


ELECTROPHYSIOLOGY OF RETINA

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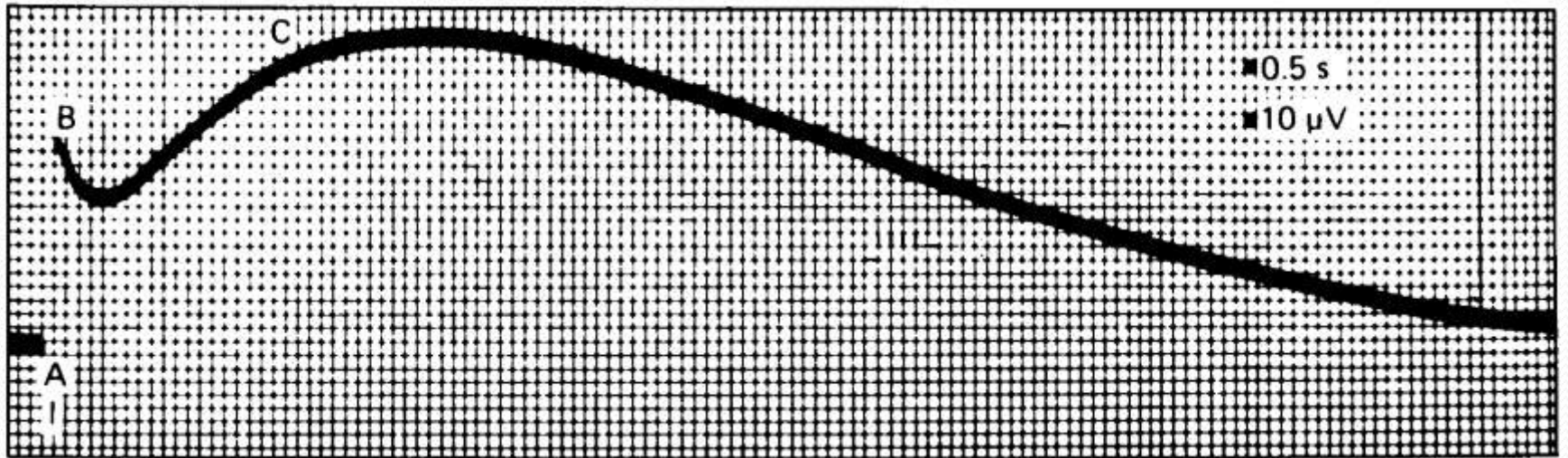
INTRODUCTION

- Electrical activity in the retina & visual pathway is the inherent property of the nervous tissues - which remain electrically active at all times, & the degree of activity alters with stimulation.
- When light excites the retina, a series of rapid & well defined electrical responses can be evoked from each layer of retina.

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- Visual transduction is the process by which light absorbed by the outer segment of the photoreceptor layer of the retina is converted into electrical energy.
 - The process is complex but a battery of electro diagnostic tests is now in clinical use, for assessing the integrity of retina & its central connections.

BACK IN TIME

- First described by Prof. E. D. Reymond who showed that cornea is electrically positive with respect to posterior pole of eye.
- In 1908 Einthoven & Jolly showed that a triphasic response could be produced by simple flash of light on retina.



Electrophysiological tests

Electroretinography (ERG).

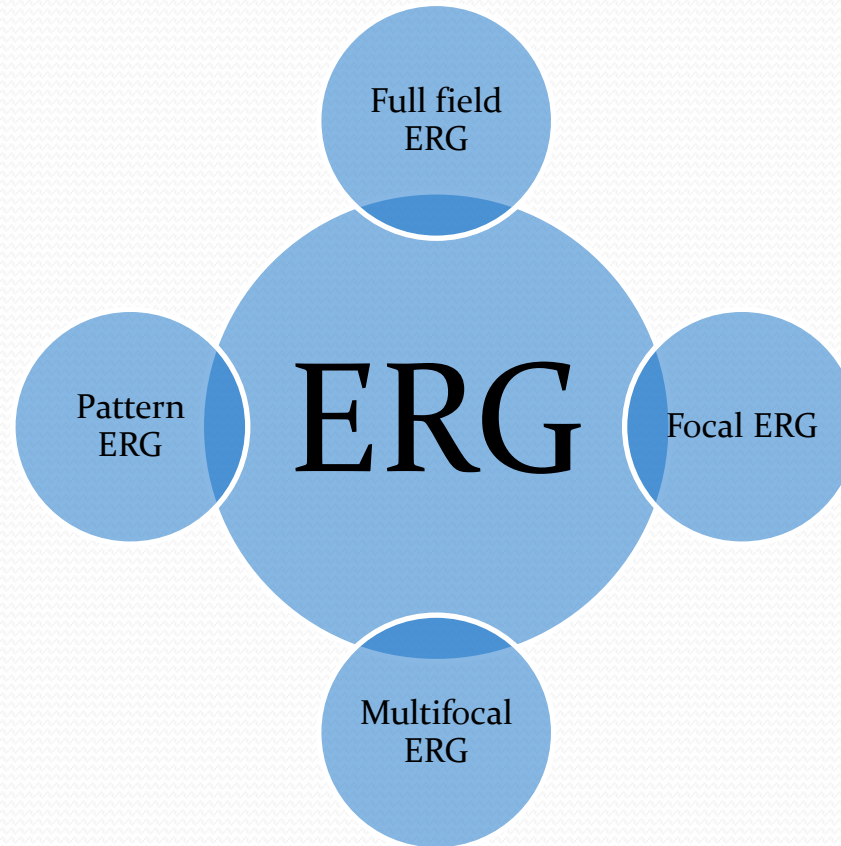
Electrooculography (EOG).

Visually evoked response (VER).

ELECTRORETINOGRAPHY

- ERG is the corneal measure of an action potential produced by the retina when it is stimulated by light of adequate intensity.
- It is the composite of electrical activity from the photoreceptors, Muller cells & RPE.

TYPES OF ELECTRORETINOGRAM



Full field electroretinogram

- ERG is the record of an action potential produced by the retina when it is stimulated by light of adequate intensity.
- A small part of the current escapes from the cornea, where it can be recorded as a voltage drop across the extracellular resistance, the ERG.

Technique of ERG recording

- Recording of ERG requires:-
 1. Recording, reference & ground electrodes.
 2. Ganzfeld bowl stimulator.
 3. Signal averager & amplifier.
 4. Display monitor & printer.



Patient preparation

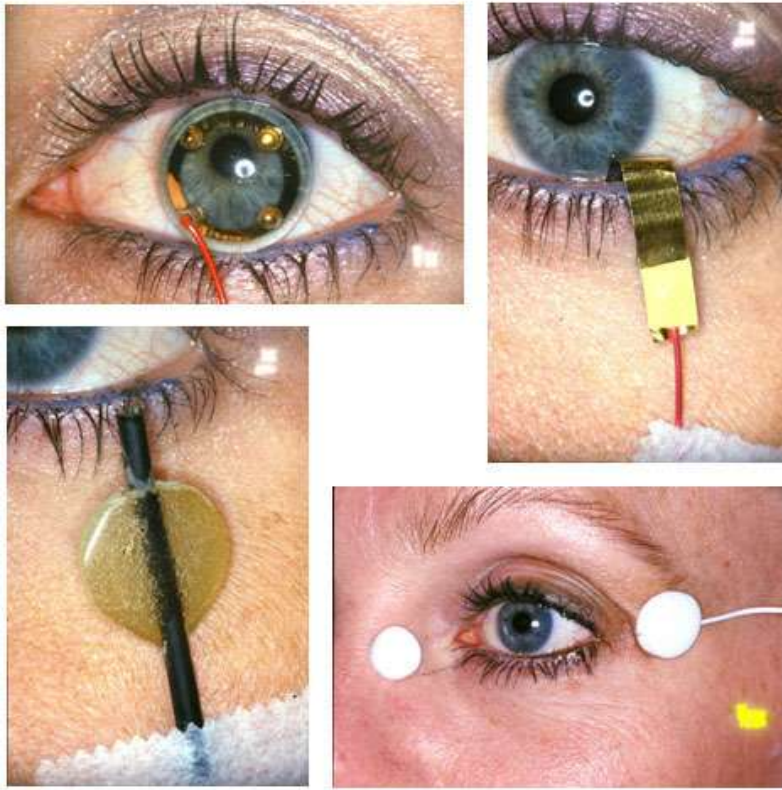
- Pupil dilated
- 30 min dark adaptation-scotopic responses
- 10 min light adaptation-photopic
- No FFA before test, if done dark adaptation for 1 hour.

Application of electrodes

ACTIVE ELECTRODE

- It's the main electrode.
- Recording electrodes are of various types-
- Hard contact lenses that covers sclera such as Burian-Allen electrode, Doran gold contact lens, Jet electrode(disposable)





some corneal ERG electrodes

- Lens lubricant and corneal anaesthesia used
- Filament type electrode placed on lower lid include
Gold foil electrode ,DTL
Fiber electrode and
HK-Loop electrode

REFERENCE ELECTRODE

- The silver chloride electrode.
- Placed on the patient's forehead, it serves as the negative pole as it is placed closer to the electrically negative posterior pole of the eye.

GROUND ELECTRODE

- It's placed on the earlobe.



THE STIMULUS

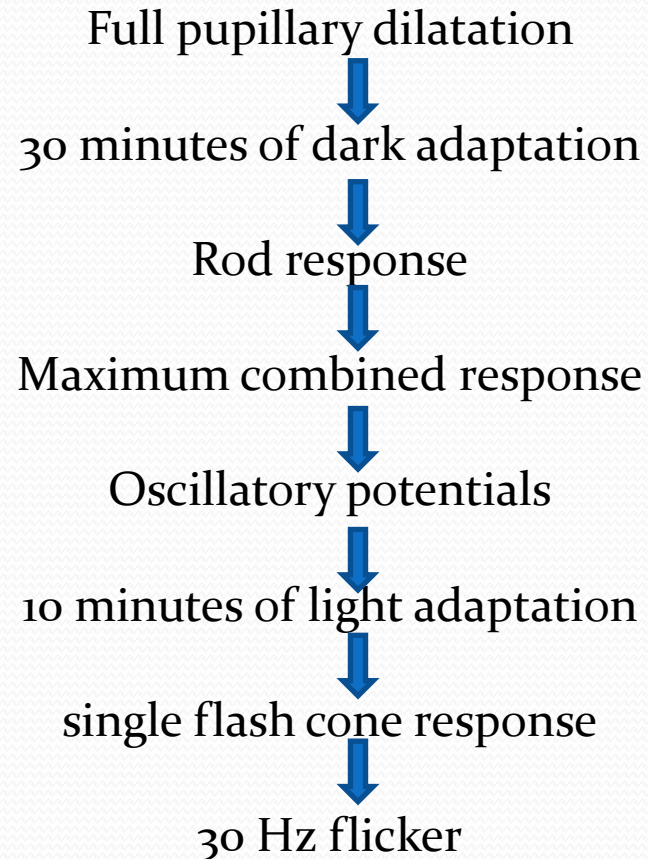
- The Ganzfeld bowl is large white bowl which is used to stimulate the retina during the recording of the ERG.
- It diffuses the light & allows equal stimulation of all parts of retina.



RECORDING & AMPLIFICATION

- The elicited response is then recorded from the anterior corneal surface by the contact lens electrode
- The signal is then channeled through consecutive devices for pre-amplification, amplification & finally display.

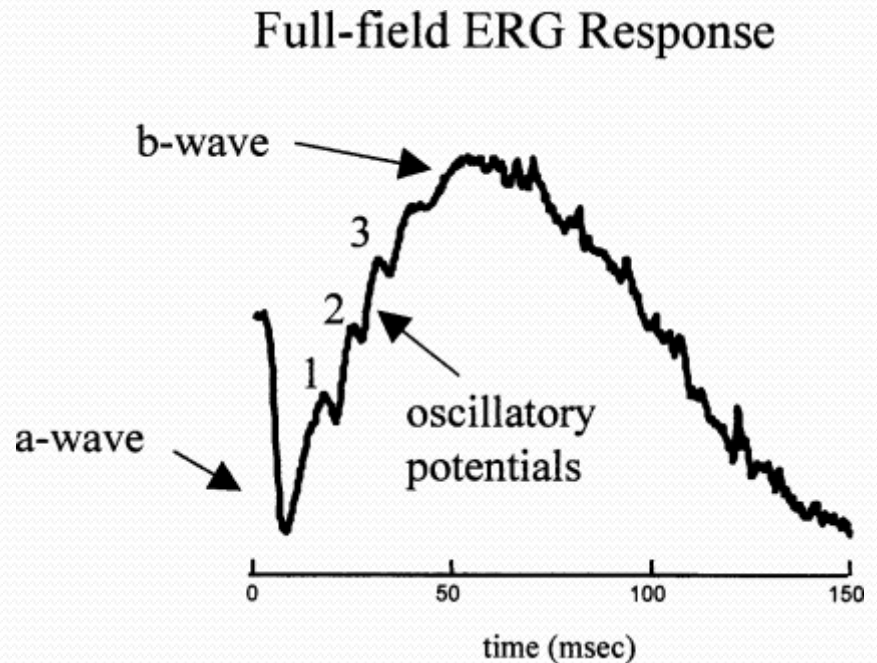
Recording protocol



Normal Waveforms

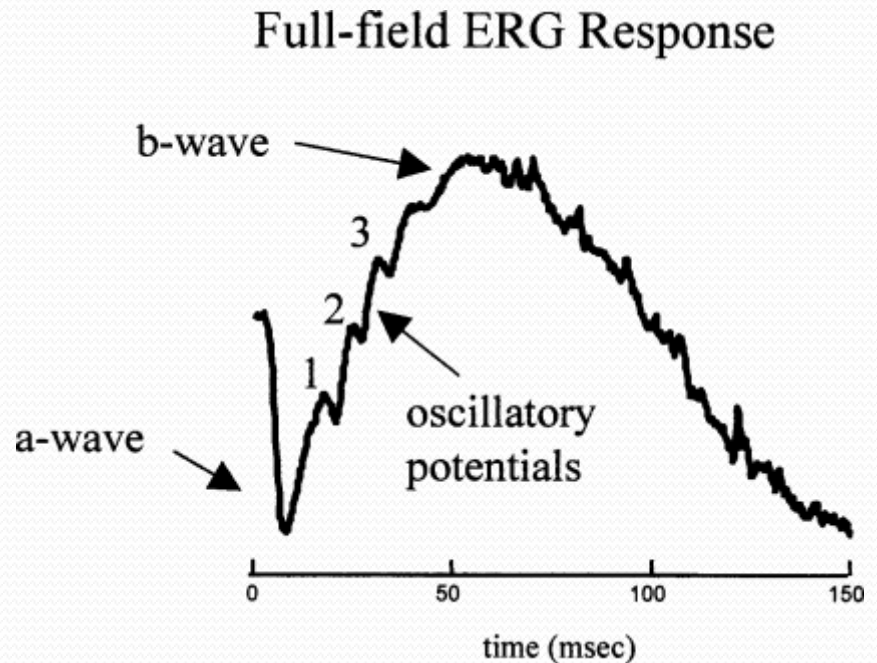
A-WAVE

- Initial negative wave.
- In dark adapted condition primarily from photoreceptors

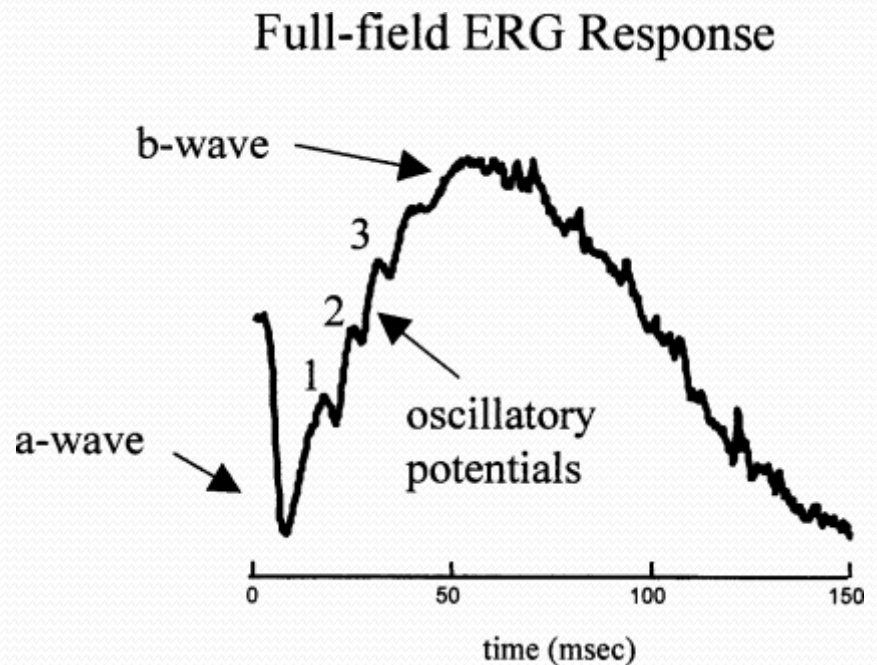


B-WAVE

- Large positive wave.
- Arises from the Muller cells, representing the activity of bipolar cells.

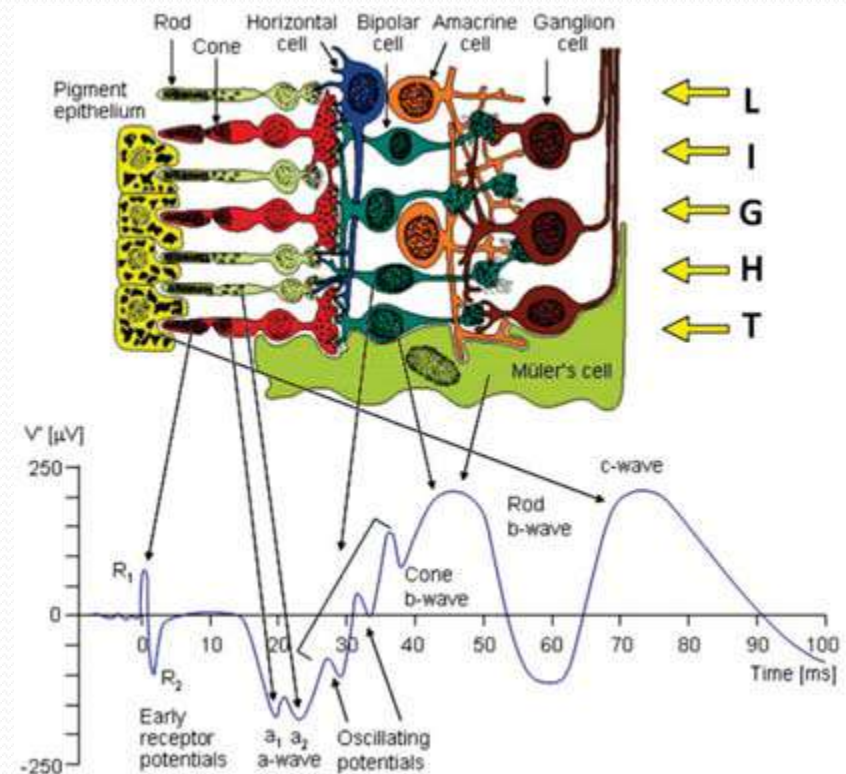



- Distributed by a ripple of 3 or 4 wavelets at the ascending limb k/a *oscillatory potential*.



C-WAVE


- Prolonged positive wave with a lower amplitude.
- Considerably slower so not used clinically.
- Represents the metabolic activity of RPE.



- 
- Thus the normal response is actually a summation of individual rod & cone response.
 - In order to derive clinical information from ERG recording it is essential to separate out the cone response from the rod response.
 - This can be easily achieved by following techniques:-

Cone ERG

- The cone function in the ERG can be easily be separated out by either light adapting the patient or by using a flickering stimulus.
- In a light adapted condition (photopic) only the cones respond as the rods get saturated.

- 
- Cones are capable of responding to flickering stimuli of up to 50 Hz, after which point individual responses are no longer recordable
 - Rods do not respond to flickering stimulus of more than 10 to 15 Hz.
 - Thus by using 30 Hz flicker stimulus, only the cone function can be recorded.

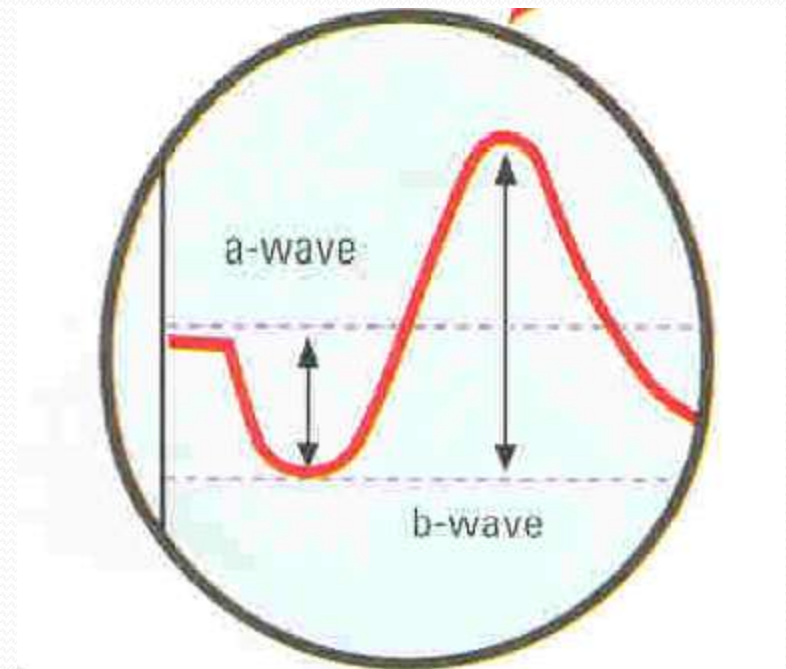
Rod ERG

- In a dark adapted state (scotopic), only the rods are sensitive enough to respond to dim light stimulus.
- Thus stimulating the dark adapted retina with a dim white or blue light will elicit only rod response.
- However, if a bright light stimulus is used in the dark adapted state both the rods & cones will respond called mesopic ERG

Measurement of ERG Components

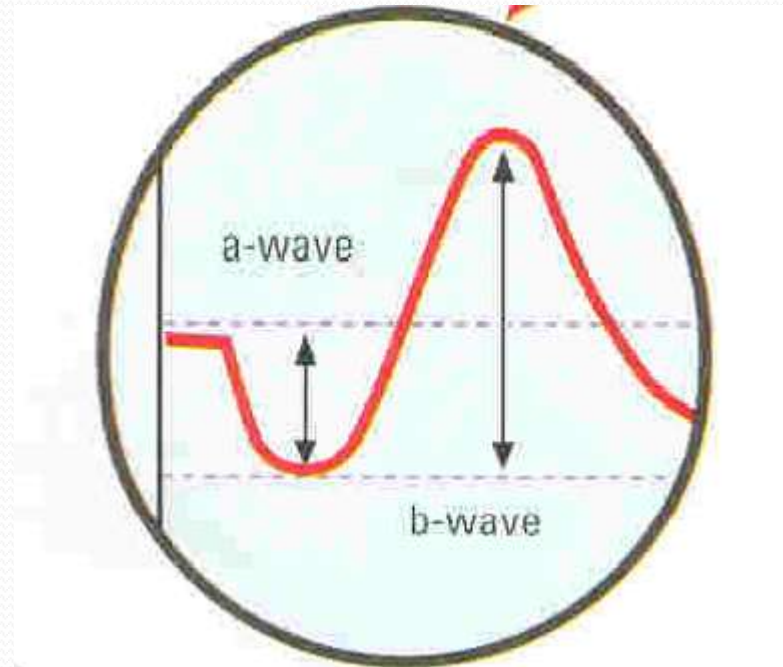
AMPLITUDE

a wave measured from the baseline to the trough of a-wave.



B WAVE

- measured from the trough of a-wave to the peak of b-wave.



TIME SEQUENCES

- Latency:- it is the time interval b/w onset of stimulus & the beginning of the a-wave response. Normally it's 2 ms.
- Implicit time:- time from the onset of light stimulus until the maximum a-wave or b-wave response.
- Considering only a-wave and b-wave response the duration of ERG is less than $1/4^{\text{th}}$ s

Physiological basis of origin of ERG

A-WAVE

- A-negative downward wave

Photoreceptors

Photo activated rhodopsin

Transducin

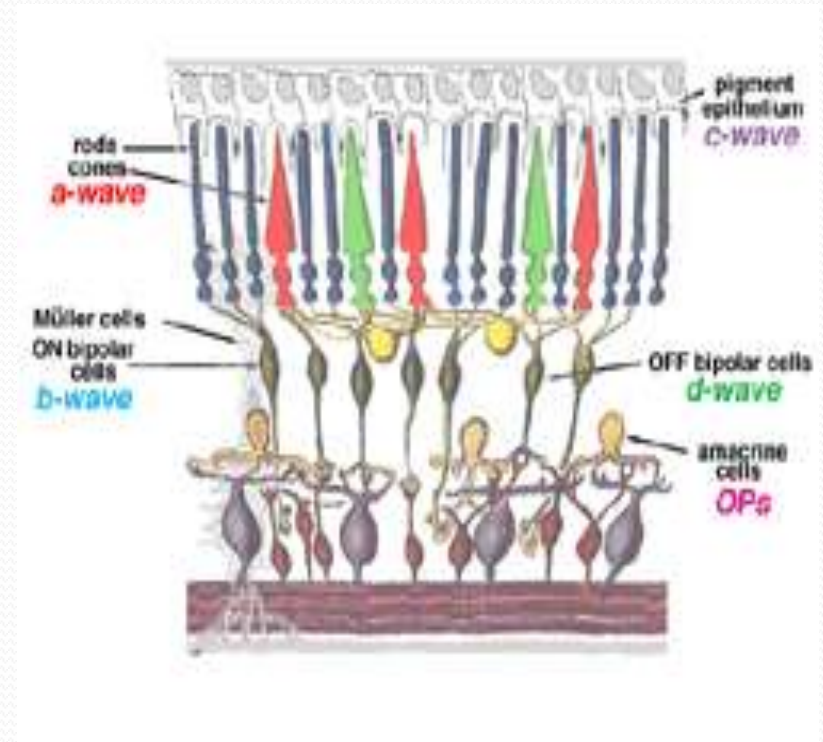
cGMP photodiesterase

Reduced cGMP

Closure of Na channel

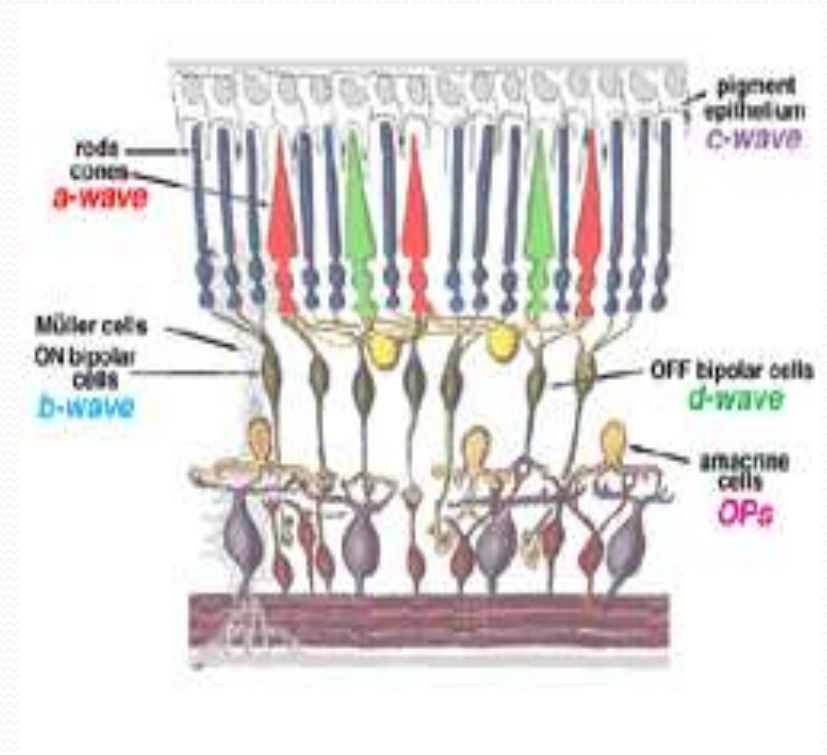
-ve intracellular potential

- a wave

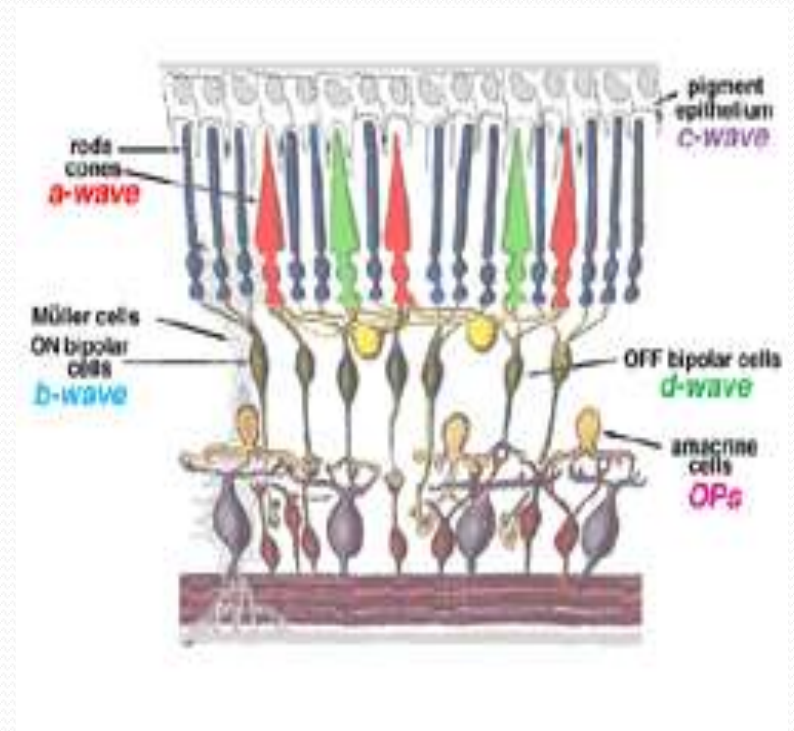


B-WAVE

- B-positive wave
- Muller and bipolar cells
- Increase extra-cellular K level
- + B wave

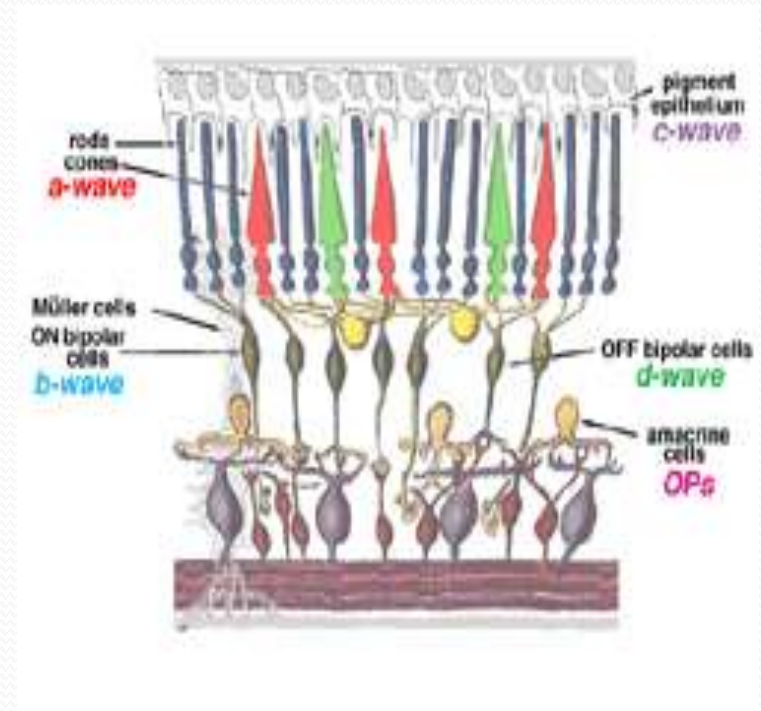


- These can be selectively abolished in animals by clamping the retinal circulation and a similar effect is seen in humans in CRAO & DR.



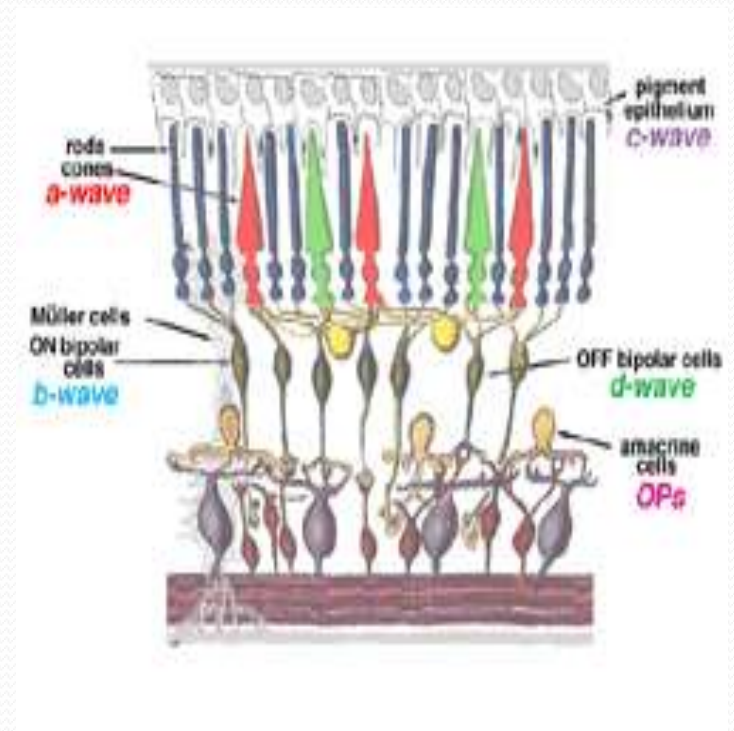
C-WAVE

- This positive wave is generated from RPE in response to rod signals only.
- This is because rod cells are in direct contact with apical ends of RPE while the cones do not appear to make such contact.



OSCILLATORY POTENTIAL

- inner retina
- Superimposed on ascending limb of the B wave after stimulation of intense light flash
- Generated from amacrine cells
- Frequency of 100-160 Hz
- Decreased in ischemic disorder-DR, CRVO



ISCEV

- International society for clinical electrophysiology of vision
- Standard protocol for ERG, EOG, VEP
- Global standard, easy understanding and comparable

Principle Responses demanded by ISCEV

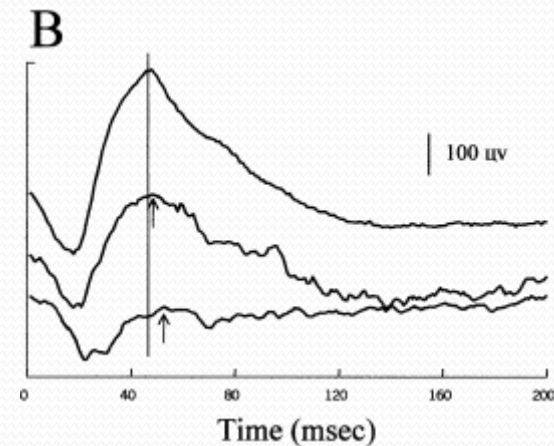
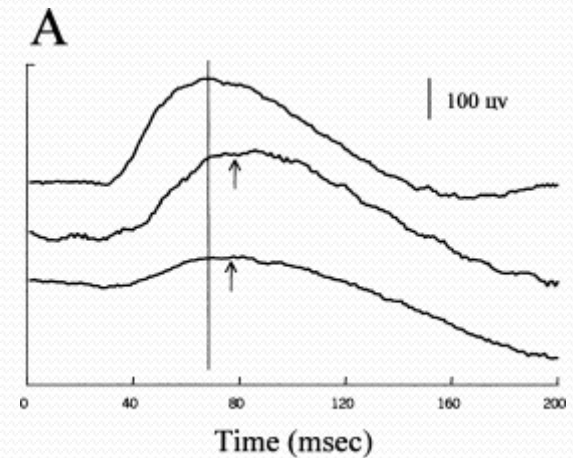
- Scotopic rod response
- Scotopic maximal combined response
- Photopic single flash cone response
- Photopic 30 Hz flicker response
- Oscillatory potentials

Scotopic rod response

- Measure of the rod system of retina
- Low intensity flash
- Flash white or blue
- Slow positive going response with only b wave visible

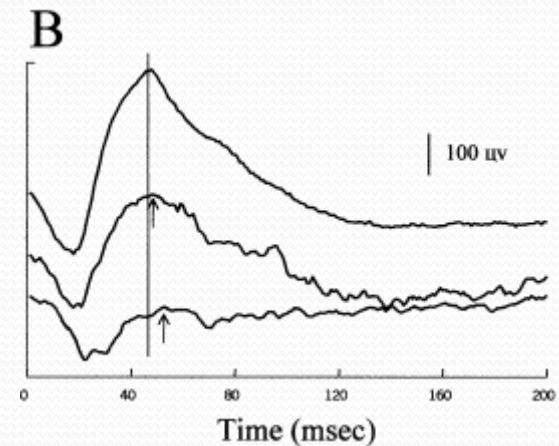
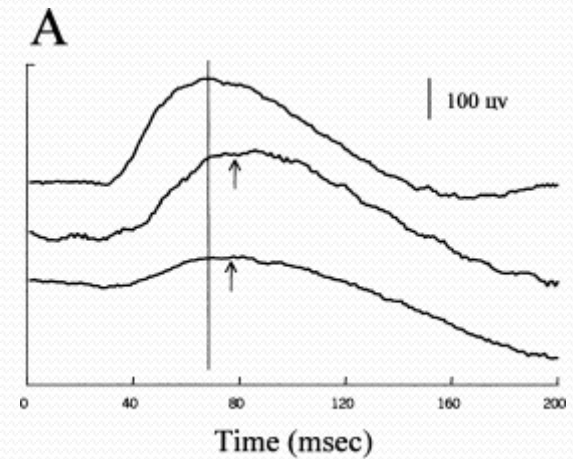
Example –

Normal, cone dystrophy,
RP



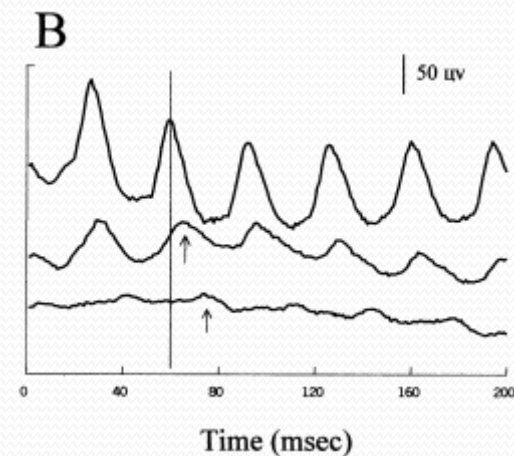
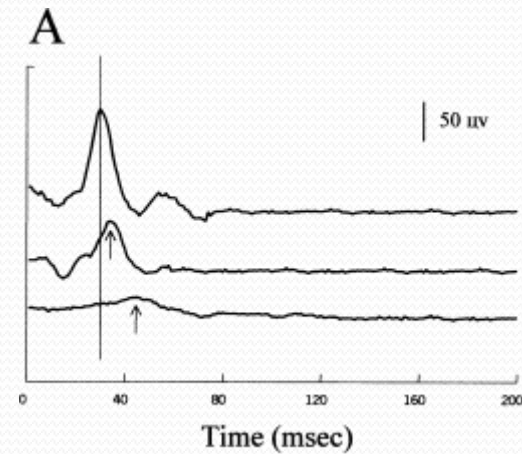
Scotopic maximal combined response

- Standard flash(odB)
- Rod and cone response
- Large a & b waves
- Example-normal, early cone dystrophy, RP.



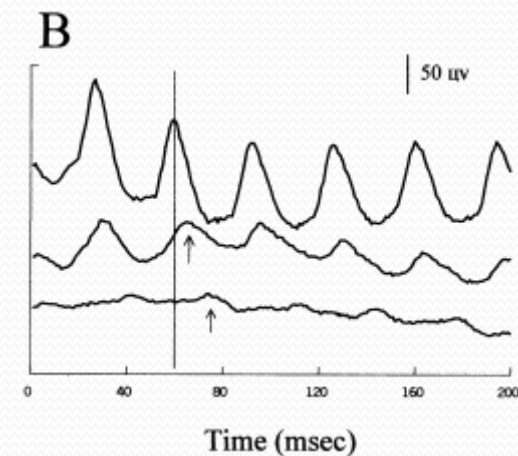
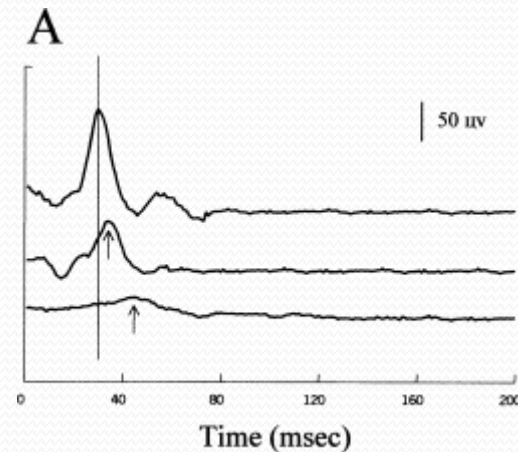
Photopic single flash

- Measure of the cone system
- 10 min adaptation to background light suppresses rod activity
- a & b waves smaller
- Lesser implicit time
- Abnormal in congenital achromatopsia, acquired cone degeneration, RP
- Example-normal, RP, Progressive cone dystrophy

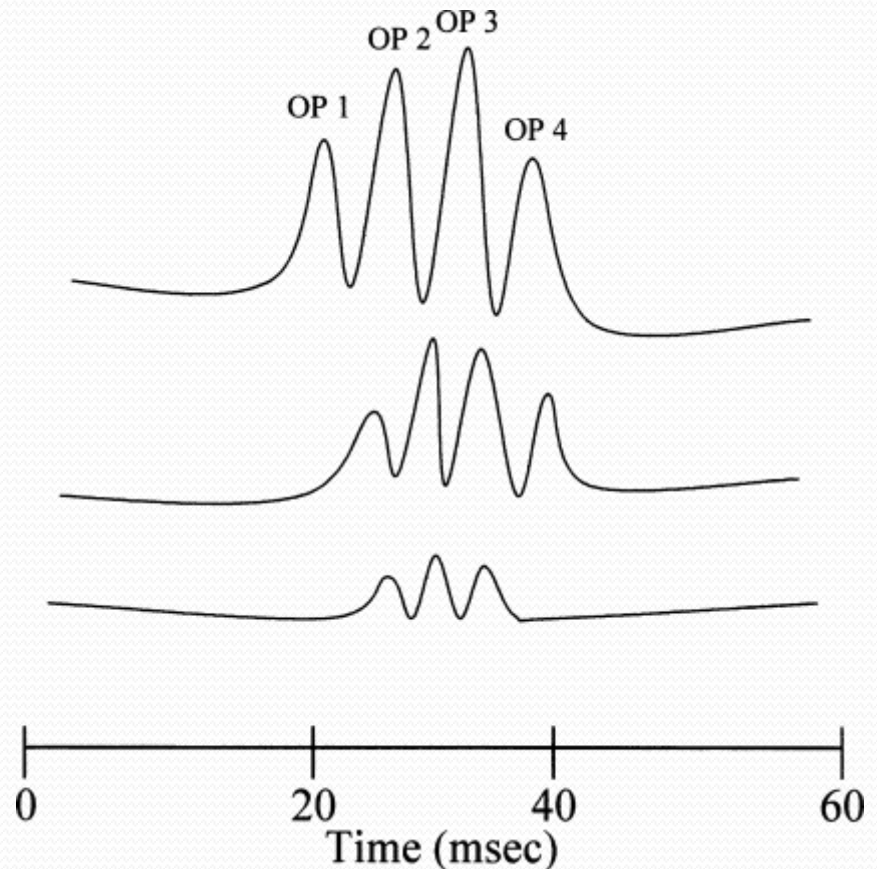


Photopic 30-Hz flicker response

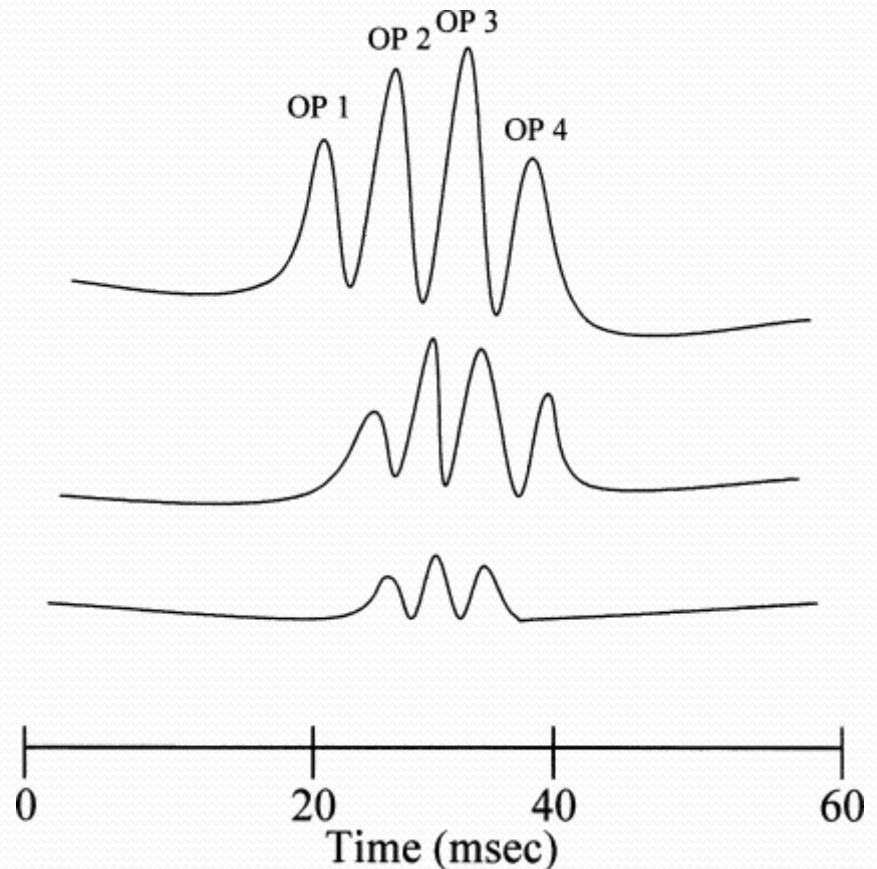
- Repetitive stimuli flickered at a rate 30 Hz
- Cone activity
- Flicker implicit time measure is sensitive before amplitude
- Abnormal in RP, cone dystrophy



- high-frequency wavelets that are said to be riding on the b-wave
- To record OPs, the band-pass filters on the amplifiers are changed to eliminate the lower frequencies while allowing the higher frequencies to pass



- believed to represent a complex feedback circuit with bipolar cells, amacrine cells, and interplexiform cells
 - sensitive to the effects of ischemia
 - Central serous retinopathy, CSNB Type 2, Birdshot choroidopathy, Retinoschisis
- Carriers of X-linked CSNB



- Example-normal ,early DR,PDR.

Interpretation of ERG

- ERG is abnormal only if more than 30% to 40% of retina is affected
- A clinical correlation is necessary
- Media opacities, non-dilating pupils & nystagmus can cause an abnormal ERG
- ERG reaches its adult value after the age of 2 yrs
- ERG size is slightly larger in women than men

Abnormal ERG response

- The b-wave with a potential of <0.19 mV or > 0.54 mV is considered abnormal.
- Abnormal ERG is graded as follows:-

SUPERNORMAL RESPONSE-

- Characterized by a potential above normal upper limit.
- Such a response is seen in:-
 1. Sub-total circulatory disturbances of retina.
 2. Early siderosis bulbi.

SUB-NORMAL RESPONSE

- Potential < 0.08 mV.
- Indicates that a large area of retina is not functioning.
- Seen in:-
 1. Early cases of RP.
 2. Chloroquine & quinine toxicity.
 3. Retinal detachment.
 4. Systemic diseases like vit. A deficiency, hypothyroidism, mucopolysaccharidosis & anemia

EXTINGUISHED RESPONSE

- Complete absence of response.
- Seen in:-
 1. Advanced cases of RP.
 2. Complete RD.
 3. Choroideremia.
 4. Leber's congenital amaurosis
 5. Luetic chorioretinitis

NEGATIVE RESPONSE

- Characterized by large a-wave.
- Indicates gross disturbances of retinal circulation as seen in arteriosclerosis, giant cell arteritis, CRAO & CRVO.





APPLICATIONS OF ERG

Diagnosis & prognosis of retinal disorders

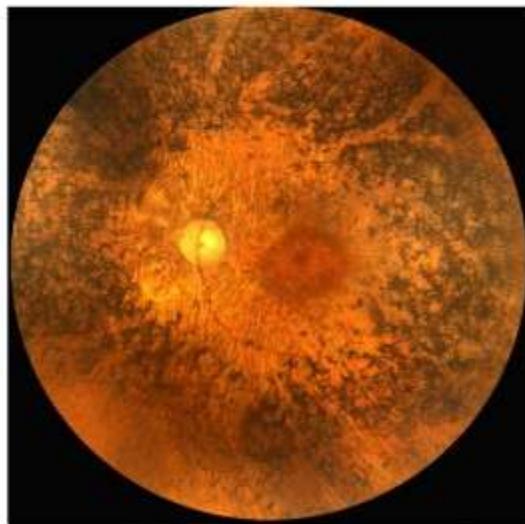
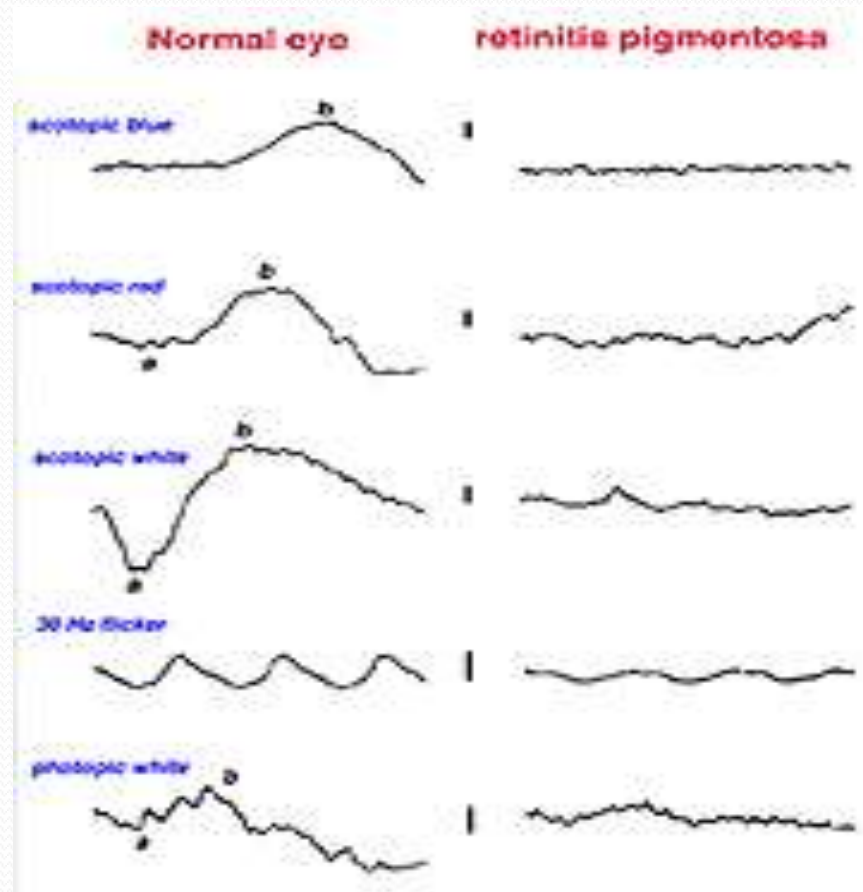
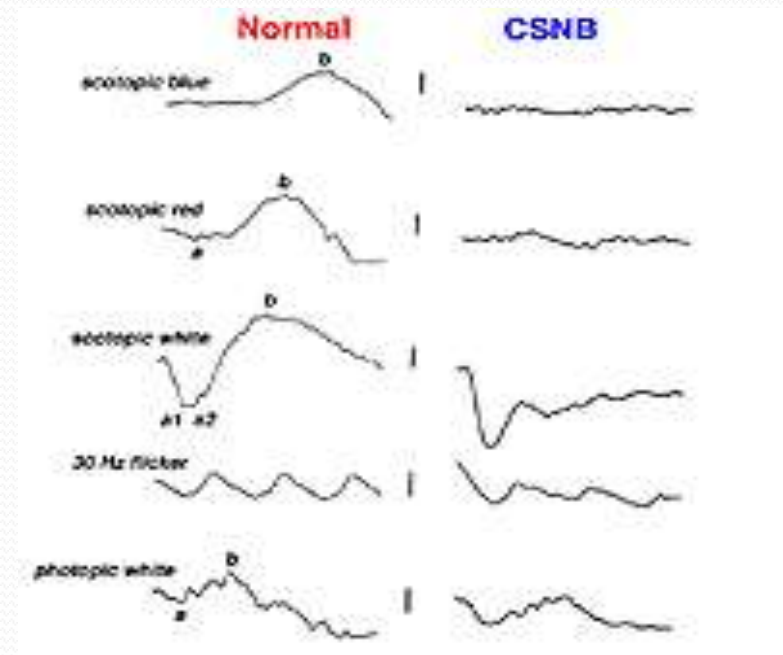


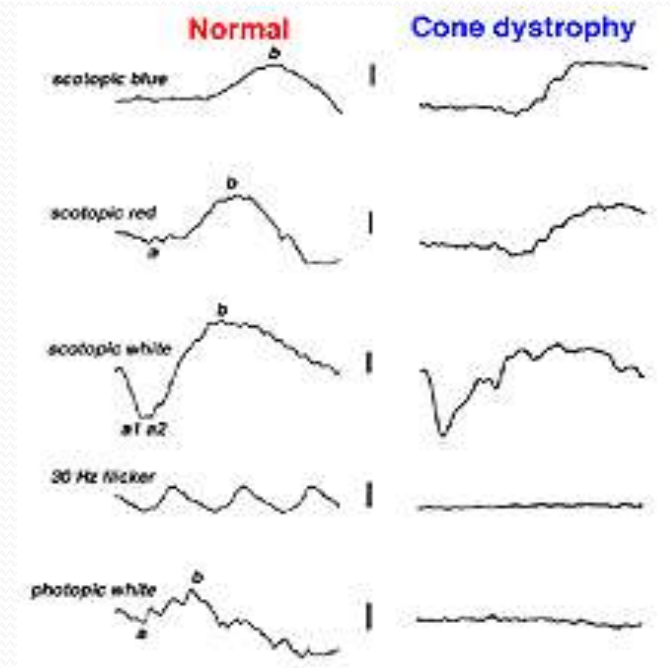
Fig. 12b. Fundus photo of a patient with retinitis pigmentosa.



Congenital stationary night blindness type 2



Cone dystrophy



CRAO

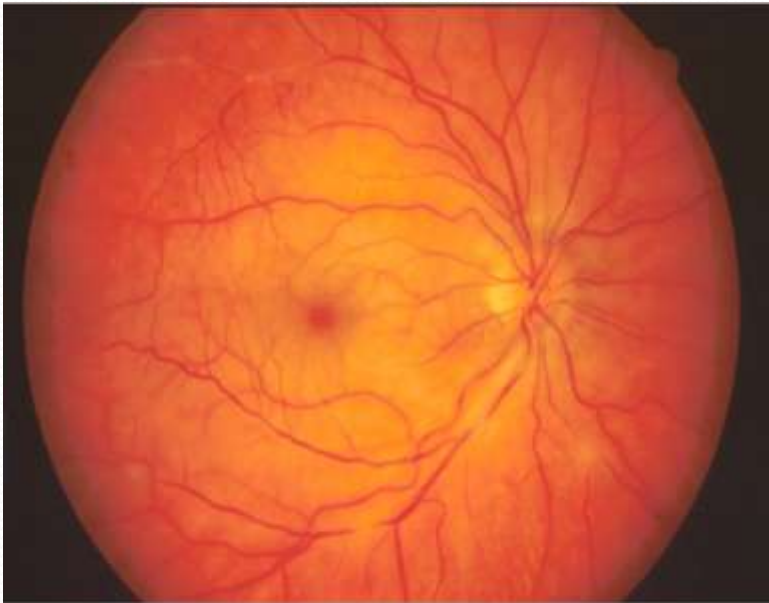
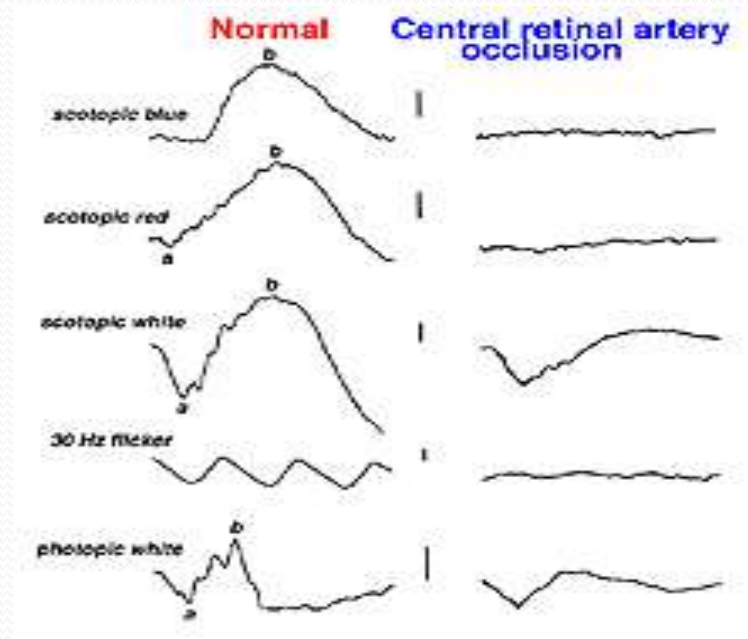
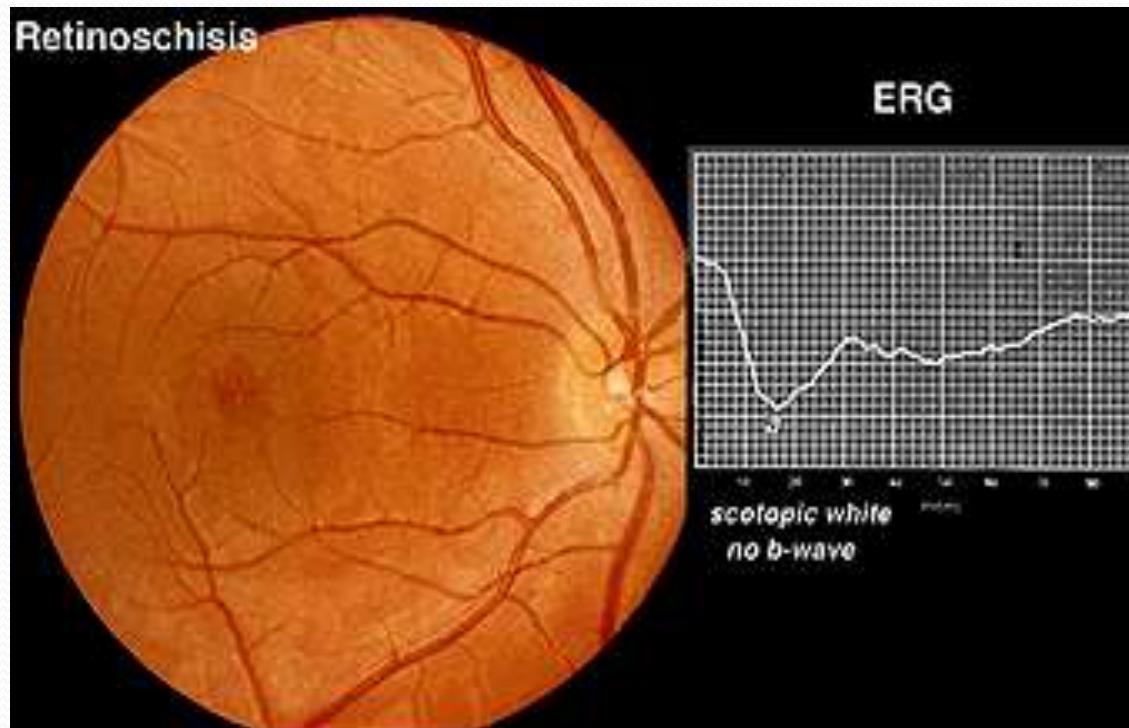



Fig. 28a. Fundus photo of patient with central retinal artery occlusion.



Leber's amaurosis:-

- ERG plays a primary diagnostic role.
- When a child is suspected of having Leber's amaurosis, ERG should be included in the examination



- 
- ERG plays a diagnostic role include choroideremia, gyrate atrophy, pathological myopia & other variants of RP
 - Important role in juvenile diabetics with a disease duration longer than 5 years has been shown to be valuable for the identification of those at risk for the development of proliferative retinopathy

To assess retinal function when fundus examination is not possible

- ERG can be recorded even in presence of dense opacities in the media such as corneal opacity, dense cataract & vitreous hemorrhage.
- In these cases the stimulus should be sufficiently bright, the response should be normal in absence of disease.

Limitations of ERG

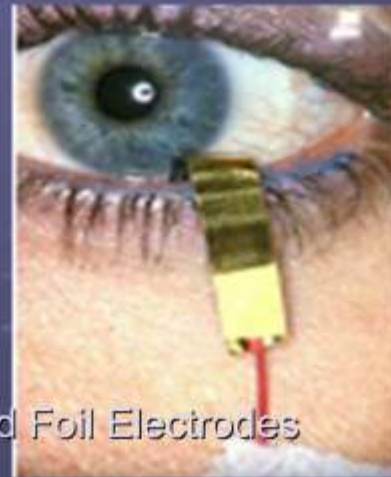
- Since the ERG measures only the mass response of the retina, isolated lesions like a hole hemorrhage, a small patch of chorioretinitis or localized area of retinal detachment can not be detected by amplitude changes.
- Disorders involving ganglion cells (e.g. Tay Sachs' disease), optic nerve or striate cortex do not produce any ERG abnormality

Focal ERG

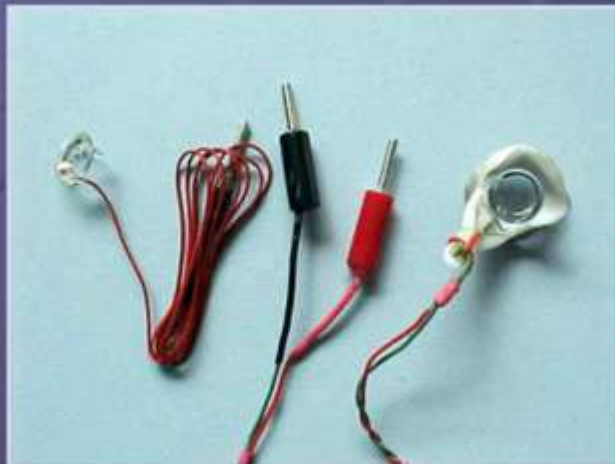
- Local measure of ERG function
- Provide topographic information
- Provides information about smaller areas of retina



BURIAN ALLEN



Gold Foil Electrodes




Problem with FERG

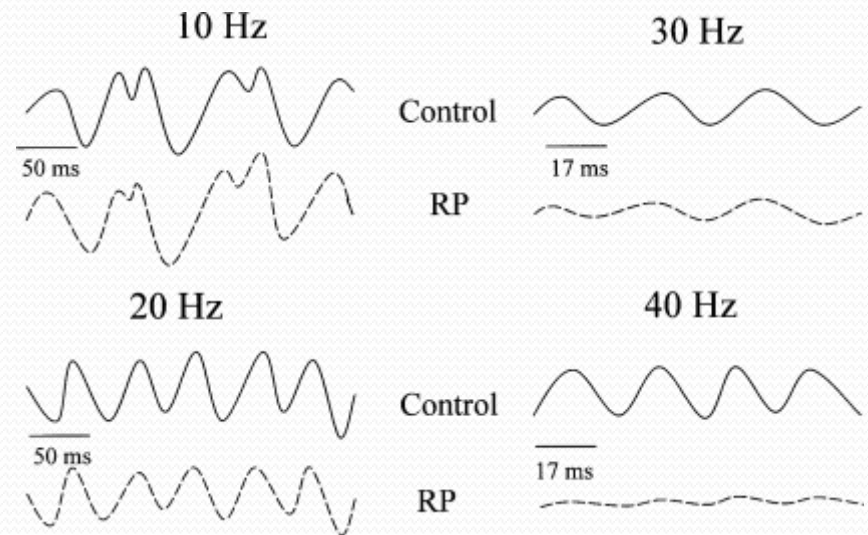
- Scattered light
- Poorer signal to noise ratios.
- single retinal area at a time
- Problems overcome by temporally modulated stimuli under photopic condition
- Photopic condition desensitize nonstimulated retina
- Rod driven FERG
- Cone driven FERG

METHOD OF RECORDING

- 9 Degree array of red light emitting diodes
- Flickered at temporal frequencies 10 to 40 hz
- Amplitude reduction increases with temporal frequency

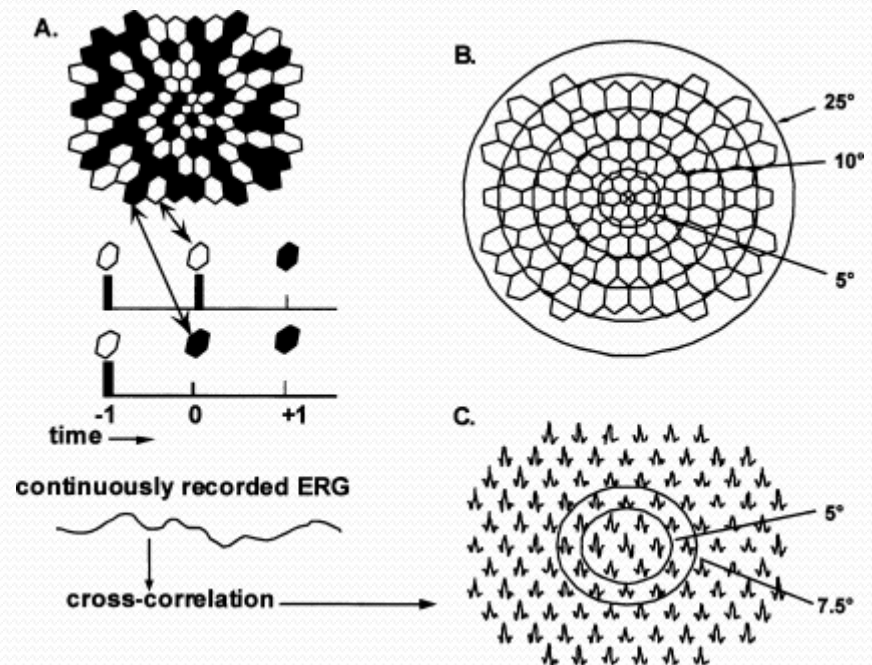
- 
- Abnormal in
 - stargardt disease
 - Macular dystrophy
 - RP
 - ARMD.
 - Macular hole
 - In macular dystrophy intermediate temporal frequency sparing seen

- In RP,
- Amplitude decreases with increase in temporal frequency

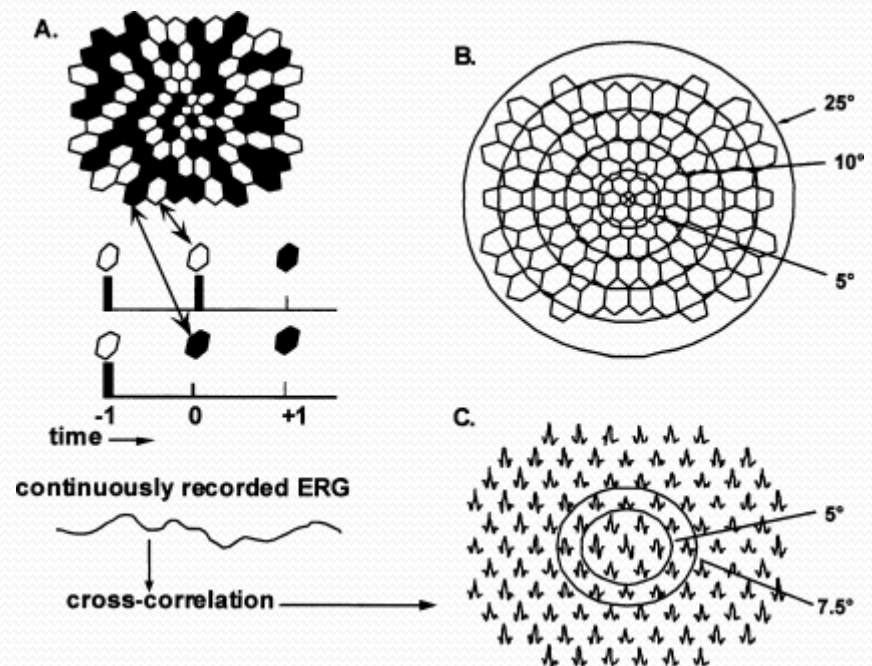


Multifocal electroretinogram

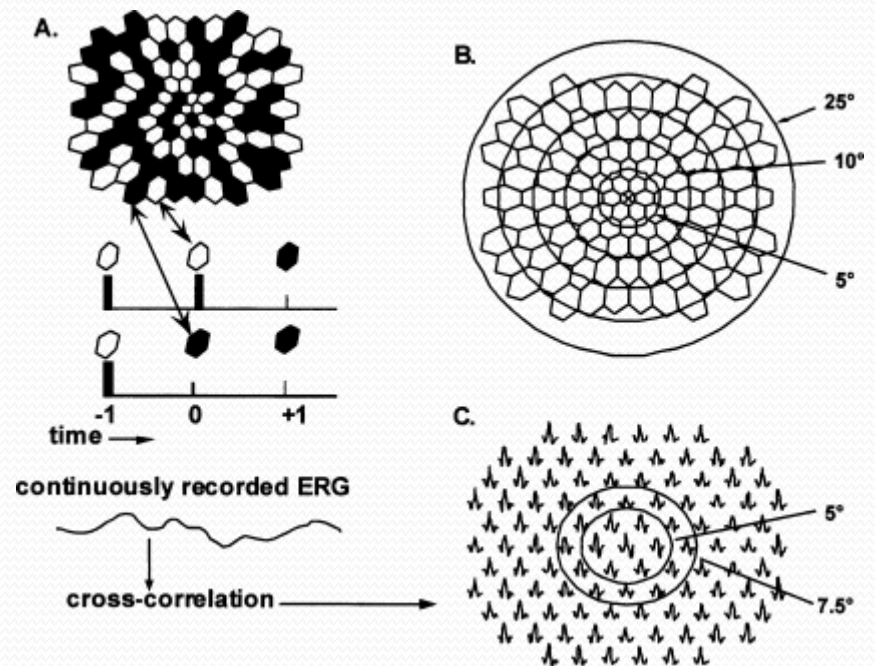
- 103 stimuli (hexagons) are displayed on a computer monitor
- every frame change (13.3 milli- seconds) of the monitor, each hexagon can be either white or black based on a pseudo-random probability sequence (called an m-sequence)



- mathematical algorithm is used to extract the signal associated with each hexagon
- Technically, that hexagon's sequence of black-and-white events is cross-correlated with the continuously recorded ERG signal

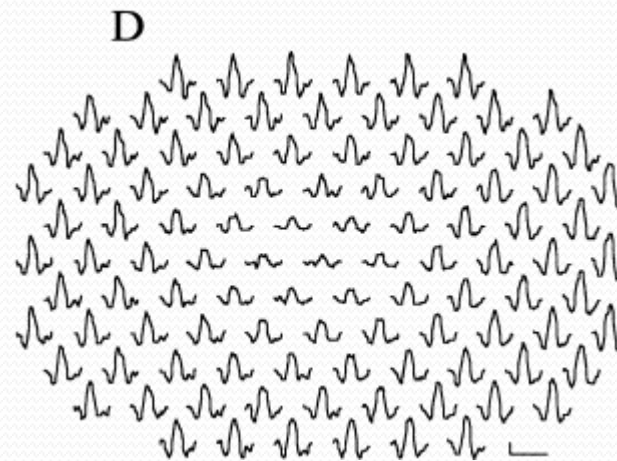
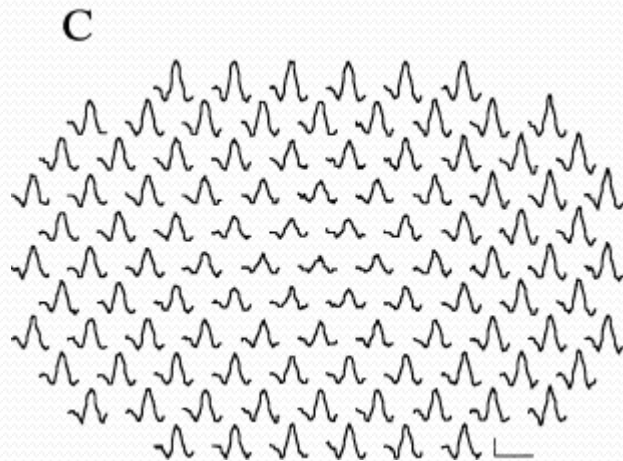
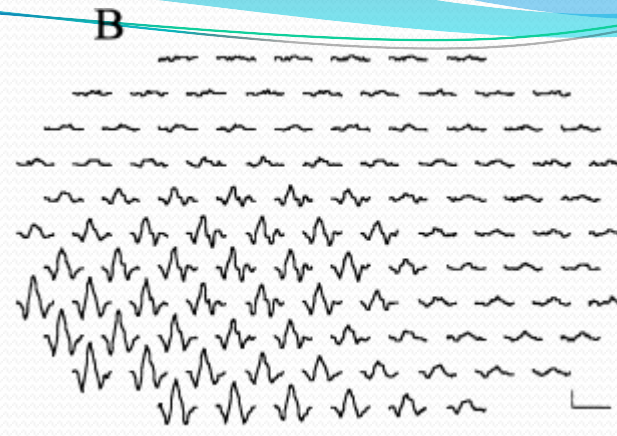
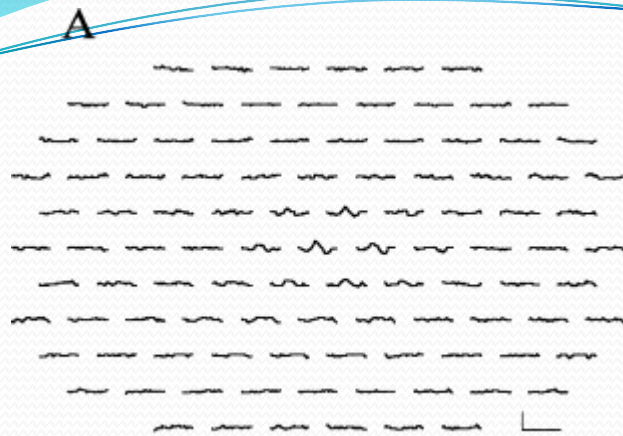


- yielding an array of local ERG responses each one associated with the stimulation of a particular hexagon.



USEFUL IN

- Maculopathies.
- Glaucoma.
- Diabetes.
- RP
- ARMD
- Stargardt disease
- Cone dystrophy
- Acute zonal occult retinopathy
- CSR



A,B-RP

C-cone dystrophy

D-Stargardt disease

Left Eye

Field view

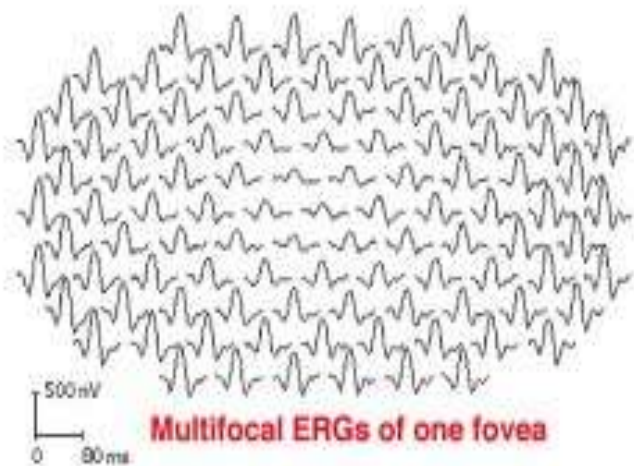


Fig. 42. Multifocal ERG recordings in a patient with early age related macular degeneration (AMD).

Field View

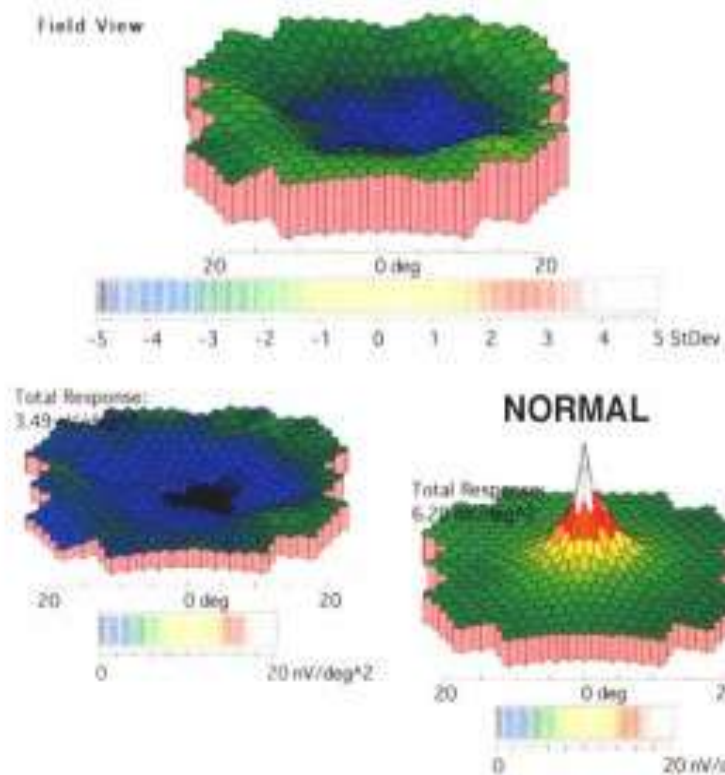
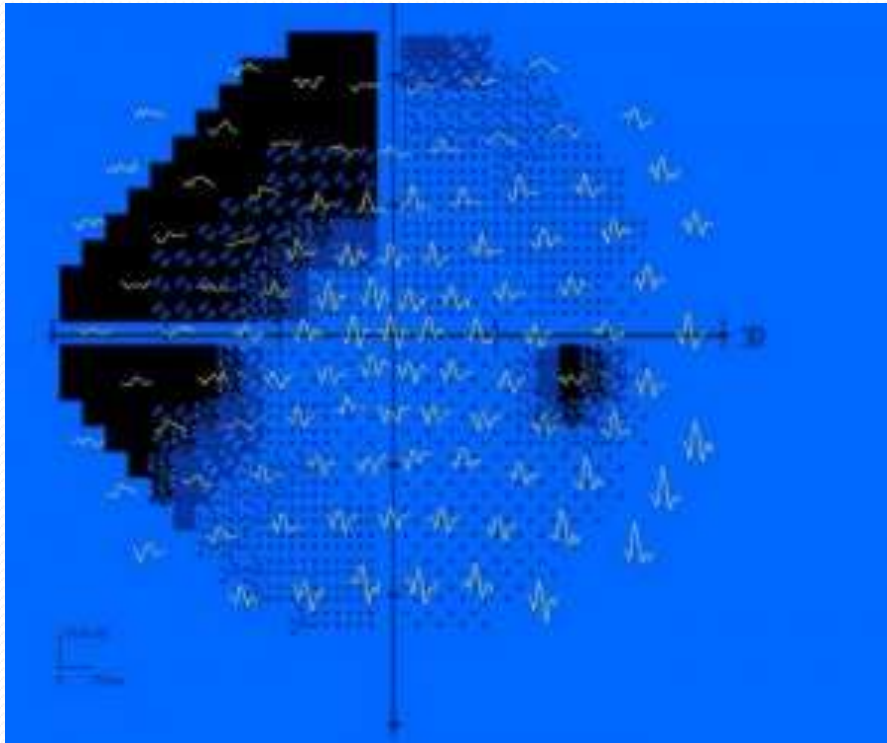


Fig. 43. Multifocal ERG recordings transformed into color maps of the macular area in a patient with AMD compared to a normal patient.



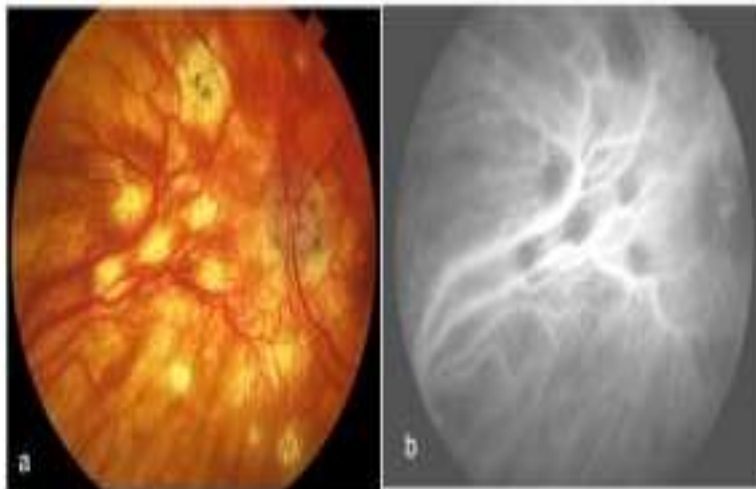


Fig. 45. Birdshot retinochoroidopathy. a) Fundoscopy reveals characteristic multifocal hypopigmented, ovoid, cream colored lesions at the level of the choroids and RPE in the fundus. b) Indocyanine green (ICG) angiography reveals multiple non fluorescent spots corresponding with the birdshot lesions.

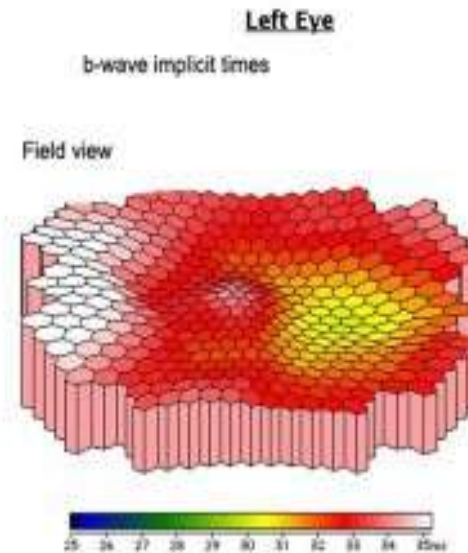
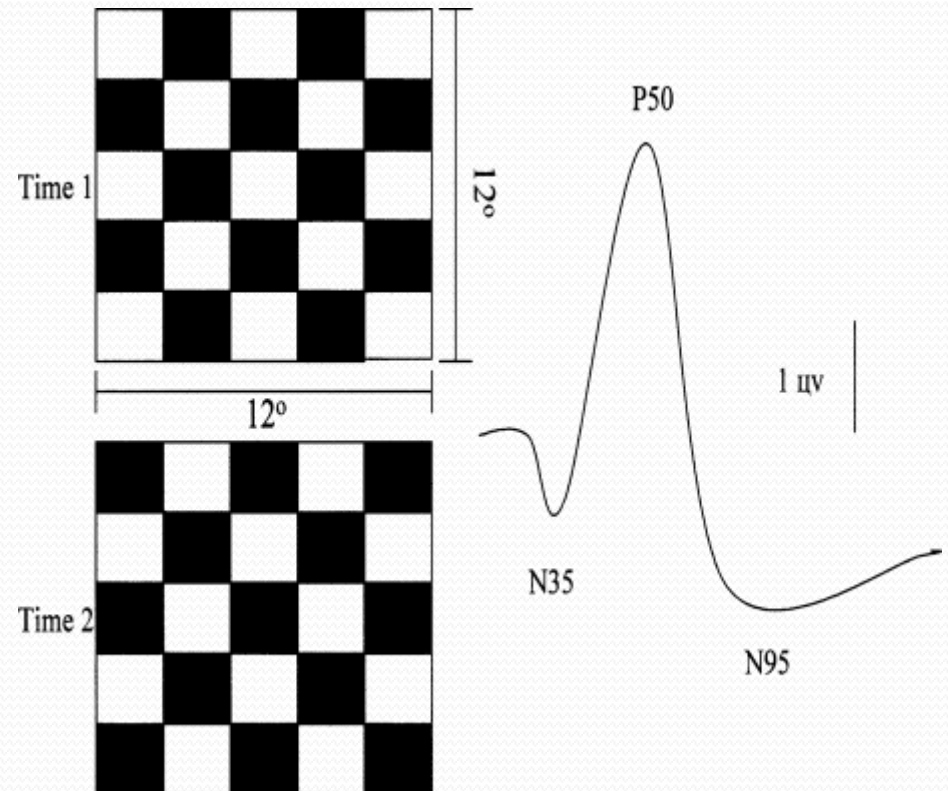


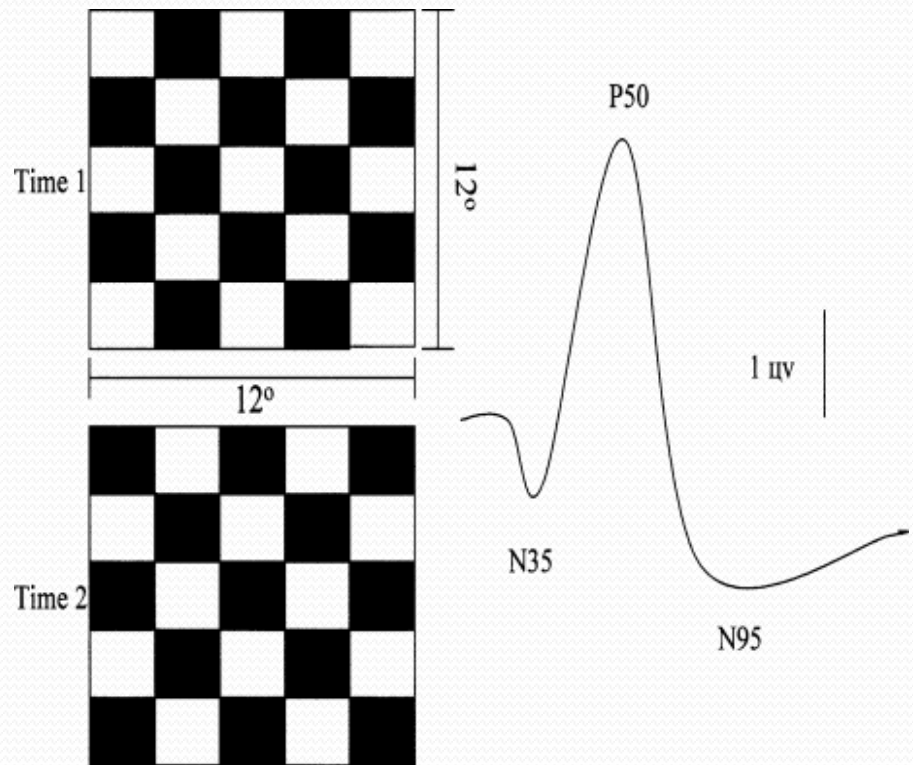
Fig. 46. Birdshot retinopathy. Multifocal ERG implicit times map the distribution of slow implicit times across the retina.

Pattern ERG

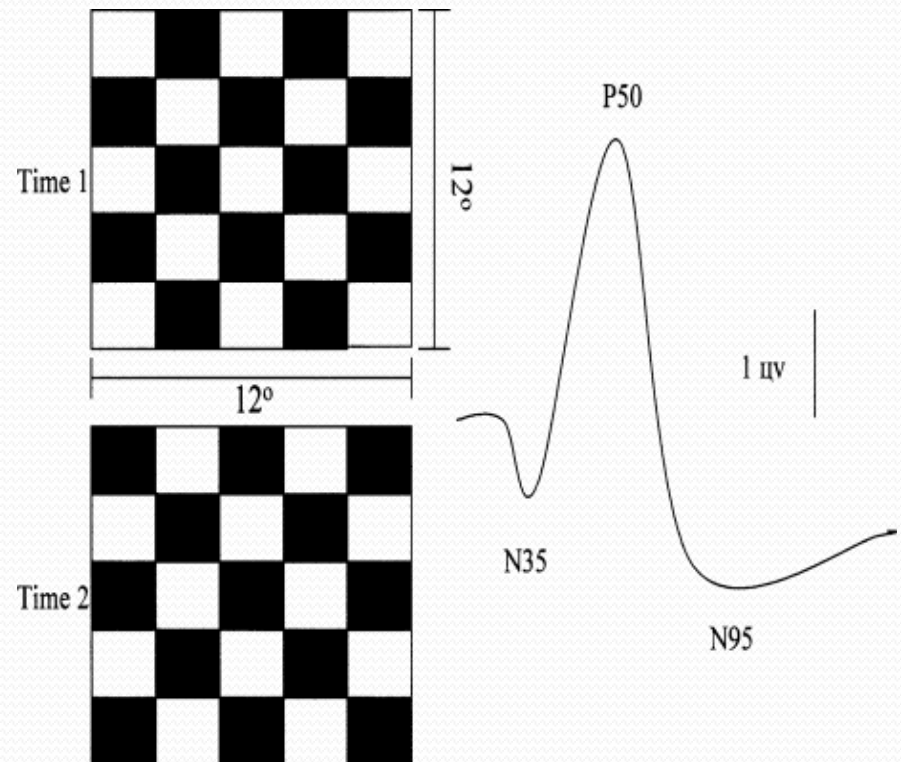
- Patterned stimulus
 - checkerboard
 - grating pattern
- Contrast reversing pattern with no overall change of luminance
- Display vary in size but not beyond 20 degree



- Transient PERG-clinical use
- steady state PERG(14 Hz rate)
- Stimulus rate 2 to 6 reversal per second
- Recorded with normal pupil
- Refraction needed
- Clear optical image necessary

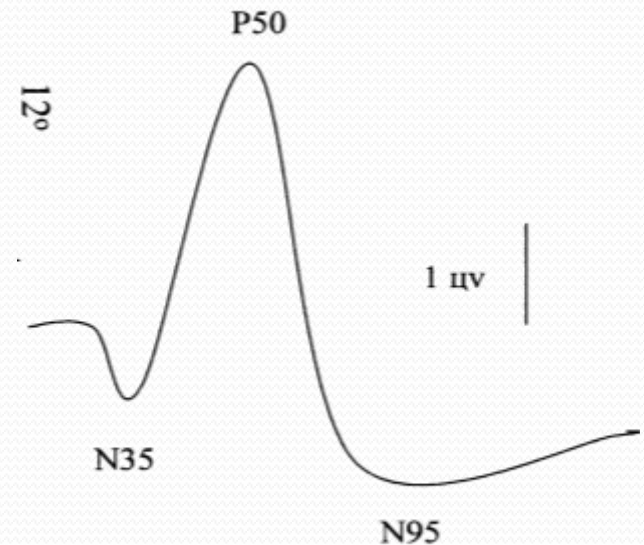


- Electrodes-gold foil electrode , loop electrode and fiber electrode over lower lid
- Mainly macular area stimulated.



Wave form

- Initial negative going component N₃₅ occurs at 35 milliseconds
- P₅₀-positive component -activity distal to ganglion cells
- P₉₅ negative component -ganglion cell activity



uses


- Most effective in distinguishing between abnormality at ganglion cell level and distal lesions
- N95 abnormal in optic nerve disease
- Example optic nerve atrophy ,optic nerve compression and glaucoma


THE ELECTRO-OCULOGRAM

- Clinical measure of integrity of the retinal pigment epithelium layer
- Based on the measurement of resting potential of the eye which exists b/w the cornea (+ve) & back of the retina (-ve) during fully dark-adapted & fully light-adapted conditions

Technique of recording


- Electrodes are placed over the orbital margin near the medial & lateral canthi.
- A forehead electrode serves as a ground electrode.
- Pt. sits in a room in erect position.

- 
- Head position is controlled at a certain fixed distance from 3 fixation lights (dimly lit, usually red), which are placed in pts. line of vision.
 - The central light serves for central fixation & the 2 side lights which can be fixed after an excursion of anywhere from 30-60 degrees serves as the right or left fixation lights.

- 
- an arrangement is made to make the eyes light adapted with the help of a bright, long duration stimulus.
 - Pupil size is controlled by instillation of mydriatics.
 - Ordinarily, a pupil size > 3 mm allows a little variation of EOG.

Recording

- The patient is asked to move the eye sideways (medially & laterally) by fixating the right & left fixation lights alternately & keep there for few seconds, during which the recording is done.
- In this procedure the electrode near the cornea becomes positive.
- The recording is done every 1 min.
- to begin with, the recording is started with the stimulus lights on.

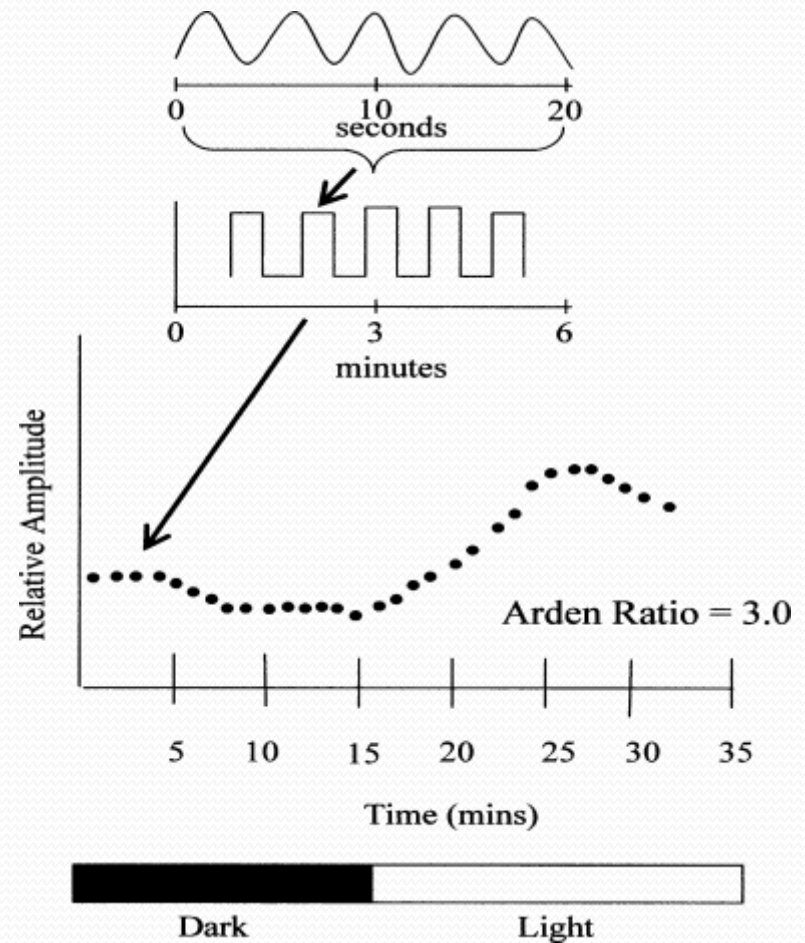
- 
- After a standardized period of light adaptation, all lights are extinguished (except for fixation lights) & responses recorded for 15 min. under dark adapted conditions
 - The stimulus lights are then turned on again & responses recorded for 15 min. under light adapted conditions

Measurement & interpretation

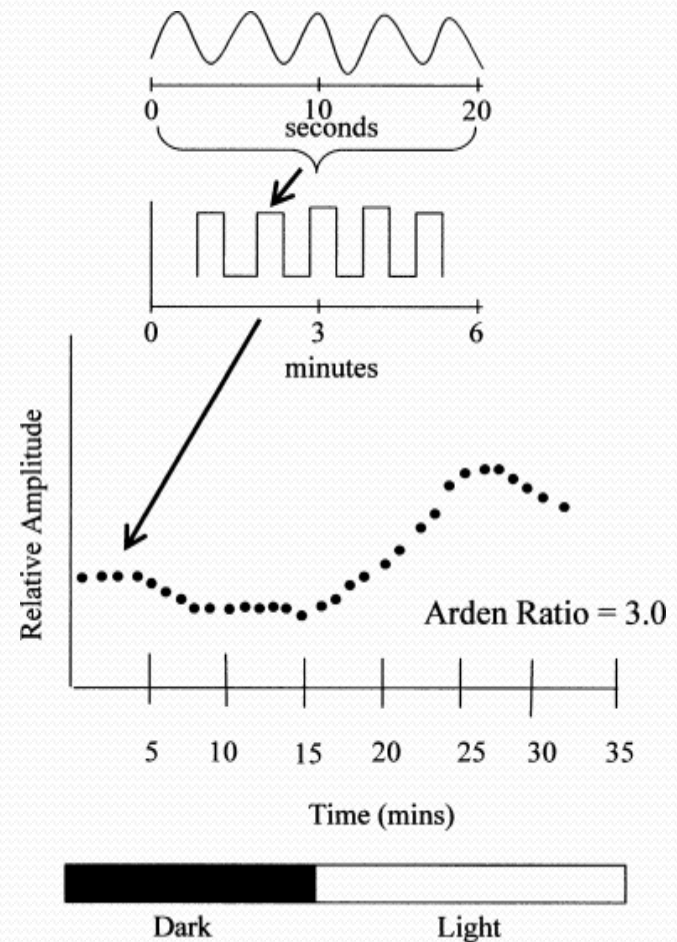
- Normally the resting potential of the eye progressively decreases during dark adaptation reaching a *dark trough* in approx. 8 - 12 min.
- With subsequent light adaptation the amplitude starts rising & reaches to light peak in approx. 6-9 min.


Results of EOG are interpreted by finding the *Arden ratio* as follows:-


- The largest peak to trough amplitude in the light is divided by the smallest peak to trough amplitude in the dark.
- Barometer of RPE function
- Ratio of light peak to dark adapted baseline is also acceptable EOG measure.



- Normal 3.0
- Best disease below 1.5
- Arden ratio = $LP/DT * 100$
- Normal light rise values are 185 or above
- Abnormal values are below 165



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- Thus EOG is affected in diseases such as RP & other hereditary degeneration's, vitamin A deficiency, RD, toxic retinopathies & retinal vascular occlusions

- 
- As a general rule those conditions which cause a reduction in size of b-wave in ERG also produce reduction in value of Arden ratio.
 - EOG serves as a test that is supplementary & complementary to ERG.
 - In certain conditions it is more sensitive than ERG e.g., patients with vitelliform macular degeneration, fundus flavimaculatus, & generalized drusen often show a striking EOG reduction in presence of normal ERG.

VISUALLY EVOKED RESPONSE

- Recording of electrical potential changes produced in the visual cortex from the nerve impulses in the eye.
- Thus VER is nothing but the *EEG records taken from occipital lobe*.
- Macula dominated response.
- ***VER is the only objective technique available to assess clinically the functional state of the visual system beyond the retinal ganglion cells.***

Types of VER

- ***FLASH VER***
- In this a diffuse flash of light is used as a stimulus.
- The recording is done in patients who do not cooperate for pattern VER e.g. children, unconscious pts & pts with low visual acuity.
- Not affected by opacities in the ocular media.

PATTERN VER

- In this the checker board pattern on a TV monitor is used as a stimulus source.
- It is further of 2 types:-
 1. Pattern appearance VER:-
 - The checker board is presented in on-off sequence


2. Pattern reversal VER:-

The pattern of stimulus is changed I.e., the white squares go black & vice-versa.

- The pattern VER depends on form sense & thus gives a rough estimate of the visual activity.
- Most commonly used

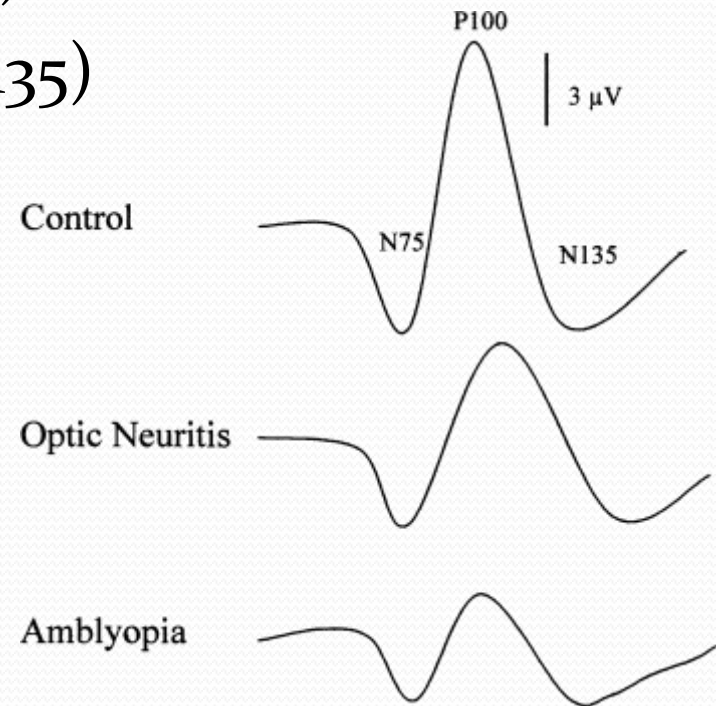
VER RECORDING

- Done with *undilated pupils*.
- The midline forehead ,vertex & the occipital electrodes are placed .
- An ear lobe electrode serves as a ground electrode
- Pt. wears his refractive correction , if any.
- He or she sits at the distance of about 1 meter from the T.V. monitor

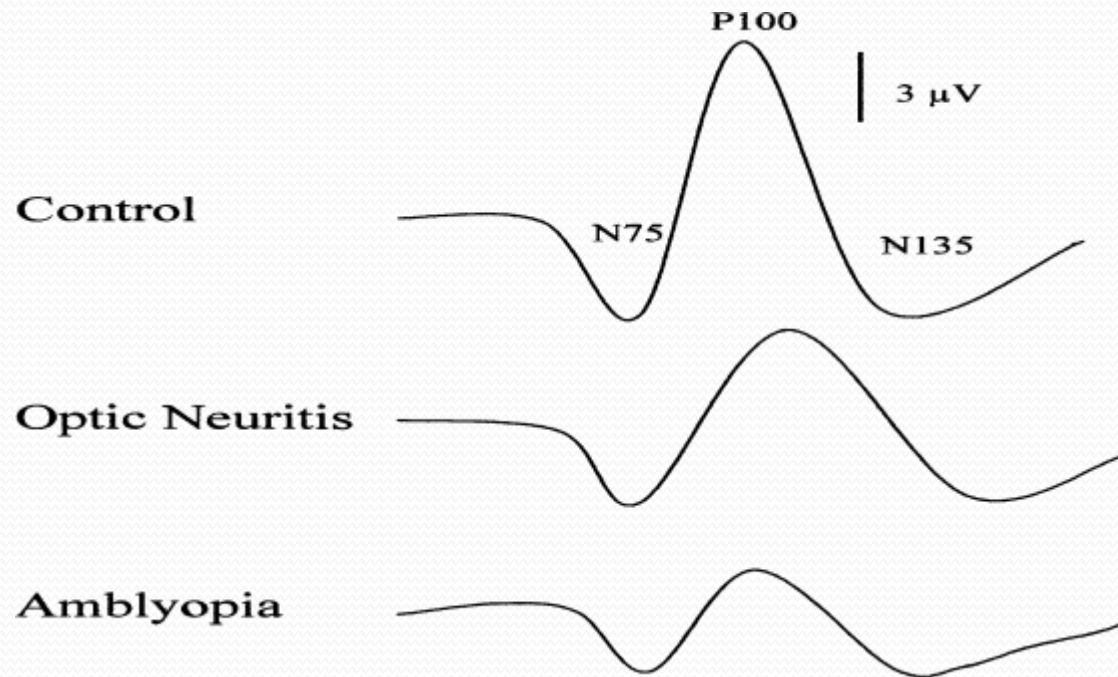
- 
- Usually one eye is tested at a time with the other eye being properly patched.
 - The recordings are done with 2 to 3 different checker sizes

Normal waveform

- Negative going response(N75)
- Positive going response(P100)
- Second negative response(N135)



- Implicit time of P100 response most commonly used to assess integrity of optic pathway



Clinical applications

OPTIC NERVE DISEASE

1. Optic neuritis:-

- Involved eye shows a reduced amplitude & delay in transmission i.e. increased latency as compared to normal eye
- These changes occur even when there is no defect in the VA, color vision or field of vision.

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- Following resolution, the amplitude of VER waveform may become normal, but the latency is almost always prolonged & is a permanent change.

2. Compressive optic nerve lesions:-

- Usually associated with a reduction in the amplitude of the VER without much changes in the latency

3. During orbital or neurosurgical procedures:-

- A continuous record of the optic nerve function in the form of VER is helpful in preventing inadvertent damage to the nerve during surgical manipulation.



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MEASUREMENT OF VA IN INFANTS, MENTALLY RETARDED & APHASIC PTS

- VER is useful in assessing the integrity of macula & visual pathway.
- Pattern VER gives a rough estimate of VA objectively.
- Peak VER amplitude in adults occurs for checks b/w 10 & 20° of arc & this corresponds to a VA of 6/5.




MALINGERING & HYSTERICAL BLINDNESS

- pattern evoked VER amplitude & latency can be altered by voluntary changes in the fixation pattern or accommodation.
- However, the presence of a repeatable response from an eye in which only light perception is claimed indicates that pattern information is reaching the visual cortex & thus strongly suggests a functional component to the visual loss.

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- A characteristic of hysterical response seems to be large variations in the response from the moment to moment.
 - The first half of the test may produce an absent VER & 2nd half a normal VER.

LATERALIZATIONS OF DEFECTS IN THE VISUAL PATHWAY

- VER provides a useful information for localizing the defects in visual pathway in difficult cases e.g. children & non-cooperative elderly pts.
- Asymmetry of the amplitudes of VER recorded over each hemisphere implicit a hemianopic visual pattern.

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- However, the differentiation of tract lesion from that of optic radiation lesion is difficult.
 - Decreased amplitude of VER recorded over the contralateral hemisphere, when each eye is stimulated separately indicates a bitemporal visual deficiency & may localize the site of chiasmal pathology

Unexplained visual loss

- useful in general & in pts. with orbital/head injury

Assessment of visual potential in pts. with opaque media

- like corneal opacities, dense cataract & vitreous hemorrhage.

Amblyopia

- flash VER is normal but pattern VER shows decrease in amplitude with relative sparing of latency

So pattern VER is used in the detection of amblyopia & in monitoring the effect of occlusion on the normal as well as the amblyopic eye, esp. in small children.

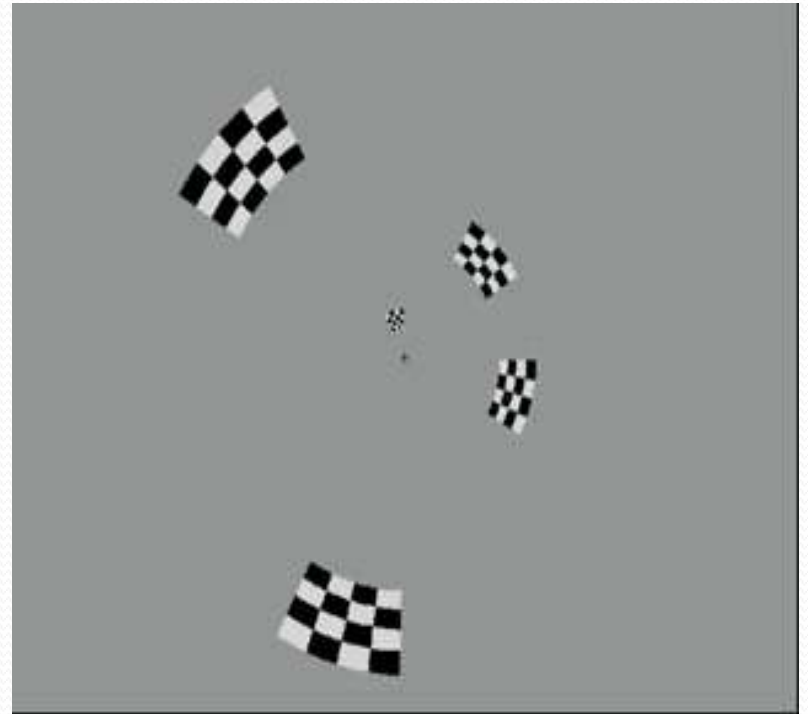
Glaucoma

- helps in detecting central fields

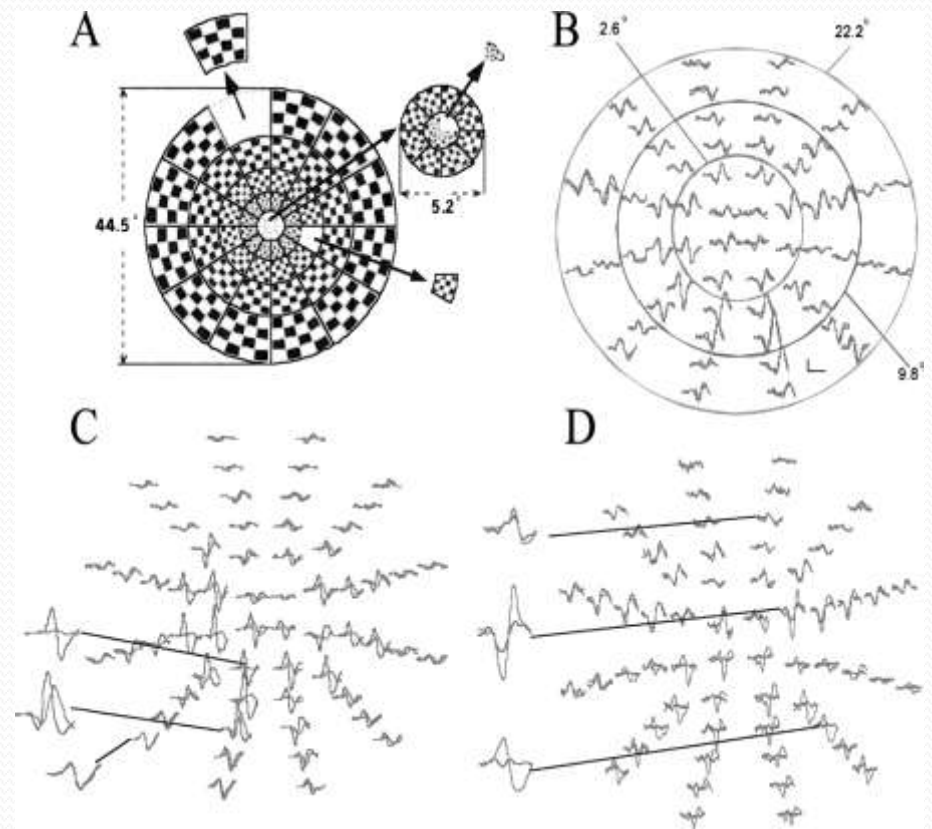
multifocal visually evoked potential


- provides local topographic information
- mfVEP recording technique is similar to that for a standard VEP, but the stimulus and analysis techniques are different

- typical stimulus array for the mfVEP is a dartboard display
- composed of a number of sectors, each with a checkerboard pattern.
- The sectors vary in size with retinal eccentricity



- Each sector is an independent stimulus that reverses in contrast in a pseudo-random fashion (m-sequence).
- mathematical algorithm is used to extract separate responses for each of the sectors from a single continuous EEG signal.



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- unilateral disease is relatively easy to detect
 - Useful in:
 - Optic neuritis
 - Multiple sclerosis
 - glaucoma, with local visual field effects
 - Ischemic optic neuropathy



THANK YOU