoria or abnormal pupil size, the interpretation of potential abnormality may need modification. Appropriate refractive correction in place ensures a well focused pattern. Recordings are best taken at a fixed distance from the monitor to standardize the visual angle of the stimulus checks. The non-stimulated eye should be occluded. Muscle and movement artifacts should be minimised by providing a fixation target and a relaxed sitting position of the patient. It should perhaps be noted that the reversal VEP is of limited value in a patient with nystagmus in the primary position of gaze, and interpretation of reversal VEPs must proceed with great caution if nystagmus is present during recording.

The transient VEP (<3/sec; 1.5Hz) waveform consists of a prominent positive component at approximately 100 ms (P100) preceded and followed by negative components (N75 and N135) (Figure 13). The main measurements are of the size and timing (usually, but incorrectly, called latency) of the P100 component. The amplitude can be measured as N75-P100; P100-N135; or as a mean of those two measures. Many non-pathological recording conditions influence P100 latency including contrast, luminance, field size and check size and it is essential for each laboratory to establish their own normal controls. As the VEP peak time varies with age, it is also important that age related normative control data are obtained.

The size of the stimulus field is particularly relevant to the use of hemi-field stimulation. There is paradoxical lateralization of the hemi-field pattern VEP with a large field, large check stimulus (as recommended by ISCEV); such that the hemi-field response is recorded over the hemisphere ipsilateral to the stimulated hemi-field, but anatomical lateralization occurs with a small field, small check stimulus. This latter small field, small check stimulus facilitates accurate identification of the P100 component in case of doubt. This only applies when multi-channel recording is being used. With a single midline channel there is no real way of predicting how much each hemisphere of the brain is contributing to the signal recorded at the midline to a full-field stimulus.

Flash VEP is helpful in eyes with hazy media or uncooperative patients and also infants and small children.

The stimulus used should subtend a visual field of at least 20 degrees. Most commonly this will be a hand help stroboscope. Use of a Ganzfeld for flash VEP usually results in recordings markedly contaminated by muscle artefact in relation to the use of a chin rest. Generally, a position where the chin is forwards, such as when a chin rest is used, is inappropriate to achieve the desired relaxation of the neck muscles. The flash VEP is a complex waveform (Figure 13) that shows marked inter-individual variation. Generally there is a prominent positive component at 100-120 milliseconds. Although there is much higher inter-individual variability in the flash VEP, within the same patient interocular and interhemispheric (if recorded) asymmetries are of a similar magnitude and variability to pattern reversal VEPs.

The pattern onset-offset response has wider inter-subject variability but is useful in the assessment of potential malingerers, as it is difficult to defocus a rapidly appearing and disappearing stimulus pattern. It is also useful in patients with unsteady fixation or nystagmus as that has little effect on the waveform. Usual adult responses show three peaks - C1, a positive peak at 75 milliseconds, negative C2 peak at 125 msec and C3 positive peak at 150 milliseconds. Use of a short duration stimulus, perhaps 40ms, is appropriate for visual acuity assessment and detection of intracranial misrouting associated with albinism. Many other types of VEP recordings are possible for assessing intracranial visual pathway lesions. These help in checking the integrity of the visual system beyond the chiasma and the chiasmal structure such as in ocular albinism. These are beyond the scope of the present lecture.

VEP interpretation should never be in isolation in eyes with unexplained vision loss. In such cases, assessment should include PERG, flash ERG and VEP to refine the site of lesions. Visual fields are also useful in such eyes. In obvious optic nerve disease clinically, VEP can help to differentiate some conditions such as demyelination from ischemic neuropathy.

Clinical Examples

We will now look into some clinical examples to understand the clinical utility of electrophysiological recordings (Figure 14). For clearer depiction of very small or large responses, the scales of amplitude in the test and normal recordings may be different and calibration values should always be taken into account when looking at test results. Remember that visual electrophysiology results need interpretation in the context of all other clinical and investigative findings to arrive at the correct diagnosis. Electrophysiological recordings should never be interpreted in isolation; potentially serious errors could occur.

Dysfunction of the retinal pigment epithelium

Dysfunction at the level of the RPE is assessed by EOG. The most common disorder where EOG is diagnostic is Best's disease (vitelliform macular dystrophy), a dominantly inherited disorder related to mutation in *VMD2*. The data shown in Figure 15 come from a patient with reduced visual acuity and bilateral macular lesions. The ERGs are completely normal, but the EOG shows an extremely poor light rise. The data therefore indicate severe generalised dysfunction at the level of the RPE and are in keeping with Best's disease.

Photoreceptor dysfunction

ERG readily depicts photoreceptor dysfunction in conditions like retinitis pigmentosa, choroideremia, and secondary dysfunctions following posterior uveitis or trauma or retinal detachment. Reduction in the a-wave of the bright flash ERG is the primary abnormality and due to the hierarchical system in visual pathways, the b-wave of the ERG from the inner retina will also be affected.

Retinitis Pigmentosa (RP): (Figure 16, 17) Retinitis pigmentosa, a group of inherited photoreceptor degenerations with many genetic causes, is a rod-cone dystrophy; that is, the rod system is more affected than the

cone system as demonstrated by ERG. The (full-field) ERG may be undetectable in severe disease, but more commonly shows a rod-cone pattern of dysfunction. Typically, the rod ERG is reduced or undetectable showing loss of rod-system function, but that abnormality is non-specific for the level of dysfunction. The reduction seen in the bright flash ERG a-wave confirms the dysfunction to be at the level of the photoreceptor. Cone ERGs will also be abnormal; in the vast majority of cases, and there is usually a shift in the peak time of the flicker ERG. A delayed 30Hz ERG is commonly seen in the context of generalised cone system dysfunction. The most severe phenotype occurs in X-linked disease.

Retinal degeneration associated with restricted disease, such as sector RP, where there is restricted pigmentary deposition usually affecting the inferior fundus, is associated with a better long-term prognosis. Some patients with restricted pigmentation have generalised retinal dysfunction and the ERG can be very useful. Amplitude reduction but no timing shift usually reflects restricted disease, but timing shift, best seen in the 30Hz flicker ERG, tends to suggest generalised dysfunction even in the presence of localised pigmentary change.

In RP eyes where the macula is spared, the PERG can be normal (Figure 17). Figure 16 shows the ERG of a patient with undetectable PERG and undetectable ERG due to the involvement of both central and peripheral retina. In Figure 17, there is preserved PERG in a patient of RP with undetectable flash ERG showing macular sparing. Visual acuity in this 25 year old male was 20/25 and visual fields showed central island of 10 degrees. The patient usually presents with night blindness and/or visual field constriction. The fundus will have diffuse grey appearance due to RPE degeneration and often but not always, show bone spicule intra-retinal pigmentation due to pigment migration from RPE consequent upon photoreceptor cell death.

Cone-rod dystrophy (CRD): Generalised photoreceptor degenerations where the cone ERG is more abnormal than the rod ERG are known as cone-rod dystrophies. The patient will usually present with photophobia and progressive reduction in visual acuity due to central retinal involvement and may have a visible abnormality at the macula. The role of the ERG in any such patient is to distinguish between a cone dystrophy, where there is generalised retinal cone system dysfunction but the rod system is normal or near normal; a cone-rod dystrophy; and a macular dystrophy where, by definition, the full-field ERGs are completely normal and the dysfunction is confined to tests of central retinal function such as the PERG or mfERG. The patient shown in Figure 18 had a visual acuity (VA) of 20/60 in both eyes. Fundus photographs show bilateral bull's eye lesions at the maculae, mild arterial narrowing, peripheral RPE degeneration and disc pallor. In this very severe example, the ERG (Figure 18) shows absent cone ERGs with subnormal but recordable isolated rod responses (the rod ERG and the SF ERG). Note large blink artefacts towards the end of recordings (arrows), commonly seen due to photophobia in these subjects.

Cone dystrophy (CD): A cone dystrophy is a retinal degeneration where there is generalised retinal cone system dysfunction but normal or near normal rod ERGs. Patients will usually present either with photophobia and/or visual acuity reduction, and may have a visible abnormality at the macula, perhaps a Bull's eye lesion as seen in Figure 19.

Macular Dystrophy: By definition, a true macular dystrophy has dysfunction confined to the macula and so the full-field (flash) ERG is normal. Figure 19 shows a 36 year old male with a VA of 20/200, color vision loss and central scotoma. Only macular photoreceptors are affected causing severely reduced and delayed P50 in PERG (Figure 19a). Other flash ERG responses are normal including photopic responses as the peripheral cones (that are more in numbers than macular cones) are uninvolved. Some disorders, for example ABCA4 mutation, may predominantly give a macular dystrophy, in this case Stargardt's disease, but severe mutations can result in a CD or CRD phenotype. The full-field ERG has

prognostic value. Figure 20 shows a 24 year old female with macular flecks more in the left than right eye. The flash ERG is equal and normal in both eyes, but the PERG, driven by the macular photoreceptors, is abnormal. Multifocal ERG would also be abnormal in such cases. EOG is normal in both eyes. FFA shows characteristic choroidal hypofluorescence with foveal involvement in left eye and foveal sparing in right eye.

Rod Monochromatism: Generalized cone dysfunction is the hallmark on ERG (Figure 21). Photophobic child of eight years had a VA of 20/400, and a congenital nystagmus that had reduced with age. There was complete achromatopsia. ERG had poorly recordable PERG, which can occur in association with the nystagmus or macular cone dysfunction, and absent cone mediated ERGs (photopic, 30Hz) with normal rod mediated responses (rod, SFR). Most of these patients have a stable course, though rarely some eyes have progressive deterioration.

Inner Retinal Dysfunction

Diseases that spare photoreceptor function, and affect only the inner retinal layers (e.g. the bipolar cells) or the first synapse, show a negative ERG waveform in the SFR. A negative ERG is where a normal amplitude a-wave is larger than the b-wave in the standard flash response. A "negative waveform", so described because the waveform is dominated by the negative a-wave, indicates that dysfunction is occurring post-phototransduction (Figure 14). Common inherited causes of a negative ERG include congenital stationary night blindness (CSNB) and X-linked juvenile retinoschisis; the most common acquired cause is retinal vascular occlusion, usually central retinal artery occlusion (CRAO) and less commonly central retinal vein occlusion (CRVO). Some other causes include birdshot chorioretinopathy, quinine toxicity, melanoma associated retinopathy (MAR), Batten disease, siderosis bulbi and some cases of cone rod dystrophy.

Congenital Stationary Night Blindness (CSNB):

The two most common forms of CSNB are the so-called "complete" and "incomplete" X-linked forms. The distinction was originally made on the basis of the rod ERG and psychophysics, but it has subsequently been shown that these reflect two genetically distinct entities. Complete CSNB (cCSNB) relates to mutation in *NYX*, which encodes nyctalopin, which may play a role in the development of retinal interconnections involving the ON-bipolar cells. The phenotype of "complete" CSNB is therefore that of involvement of the ON- pathway in both rod and cone systems, but sparing of the OFF –pathway. The gene for incomplete CSNB (iCSNB), *CACNA1F*, encodes a pore-forming sub unit of a voltage-gated calcium channel believed to modulate transmitter release from photoreceptor pre-synaptic terminals. Thus, both ON- and OFF- pathways are affected in iCSNB. The differences are reflected in the ERG findings, although both have a similar appearing, profoundly electronegative SFR. The cCSNB (Figure 14) has an undetectable rod-specific ERG. The cone flicker and photopic (single flash) ERGs show distinctive abnormalities. The photopic ERG has a broad a-wave followed by a b-wave lacking photopic OPs and showing a low b:a ratio. This appearance is thought to reflect loss of cone ON-bipolar contribution but preservation of the OFF- pathway found in long and medium wavelength cone systems. This is confirmed by the results of long duration ON- OFF- ERGs, which reveal a normal a-wave, a selectively diminished ON-b-wave and preservation of the OFF- d-wave, consistent with involvement of the depolarising ON- bipolar cell pathway. S-cone ERGs are also affected, confirming the defect to be post-phototransduction in rods and all cone types. The electroretinographic changes in cCSNB are identical to those in melanoma associated retinopathy, and demonstrate the importance of always placing electrophysiological data in clinical context.

Although also showing a profoundly electronegative SF dark adapted ERG, iCSNB typically has a detectable, but subnormal or delayed, rod-specific ERG. These are accompanied by a subnormal, delayed 30Hz flicker ERG

that has a typically bifid appearance. The photopic single flash ERG may be markedly subnormal and occasionally has an "electronegative" waveform. Overall, the cone-mediated photopic ERG abnormalities in iCSNB are more apparent than those of cCSNB (Figure 22) as both ON- and OFF-responses are affected.

Inner retinal dysfunction of vascular etiology

ERG changes are profoundly helpful to detect inner retinal ischemia. Fundus fluorescein angiography or fundus appearance may not always detect the true extent of retinal ischemia. Media haze, inability to image peripheral retinal ischemia, and extensive retinal hemorrhages can all mask the actual extent of angiographic non-perfusion. ERG bypasses all these limitations and, being a global response, gives the true extent of retinal ischemia. The non-invasive nature of ERG is a distinct advantage.

Retinal Ischaemia in central retinal vein occlusion (CRVO): Bilateral CRVO in a 40 year old male (Figure 23). Right eye has a reduced b/a wave ratio and increased latency of b-wave in MCR; reduced amplitudes and delayed stimulus-to-peak time of 30 Hz flicker. There is absence of PERG, the rod response and the OPs. The left eye has no response delay but only reduced amplitude. The CRVO was thus ischemic type in the right eye and non-ischemic in the left eye. Reduced b-wave amplitude has 80-90% sensitivity and 70-80% specificity to detect inner retinal ischemia. An absolute peak time of more than 36 msec in latency of the flicker ERG responses[29] or a difference of more than 7 msec between affected and normal eye are almost pathognomonic of ischemic type of CRVO in a given clinical setting.

Ocular ischemic syndrome: A 68 year old diabetic female with a VA of 20/50 and early cataract in each eye. Fundus evaluation had features of non-proliferative diabetic retinopathy, dilated veins and minimal disc pallor (Figure 24). ERG showed reduced amplitude of rod system mediated inner retinal responses, and a reduced b:a wave ratio in the SFR. The inner retinal ischemia was depicted by reduced amplitudes and poorly recordable OPs, with delayed stimulus-to-peak time of 30-Hz flicker ERG. Carotid artery doppler (not shown) showed moderate atheromatous changes. The patient developed neovascular glaucoma six months later without worsening of retinopathy in the right eye and, developed neovascularisation of the iris in the left eye after 8 months. Both eyes responded to panretinal photocoagulation.

Retinal arterial occlusions: A negative ERG is very characteristic of central retinal artery occlusion due to the double blood supply of the retina. The RPE/photoreceptors are supplied by the choroidal circulation, via the short posterior ciliary arteries, and are therefore spared in central retinal artery occlusion (CRAO). As the central retinal artery supplies the inner nuclear layer, the b-wave (and OPs) is selectively affected. CRAO in the left eye shows (Figure 25) preserved a-wave and reduced b-wave (negative ERG) in the SFR. All other responses are also affected. Note the reduced and delayed 30Hz flicker ERG. Right eye responses are normal. In ophthalmic artery obstruction the ERG is undetectable because photoreceptor function is completely lost.

Drug and chemical Toxicity

It is important to monitor and withdraw patients who are on drugs known to be toxic to retina/optic nerves at the earliest sign of toxicity. Commonly monitored drugs include chloroquine, antitubercular drugs such as ethambutol, and antiepileptic drugs. ERG tests are also useful in preclinical animal evaluation of new drugs by the pharmaceutical industry, before approval for clinical usage. Clinical trials of new drugs are increasingly using electrophysiology to ensure the absence of retinal toxicity.

Siderosis bulbi: ERG can detect and prognosticate siderotic changes in eyes with retained iron intraocular foreign body (IOFB). ERG may be normal or show a negative ERG

pattern in early phase of siderosis bulbi. Removal of IOFB may lead to improvement in ERG changes and a stable outcome in such cases. In advanced siderosis, media is hazy and 'rust coloured' with undetectable ERG (Figure 26). Removal of IOFB will not stop progressive visual loss and sometimes phthisis bulbi. The upper waveform shows a blink artefact.

Ganglion cell dysfunction

This can be demonstrated by the N95 component of the pattern ERG. There is also some evidence that the PhNR may also be useful in disease of the retinal ganglion cells, but that test is still in its infancy and caution should be used until large studies examining specificity and sensitivity have been published. An 18 year old male (Figure 27) had rapidly progressive, bilateral, sequential loss of vision to 20/400, over 4 months. There was bilateral optic disc pallor with ill-sustained papillary reactions but no RAPD. The pattern VEP is undetectable (TOP). Flash ERGs are normal, but the PERG shows N95 reduction with preservation of P50, confirming bilateral optic nerve/retinal ganglion cell dysfunction. Visual fields showed central 7 degrees of scotoma in both eyes. A history of antitubercular treatment during that period pointed to possible ethambutol toxicity.

Intracranial visual pathway lesions

The VEP is invaluable in the assessment of the intracranial visual pathways, but as a "downstream" response it can be affected by dysfunction anywhere in the visual pathways leading to the occipital cortices. It is important to rule out macular disease before implicating optic nerve pathology as a cause of VEP abnormalities. In general, use of the pattern ERG in addition to the pattern VEP will enable macular disease to be either confirmed or excluded. It is very important to remember that macular disease can give marked VEP delays, and that an anatomically normal macula on clinical examination does not mean normal macular function. Multi-focal ERG can also be used to assess macular function, but it is better to use the PERG as that is giving the response of the macula to the same type of stimulus as that used to give the pattern VEP. Optical coherence tomography can also be useful, but again, demonstrates structure rather than function.

In acute optic neuritis, there is usually an undetectable or poorly recordable pattern-VEP (PVEP) response (Figure 28). With recovery of vision, the waveforms of PVEP start appearing and the amplitude of the PVEP may return to normal over a period months. However, the latency of P100 remains prolonged even with apparently complete clinical recovery and only rarely returns to normal. In addition, asymptomatic eyes in multiple sclerosis (MS) patients can demonstrate delayed P100 even with normal colour vision, normal fundus examination and normal papillary responses. This sub clinical optic nerve involvement is an important diagnostic tool to confirm diagnosis of MS in a given clinical context. The flash VEP remains recordable in acute optic neuritis and recovers faster than the pattern VEP. Other optic nerve diseases will also show VEP abnormalities; the pattern VEP will often be delayed, in for example toxic or compressive optic neuropathy, but although delays and severe abnormalities can be observed in ischaemic optic neuropathy consequent upon giant cell arteritis, in non-arteritic anterior ischaemic optic neuropathy (NAAION) the typical abnormality is amplitude reduction with minimal if any latency shift. The left eye of this 62 year old diabetic patient (Figure 29) had a sudden onset of visual acuity reduction to 20/100 and a superior altitudinal field loss. FFA shows leakage from disc margins *inferiorly and late staining of the* disc. VEP to 60 and 30-minute check sizes showed reproducible waveforms with reduced amplitude of P100. The latency was prolonged only minimally as compared to normal right eye suggestive of NAAION.

In optic chiasmal dysfunction, a single channel VEP recording is inadequate to localise the dysfunction; multichannel recordings are needed. A crossed asymmetry is the classical sign of chiasmal compression, whereby the VEP from the contralateral hemisphere is more abnormal than that from the ipsilateral hemisphere from both right and

left eyes. Abnormal VEP can be recorded from eyes with no field abnormality. However, the size of stimulus field and check size can profoundly affect the type of abnormality and great caution must be exercised. It is beyond the scope of this article to discuss this issue in full, but in essence, with a large field large check stimulus (e.g. 30 degrees, 50 minutes) the VEP shows paradoxical lateralisation whereby the response from one hemisphere of the brain is recorded over the opposite hemiscalp, but with a small field small check (e.g. 10 degrees, 15 minutes) the VEP lateralisation corresponds to the anatomy and the response from one hemisphere is recorded over the ipsilateral hemiscalp. As a general rule, in the presence of any interhemispheric asymmetry in VEP, an intracranial lesion should be considered, particularly if the pattern from the two eyes is opposite (the crossed asymmetry). Although visual fields and neuroimaging can diagnose chiasmal lesions accurately, VEP may be the first indicator of chiasmal dysfunction during the initial evaluation of a patient with visual loss. The VEP can also be useful during the follow-up of medically or surgically treated cases of pituitary tumours. Both flash VEP and pattern VEP recordings may show abnormalities or absence of waveform in patients with occipital cortical lesions. These patients usually have normal pupillary reflexes and neuroimaging will show occipital cortex lesions, perhaps infarction. These patients may have visual agnosia and so visual acuity and colour vision measurements are difficult. However, a report of occipital cortex lesions that do not show abnormalities in VEP leads to a presumption that extra-geniculocalcarine pathway could mediate some of these responses.

VEPs can also be useful in the diagnosis of the intracranial misrouting associated with albinism, where the majority of optic nerve fibres from each eye decussate to the contralateral hemisphere. The VEP thus demonstrates a crossed asymmetry, but opposite to that in chiasmal compression or achiasmia in that the better response arises in the contralateral hemisphere on stimulation of either eye. This is a rather specialised application which requires pattern appearance (onset) stimulation in adults and multichannel recording. Flash VEP can be used to demonstrate the same phenomenon, particularly in young children, but the flash VEP tends to be normal after teenage years and is best used in a child under the age of 8 years.

Another invaluable use of the VEP is in the assessment of suspected non-organic visual loss. Here, the responsibility of electrophysiology is objectively to show normal function even though the symptoms reported by the patient imply otherwise. The technician needs to take great care in such a patient to ensure that the recordings are not influenced by poor compliance, particularly poor fixation or deliberate defocusing.

Figure 30 shows an algorithm using pattern ERG as the first test, to proceed and interpret various electrophysiological tests in patients with visual acuity loss of unknown cause. This helps to detect the level of dysfunction of the visual pathways in eyes with unexplained visual loss. Full field flash ERG detects photoreceptor disorders as well as diseases that affect the inner-retina. Pattern ERG is a useful clinical test to assess the extent of macular involvement and to assist in the differentiation between macular and optic nerve dysfunction as a cause of a delayed pattern VEP. An abnormal pattern VEP in the presence of a normal P50 component of the PERG points to optic nerve dysfunction.

Applications of Multifocal ERG

Multifocal electroretinography can provide invaluable information regarding the spatial extent and characteristics of central retinal cone system dysfunction, but as the results are absolutely dependent upon the patient being able to maintain good fixation, again the data may need to be treated with caution. In general, mfERG data should be used in conjunction with conventional ERG as only the central retinal cones are being tested by mfERG. Although it can provide important research data, such applications are beyond the remit of this document.

The mfERG is particularly valuable in cases in which the fundus appears normal, and it is difficult to distinguish between diseases of the outer retina and diseases of the ganglion cells and/or optic nerve. The mfERG can also help to differentiate among outer retinal diseases, to follow the progression of retinal diseases and may help to differentiate between organic and nonorganic causes of visual loss.

The following pearls would illustrate this:

a) In diseases of the outer retina, the mfERG provides spatial information not readily available in the full-field ERG. For instance, the full-field 30 Hz flicker responses from patients with RP are summed from multiple regions in different states of the disease. Multifocal ERG readily shows these different hidden states not seen in the full-field ERG. The typical finding in RP is decreased amplitude and delayed implicit time. This is especially in the peripheral regions, where visual fields are most affected, signifying photoreceptor damage.[30] Very large delays (e.g. > about 7 ms) or relatively large response amplitudes with moderate delays (e.g. >about 4 ms) imply damage beyond the outer segment. The site is most probably in the outer plexiform layer, somewhere in the chain of action between the cone inner segment and bipolar post-synaptic membrane (Figure 31). Localised areas of normal and abnormal retinal function can be well mapped using mfERG (Figures 32, 33).

b) To differentiate diseases that affect the outer retina from those that affect the ganglion cell or optic nerve. A large delay in the timing of the mfERG is associated with damage to the photoreceptors/outer plexiform layer.[23] Damage to bipolar, amacrine, or ganglion cells yield relatively small changes in the implicit time of P_1 and may even shorten it.

c) The mfERG can help to follow the effects of clinical intervention.

i) Patients followed before and after treatment for retinal detachment with mfERG show temporal sequence of functional recovery. Observations show that it takes over a month or more for the mfERG to recover, and the mfERG changes correlate with the recovery of visual acuity and visual field sensitivity, although the mfERG may be more disturbed than expected from the visual fields.[31]

ii) Greenstein and colleagues have followed patients with macular edema, secondary to diabetic retinopathy, before and after laser treatment with mfERG. This demonstrated the widespread nature of timing deficits that are associated with clinically significant macular edema (CSME).[32]

iii) The mfERG has been used to objectively assess the functional improvement after procedures such as macular hole surgery with improvement of mfERG amplitudes having been noted after surgery.[33]

iv) It should be particularly useful in situations where one expects localized changes such as with experimental retinal transplant procedures[34] and local drug injections.

d) Non-organic disorders may be diagnosed using mfERG. The advantage of the mfERG over the conventional ERG is that it provides a topographical representation compared with the patient's visual fields. A normal mfERG does not establish a visual deficit as non-organic, all by itself. If the mfERG is normal, then a multifocal VEP is desirable to rule out damage to the optic nerve/ganglion cells.

e) Studying local responses from the normal retina. The full-field, cone ERG is comprised of different waveforms. The spatial aspect of the mfERG offers an advantage for studying the normal retina as well. Earlier studies of focal cone ERGs indicated that the waveform of the ERG varies with retinal location.[34] Using a slowed down m-sequence, one can readily see and study these variations with the mfERG. This has immense research potential.[36, 37]

Conclusion: Electrophysiological tests are useful to provide answers in a wide variety of clinical situations including retinal dystrophies, retinal vascular disorders, drug toxicity, visual loss of unknown etiology and trauma. For further details, text- books and chapters on electrophysiology are suggested below.[18, 38-40]

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