CLINICAL ASPECTS OF THE ELECTRICAL RESPONSE OF THE HUMAN EYE TO AN INTENSE LIGHT STIMULUS

by

N.R. GALLOWAY, B.A., MB.ChB., D.O., F.R.C.S.

CONTENTS

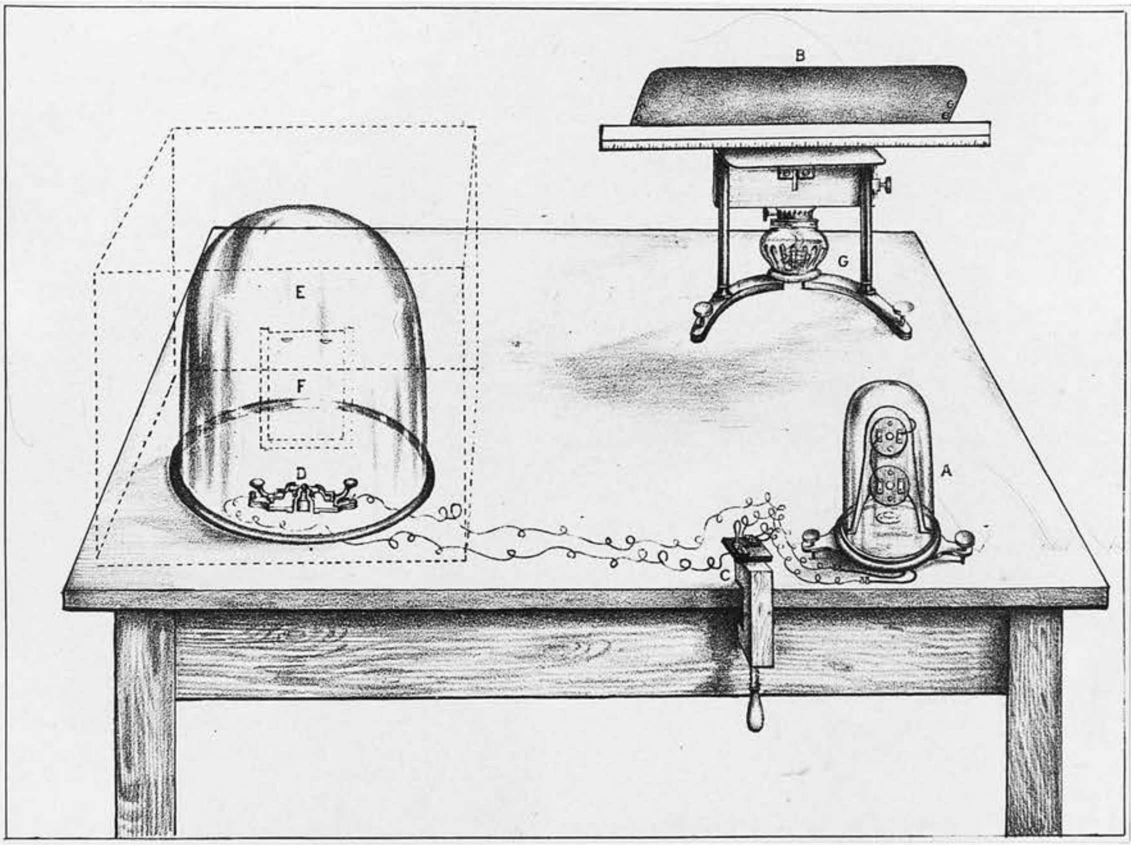
INTRODUCTION

This thesis describes the electrical response of normal and diseased human eyes to an intense light stimulus. The apparatus and technique has been developed from a standard clinical procudure known as electroretinography The method to be described enables one to observe the response in more detail than has been hitherto possible Two recently discovered components of the electroretinogram are clearly shown using this technique. One of these components, the Early Receptor Potential, has not been previously described in the human eye when the work was begun.

The technique was applied to a series of normal subjects and subsequently to a series of patients with a variety of eye diseases.

Two introductory papers have already been published by the author on this subject, (Galloway, 1967 and Galloway, 1968).

HISTORICAL BACKGROUND


B
E
F
D
G
A
C

HISTORICAL BACKGROUND.

The study of electrical changes in the eye has been pursued for over one hundred years. Most of this work however has been carried out in the laboratory using experimental animals and clinical electroretinography has only been introduced on a large scale in the last twenty years. The need for complicated equipment has restricted expansion into the clinical field, but advances in electronic engineering have now made the necessary equipment more freely available.

THE DISCOVERY OF THE RESTING POTENTIAL AND THE ELECTRORETINOGRAM.

The first work in this field was concerned with the corneo-retinal or resting potential of the eye, which may be defined as the difference in electrical potential between the cornea and the posterior pole of the eye. It was first discovered by Emil Du Bois Reymond, professor of physiology at Berlin (Du Bois Reymond, 1849). He was a contempory of Michael Faraday but unlike Faraday his main achievements were in the study of electrical changes throughout the body. His measurements were necessarily crude by modern standards because electricity was in its infancy.

It was not until sixteen years later that Holmgren observed that the resting potential was modified by the action of light shining on the retina, (Holmgren, 1865). Shortly after this Dewar and McKendrick working in Edinburgh rediscovered this quite independantly and they came upon Holmgren's paper after their own results had been published. The illustration taken from their original paper throws an interesting light on research methods of the time and depicts the apparatus they used for detecting the electroretinogram in the eye of an experimental animal, (Dewar and McKendrick, 1873). They used Du Bois Reymond's non polarisable electrodes and recorded the electrical changes with Thomsen's galvanometer. From their experiments they were able to reach the following conclusions:

(1) Variations in E.M.F. on impact of light amount to 3-10% of the normal resting potential.

(2) The electrical alterations can be traced to the brain.

(3) The rays regarded as most luminous give the maximum variation.

(4) Electrical alterations are due to the action of light on the retinal structure as they are independant of the anterior portion of the eye.

Initially their experiments were carried out by placing electrodes on the cornea and posterior pole respectively, but they subsequently discovered that the response to light could still be recorded between the exposed brain and the cornea allowing the eye to be left in situ. They then found that a similar result could be obtained by placing the electrodes on the cornea and an adjacent area of skin; this finding prompted them to investigate the human electroretinogram. To perform this a trough of clay was constructed around the margin of the orbit which contained a quantity of dilute salt solution. When the subject was lying horizontally with the head properly secured, a non polarisable electrode was introduced into the salt solution and in order to complete the circuit, the other electrode was connected with a large gutta percha trough containing salt solution into which one of the subjects hands was inserted. By a laborious process of education they managed to diminish the electrical variations due to involuntary movements of the eyeball, and by fixing the eye on one point with concentrated attention, they were able to detect responses. These workers concluded that "The method is too exhausting and uncertain to permit of qualitative observations being made".

THE EARLY DEVELOPMENT OF THE ELECTRORETINOGRAM.

At the turn of the century considerable advances were made in recording electrical responses in animals with the advent of more sophisticated equipment. In 1903, Gotch, working in the physiological laboratory at Oxford recorded responses from excised frogs' eyes, measuring them with a capillary electrometer and using an arc lamp as stimulus. He was able to photograph his records and he found that the positive component of the electroretinogram measured up to 0.001 volts and was preceded by a slight dip of negativity, (Gotch, F., 1903).

At this point in the history of electroretinography then, it was known that a flash of light on the eye produced a biphasic electrical change when measured between the cornea and the posterior pole. In addition other workers had shown by dissecting out different parts of the eye, that the response arises in the retina. Bruck, Garten and Piper carried out an extensive series of experiments using the string galvanometer and showed that the response to light was similar in a wide range of vertebrates, (Bruck and Garten, 1907. Piper, 1911).

AN EARLY ATTEMPT TO ANALYSE THE RESPONSE.

In 1908, Einthoven and Jolly carried out some critical work which formed a basis for later research. Einthoven was fortunate in that his medical education had included a high standard of training in physics at Utrecht. He himself invented the string galvanometer. This instrument consisted of a very fine strand of silver coated quartz suspended between the poles of a magnet. When a current passed through the strand, it caused it to be distorted by the electromagnetic force acting on it and this movement could be detected and measured by displaying the shadow of the strand on a screen.

Einthoven gained the Nobel prize for his study of electrocardiography and his work in that field has overshadowed his valuable contributions to electroretinography. The experiments that he carried out with Jolly showed that the electroretinogram had three component waves; the initial biphasic response was followed by a further positive wave. These were what are now known as the 'a', 'b' and 'c' waves of the electroretinogram. They measured the amplitude and latency of these responses and proposed a simple mathematical analysis of the composite waveform, postulating that it was the sum manifestation of three 'substances'. The measurements they made were as follows:

Average size of 'a' wave	-70μV
Average size of 'b' wave	+1050μV
Average size of 'c' wave	+1150μV
Latent period of 'a' wave	0.01 secs. with strong stimulus.
	more than 2 secs. with weak stimulus.

(Einthoven and Jolly, 1908).

THE INTRODUCTION OF THE VALVE AMPLIFIER.

The introduction of the valve amplifier brought about a further improvement in recording technique and this was first used to measure potential differences in the eye by Chaffe, Bovie and Hampson , (Chaffe, Bovie and Hampson, 1923). In 1925 Hartline carried out a detailed series of experiments confirming that the response from intact animals was identical with that obtained from excised open eyes , (Hartline, 1925). Four years later Sachs was able to show that the human electroretinogram was typically dependant on the scotopic visual system of the retina and that the E.R.G. of protonopes was relatively reduced in red light, (Sachs, 1929). Here then was a waveform which could be accurately measured and which increased in size with dark adaptation. These findings were the first suggestions that here was an objective test of retinal function which might be of clinical value in the future.

The first electronically amplified human electroretinogram was recorded by Cooper, Creed and Granit, (Cooper, Creed and Granit, 1933), and about that time Granit performed some classical work separating the components of the cat E.R.G. By anaesthetising the animals with ether to varying depths of anaesthesia, he was able to selectively inhibit three different components which he called P1, P11 and P111. This was a development of the ideas put forward by Einthoven and Jolly; the sum of these components make up the waveform of the recorded E.R.G., (Granit, 1933).

In 1940 Bernhard noted that the scotopic and photopic mechanisms in the retina show a different electrical flicker fusion frequency. He used a flickering light to distinguish the photopic from the scotopic components of the human E.R.G. This technique is now part of the standard clinical procedure in many electro-diagnostic clinics. The Bernhard experiments made use of a recently developed dual beam oscilloscope and connection with the eye was achieved by a thread moistened with saline.

THE INVENTION OF THE CONTACT LENS ELECTRODE.

A great advance in clinical electroretinography came when Riggs introduced the contact lens electrode, (Riggs, 1941). Up till this time clinical electroretinography did not really exist and little was known about alterations in disease. In fact the use of the contact lens remained in obeyance during the war years but Karpe started publishing his clinical work from Stockholm in 1945, (Karpe, 1945). The use of the contact lens eliminated much of the interference due to background noise which had so far hampered clinical work.

INVESTIGATIONS INTO THE ORIGIN OF THE ELECTRORETINOGRAM.

Alongside the early development of clinical electroretinography, much useful work was performed to identify the exact site of origin of the E.R.G. Granit had shown that the physiological inactivation of the ganglion cells had no effect on the E.R.G., (Granit , 1933). Noell studied the E.R.G. after selectively damaging the retina with different drugs and concluded that it arises principally from the inner portion of the retinal receptors and the outer portion of the bipolar cells, (Noell, 1952). Another localising technique has been the use of microelectrodes, (Brindley, 1960: Tomita, 1956). This work seemed to confirm that the E.R.G. is generated somewhere between the inner limbs of the receptors and the inner portions of the bipolar cells.

In the meantime, the rod and cone components in the electrical response were being studied. Adrian, (Adrian, 1946) had shown that the E.R.G. can be divided into fast and slow components, the former present in the light adapted eye and more prominent in red light and the latter more prominent after dark adaptation and using light of shorter wavelength. Under suitable conditions the two responses were superimposed producing double humped 'a' and 'b' waves.

THE OSCILLATORY POTENTIAL.

The 'b' wave pattern is now known to be more complex than this. In fact as long ago as 1914 Frohlich showed the presence of several wavelets superimposed upon the 'b' wave in cephalopods, (Frohlich, 1914). Granit noted the presence of these wavelets in 1947 and suggested that they were in the nature of oscillations and were distinct from the photopic and scotopic components described by Adrian. Cobb and Morton described the phenomenon in man (Cobb and Morton, 1954) and called it the Oscillatory Potential. They counted four to six wavelets using a bright stimulus flash lasting 250μ secs.

ELECTRO-OCULOGRAPHY.

At this stage it is important to mention the development of a special technique for measuring the standing potential of the eye known as electro-oculography. In the early nineteen twenties, one or two authors had described changes in potential due to movements of the eyes. These could be recorded by electrodes placed on the skin on either side of the eye, (Meyers, 1929). However it was some time later that it was shown that these electrical changes were due solely to the existence of the standing potential and not to muscle action potentials. Mowrer, Ruch and Miller (Mowrer et al., 1936) showed that the eye behaves as a dipole and that rotation of this dipole produces a potential difference between laterally placed skin electrodes; Fenn and Hursh demonstrated that this potential difference is directly proportional to the sine of the angle of rotation of the globe, (Fenn and Hursh, 1937). Further studies have shown that slow changes of the standing potential in response to light can be measured using such a technique, (Francois et al., 1956). Arden and Kelsey evolved a clinical test which follows the standing potential first of all for twelve minutes in the dark and then for ten minutes or more in the light. The ratio of light peak to dark trough is measured and expressed as a percentage. The trace obtained is known as the Electro-oculogram. The test is now employed alongside routine electroretinography in many electrodiagnostic clinics, (Arden and Kelsey, 1962). The slow rise in the standing potential which follows exposure to a steady light if thereby measured. Diminution or absence of this light rise can be demonstrated in several eye diseases.

THE EARLY RECEPTOR POTENTIAL.

A new development in the history of recording electrical responses from the eye occurred in 1964. This was the discovery of a rapid component which preceded the 'a' wave of the electroretinogram, (Brown and Murakami, 1964). This was termed the Early Receptor Potential; it could only be elicited by an intense light stimulus and its latent period was extremely short. The extremely rapid onset of the response suggested that this must be an electrical manifestation of the very initial process in visual stimulation. The E.R.P. (early receptor potential) is composed of a small positive peak followed by a larger negative one; the latent period is less than 60μ secs. Brown and Murakami originally recorded it using microelectrodes inserted into the retina but Cone subsequently demonstrated that it could be observed as a component of the corneal electro-retinogram, (Cone, R.A., 1964).

In this thesis the recording of the E.R.P. in humans will be described using a method which enables the rest of the E.R.G. to be examined at the same time. The work began in 1965 when the first human E.R.P. was recorded and following this a series of normal subjects and a variety of pathological conditions have been examined.

REFERENCES

DuBOIS REYMOND, E. (1849) Untersuchungen Uber Itricrische Elektricitat Berlin. 2/1, 256-7.

HOLMGREN, F. (1865) Upsala Lakareforenings Forhandlingar. 1865-66. 1, 177-91.

DEWAR, J. & McKENDRICK, J.G. (1873) Trans. Roy. Soc. Edinb. On the Physiological Action of Light. 27, 141-66.

GOTCH, F. (1903) J. Physiol. The Time Relations of the Photoelectric Changes in the Eyeball of the Frog. 29, 388-410.

Von BRUCKE, E.T. & GARTEN, S. (1907) Zur Vergleichenden Physiologie der Netzhautstrome Pflugers Arch. ges. Physiol. 120, 290-348.

PIPER, H. (1911) Arch. Anat. Physiol. Lpz. Physiol. Abt. Suppl. Bd. p.133.

EINTHOVEN, W. & JOLLY, W.A. (1908) Quart. J. Exp. Physiol. The Form and Magnitude of the Electrical Response of the Eye to Stimulation by Light of Various Intensities. 1, 373-416.

CHAFFEE, E.L., BOVIE, W.T. & HAMPSON, A. (1923) J. of Optical Soc. of America. The Electrical Response of the Retina under Stimulation by Light. 7, 1-44.

HARTLINE, H.K. (1925) Amer. J. Physiol. 73, 600.

SACHS, P. (1929) Die Aktionsstrome des menschlichen Auges: Ihre Beziehung zu Reiz und Empfinlung Klin. Wahnschr. 8, 136-137.(1929).

COOPER, S., CREED, R.S. & GRANIT, R. (1933) J. Physiol. 79, 185.

GRANIT, R. (1933) Journal of Physiol. The Components of the Retinal Action Potential in Mammals and their Relation to the Discharge in the Optic Nerve. 77, 207-239.

BERNHARD, C.G. (1940) Contributions to the Neurophysiology of the Optic Pathway. Acta. Physiol. Scand. 1, Suppl. 1 (1940).

RIGGS, L.A. (1941) Continuous and Reproducable Records of the Electrical Activity of the Human Retina. Proc. Soc. Exp. Biol. Med. 48, 204.

KARPE, G. (1945) The Basis of Clinical Electroretinography. Acta. Ophthal. Suppl. 24.

NOELL, W.K. (1952) Electrophysiologic Study of the Retina during Metabolic Impairment. Amer. J. Of Ophthal. 35, 126. (1952).

BRINDLEY, G.S. (1960) Physiology of the Retina and Visual Pathway. Monograph of the Physiological Society. Edward Arnold Ltd. (1960).

TOMITA, T. & TORIHAMA, Y. (1956) Further Study on the Intra Retinal Action Potentials and the Site of E.R.G. Generation. Jap. Journal Physiology. 6, 118-136.

ADRIAN, E.D. (1946) Rod and Cone Components in the Electric Response of the Eye. J. Physiol. 105, 24-37. (1946).

FROHLICH, F.W. (1914) Beitrage zur Allgemeinen Physiologie der Sinnesorgane Z. Psychol. Physiol. Sinnesorg., II Abt. Sinnesphysiol. 48, 28-164. (1914).

COBB, W.A. and MORTON, H.B. (1954) A New Component of the Human E.R.G. J. Physiol. (Lond.). 123, (1954) 36 P.

MEYERS, I.L. (1929) Electronystagmography a Graphic Study of the Action Currents in Nystagmus. Arch. Neur. & Psychiat. 21, 901-918.

MOWRER, O.H., RUCH, T.C. & MILLER, N.E. (1936) The Corneo Retinal Potential Difference as the Basis of the Galvanometric Method of Recording Eye Movements. Amer. J. Physiol. 114, 423-428.

FENN, W.O. & HURSH, J.B. (1937) Movements of the Eyes when the Lids are Closed. Amer. J. of Physiol. 118, 8-14.

FRANCOIS, J.,VERRIEST, G. & De ROUCK, A. (1955) B.J.O. 39, 398.

ARDEN, G.B., BARRADA, A. & KELSEY, J.H. (1962) New Clinical Test of Retinal Function Based upon the Standing Potential of the Eye. B.J.O. 46, 449. (1962).

BROWN, K.T. & MURAKAMI, M. (1964) A New Receptor Potential of the Monkey Retina with no Detectable Latency. Nature. 201, 626.

CONE, R.A. (1964) Early Receptor Potential of the Vertebrate Retina. Nature. 204, 736-739.

GALLOWAY, N.R. (1967) Early Receptor Potential in the Human Eye. Brit. J Ophthalm. 51, 261 (1967).

GALLOWAY, N.R (1968) Advances in Electrophysiology and - Pathology of the Visual System. 6 ISCERG Symposium, Leipzig 403-407 (1968).

DESCRIPTION OF APPARATUS

DESCRIPTION OF APPARATUS.

The apparatus was composed of the following parts:

(1) The Light Stimulus.

(2) The Oscilloscope, preamplifier and polaroid camera.

(3) The Delay Circuit.

(4) The Electrodes.

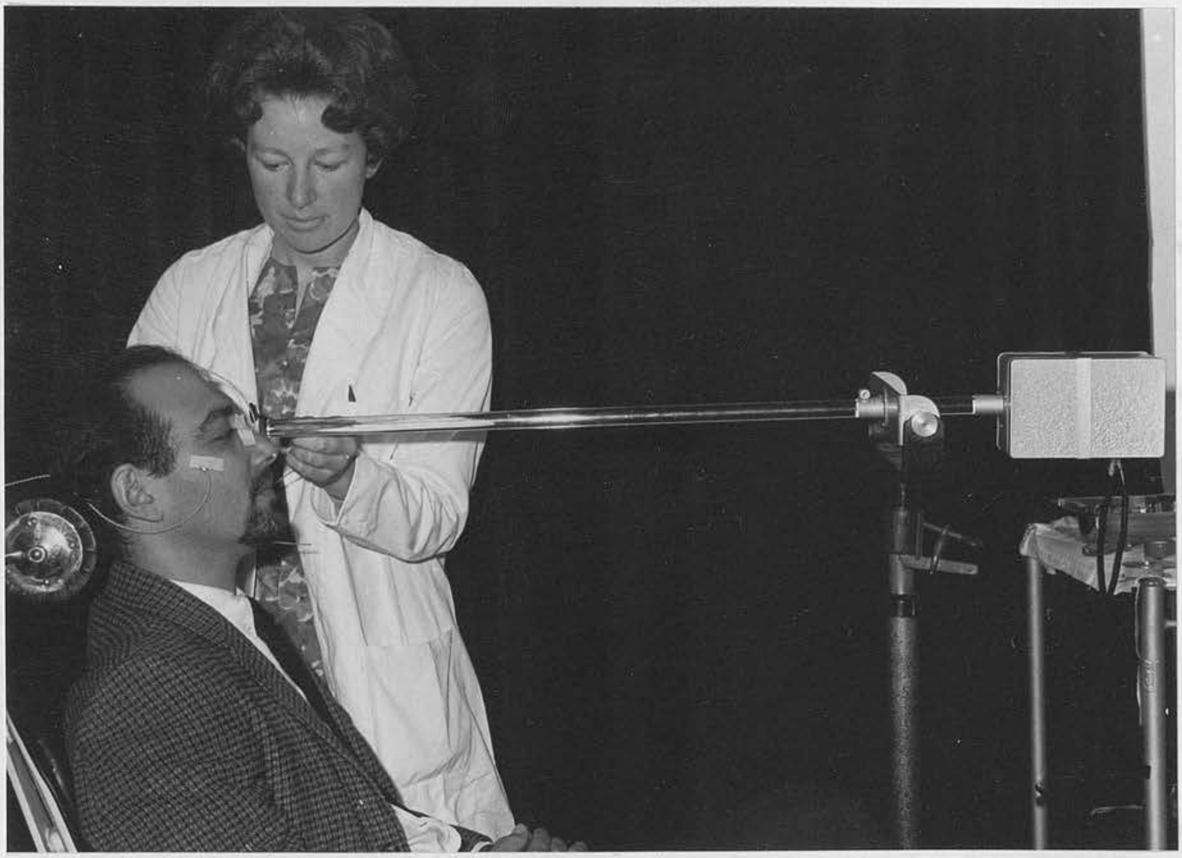


Fig. 1.

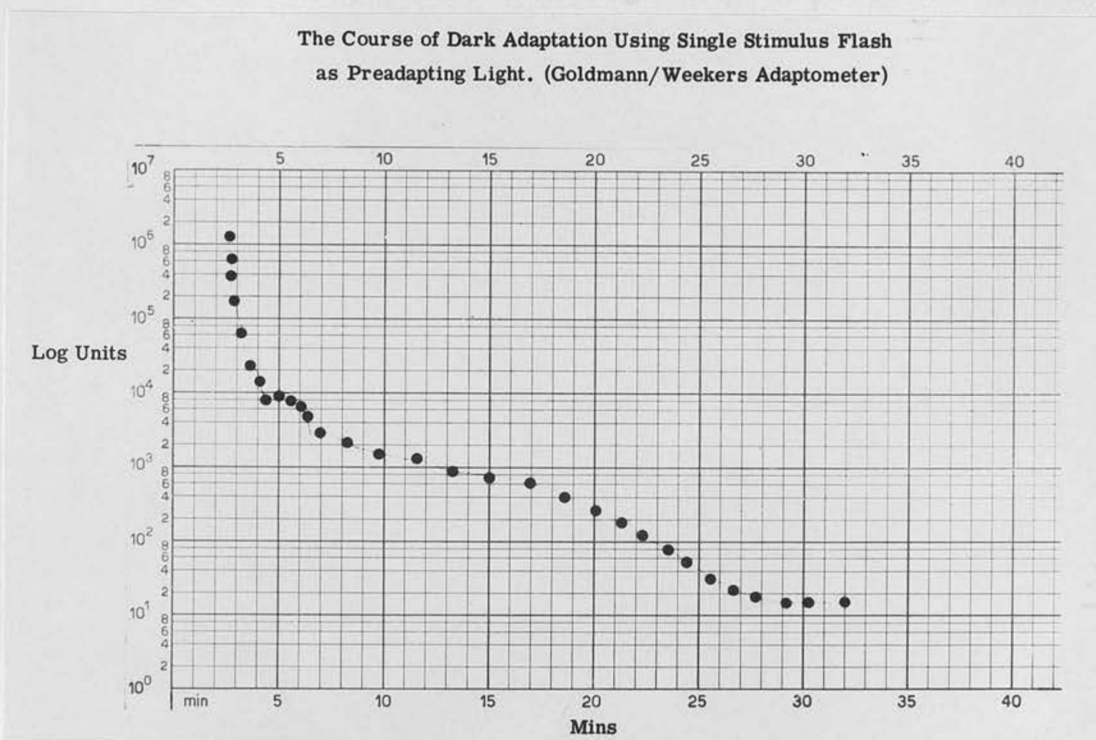

The Course of Dark Adaptation Using Single Stimulus Flash
as Preadapting Light. (Goldmann/Weekers Adaptometer)
Log Units
Mins
min

Fig. 2

(1) <u>The Light Stimulus.</u>

The light source was a photographic xenon flash tube, (Braun 'Hobby'). The strength of the flash was 45 Joules and recharging of the power pack took half a minute. The unit was screened in a metal box which was connected to earth. The xenon tube itself was fixed to the broad end of a cone of solid perspex. The narrow end of the cone was continuous with a straight perspex rod three feet long and half an inch in diameter. The perspex cone and the beginning of the rod were bound with chromium tape. A small red neon charge indicator was sunk into a recess in the cone so that a red glow could be seen on looking down the perspex rod. This was placed in position to help the subject align his eye prior to the stimulus flash. The complete unit apart from the power pack was mounted on a rotating stand. (See Fig. 1).

<u>Calibration of the stimulus.</u>

Neutral density filters of increasing value were placed in front of the light source until the flash became just invisible to the fully dark adapted subject. By this means the strength of the flash was found to be 12 log units above the dark adapted threshold. The timing of the flash was measured using a suitable photoelectric cell and recording the response with an oscilloscope. The peak time of the flash was 250μ secs.

To demonstrate the amount of light adaptation produced by the flash, dark adaptometry was carried out following a flash using the Goldmann Weekers dark adaptometer. The result is shown in Fig. 2. The normal threshold was reached about 30 mins. after a single flash in a previously dark adapted eye.

(2) <u>The Oscilloscope, preamplifier and polaroid camera.</u>

The electrical response from the subject or patient was initially amplified by a preamplifier (Tectronix type 122) and the signal was then fed to the input of an oscilloscope (Tectronix type 502A).

Since it is difficult to obtain a steady baseline using this amount of amplification with a D.C. amplifier, A.C. rather than D.C. amplification was used. Differential amplification was also used to reduce background noise.

Three leads were taken from the patient; one from the forehead, the earthed lead; one from the cheek, the negative lead and a positive lead from the cornea. These leads were fed to a junction box situated behind the patient's head and attached to the chair.

The settings of the amplifiers were as follows:

Preamplifier	High frequency cut-off	10Kc/sec.
	Low frequency cut-off	80~~Kc~~Cycles/sec.
	Gain	1000.
Oscilloscope Amplifier	Gain	0.2 Volts/cm.
	Time base	5msec/cm.

Signals appearing on the screen of the oscilloscope were photographed using a tectronix polaroid camera. Each film carried eight exposures and single exposures could be developed in ten seconds.

The shutter release button of the camera was used to trigger the whole series of events which led to the recording of the response from the patient.

(3) <u>The Delay Circuit</u>.

The timing of the stimulus flash in relation to the movement of the oscilloscope beam was an important feature. In order to examine the initial part of the response it was necessary to delay the triggering of the flash for about 5 msec. This was achieved by means of a small relay. The delay circuit is shown below.

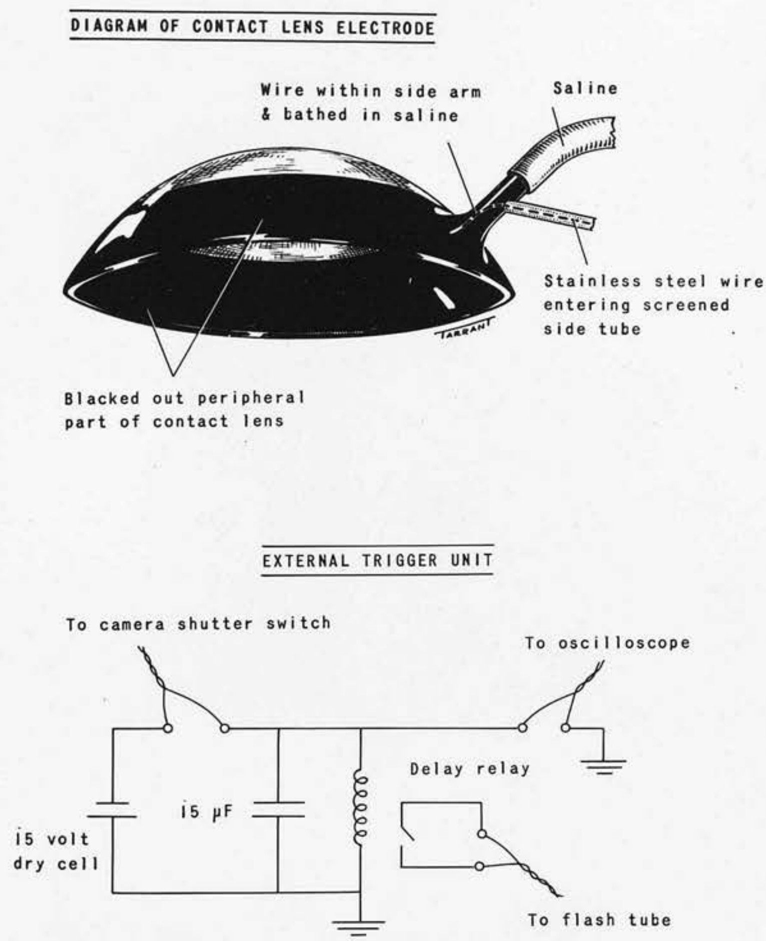


Fig. 3

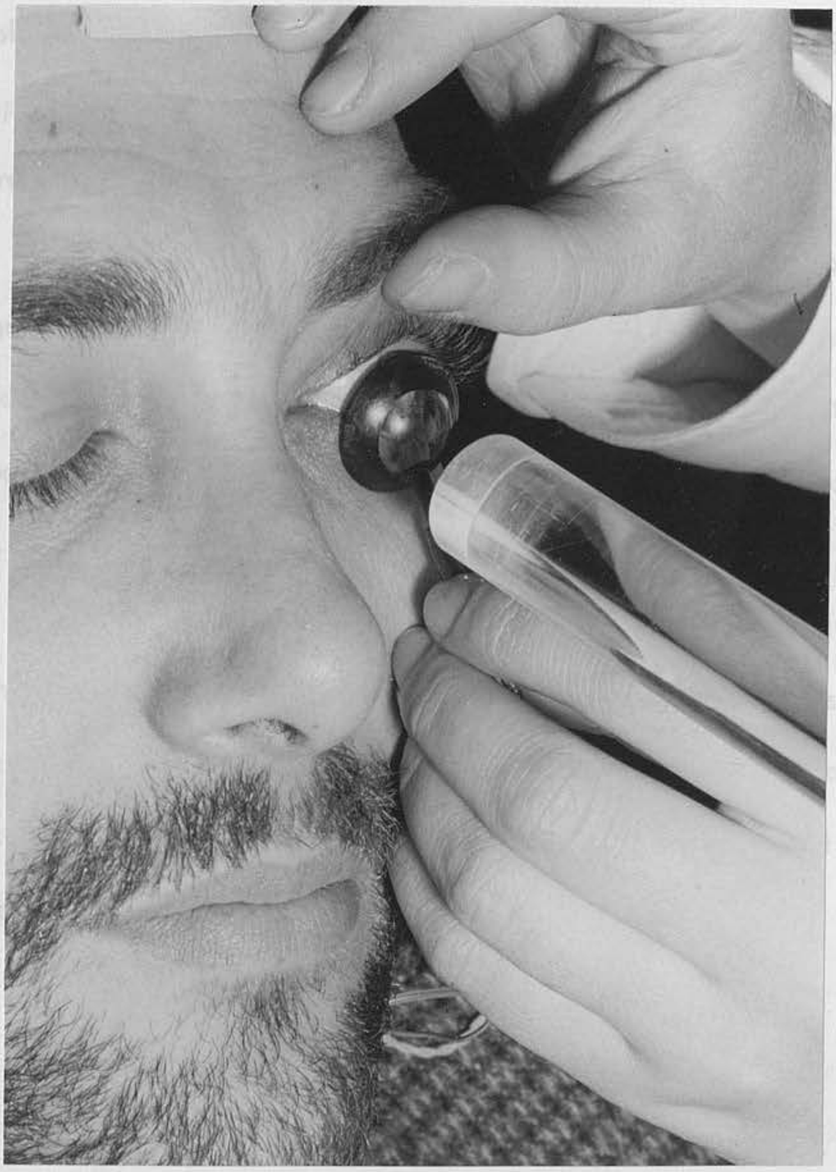


Fig. 4.

(4) The Electrodes.

Three electrodes were used, one on the left or right cheek according to which eye was being examined, one on the forehead and one on the cornea. The skin electrodes were a standard type of silver electrode used in electro-encephalography. They were held in place with strapping and a good contact ensured with electrode jelly.

Electrical contact with the cornea was obtained using a specially designed contact lens. This was similar to a lens designed by Karpe of Stockholm but it had a side arm containing a malleable stainless steel electrode. Saline could be injected through the side arm down an attached polythene tube. (See Fig. 4).

The contact lens was designed to eliminate any photo electric artefact which might be produced by light shining on it. For this reason, stainless steel rather than silver was chosen and the side arm and rim of the contact lens were blackened. When the lens was in position the polythene tube and wire lead were secured on the cheek with strapping.

Calibration and Testing of the Apparatus.

During the test the patient was seated in a dentist's chair and all three leads from the patient were plugged into the junction box. The patient's head was firmly supported to prevent movements from interfering with the response.

Electrical Artefact.

The power pack of the flash unit, the timing relay and the flash unit itself were all possible sources of electrical artefact. For this reason the flash tube was placed as far from the eye as could be conveniently managed and all apparatus was carefully screened. The absence of this type of artefact could be easily tested by carrying out the test under normal conditions but with the light pipe covered by a black velvet screen. It could then be shown that a flat trace was obtained on pressing the camera shutter release button. In practice a very small stimulus artefact could be observed under these conditions and could be used as a stimulus marker.

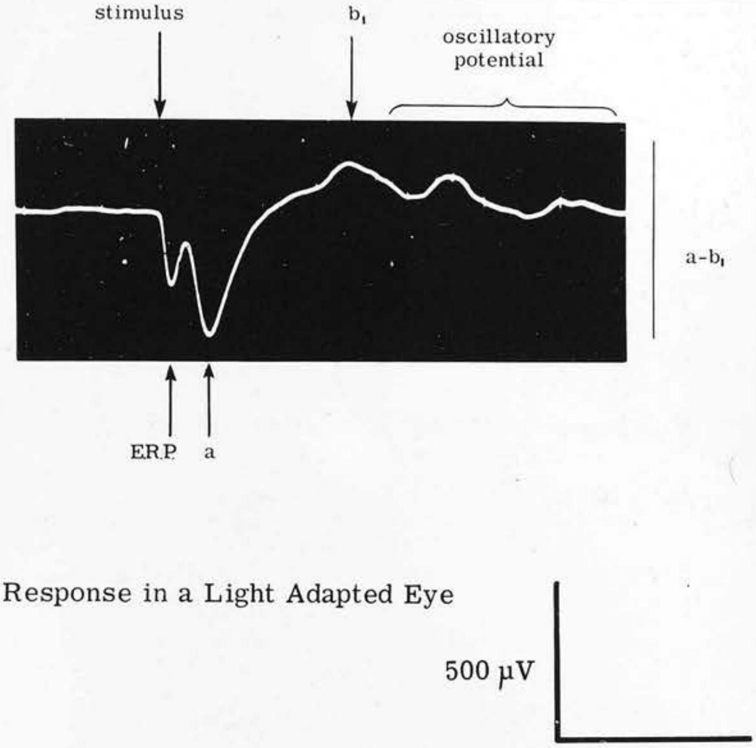
Photoelectric Artefact.

This was eliminated by masking the electrodes from stray light with black masking tape. The contact lens was designed especially for this purpose. The efficacy of the masking could be tested by immersing the electrodes in a beaker of saline and exposing them to the stimulus flash when connected to the recording equipment.

Calibration.

The complete recording apparatus was calibrated by connecting a signal of known strength in place of the patient and photographing the result.

THE NORMAL RESPONSE



The Normal Response in a Light Adapted Eye

Fig 1

THE NORMAL RESPONSE.

This was investigated in two ways.

(1) A series of experiments were carried out using one subject to see how the response varied under different conditions.

(2) The results from a series of normal subjects were analysed, using a standardised procedure.

Procedure.

The subjects pupils' were dilated and the electrodes placed in position. Before inserting the contact lens, a drop of local anaesthetic (Ophthaine) was placed on the cornea. Saline was then injected down the side arm of the lens and the base line on the oscilloscope checked by switching the oscilloscope to 'internal trigger'. The base line was also monitored with an audio amplifier so that the operator could still assess the base line whilst making adjustments to the electrodes. In fact the baseline was nearly always very steady and it has subsequently been possible to obtain good records from patients with nystagmus.

The light guide for the flash was then swung into position and the shutter release button on the camera pressed.

Fig. 1 shows a typical response produced in the light adapted eye following a single flash. The pupils were dilated by instilling a drop of Homatropine 1% and Cocaine 2% half an hour before the test. The different components of the waveform are illustrated. Measurements of E.R.P. amplitude, 'a' wave amplitude and the difference in amplitude between 'a' wave peak and 'b_i' were made on all traces. The number and size of the oscillatory potentials were also noted.

THE NORMAL RESPONSE.

1. Experiments carried out on one subject.

(a) The effect of repeated flashes on the responses.

The subjects' pupils were dilated and the eyes adapted to room light for about an hour. During the actual test, the lights were turned out. Flashes were repeated at varying intervals over a period of twelve minutes. It can be seen from Fig. 2 that a progressively diminished response was obtained although there was a considerable recovery during the three minutes between the third and fourth readings. The E.R.P. and 'a' wave are both reduced in the seventh reading in spite of the previous delay of five minutes.

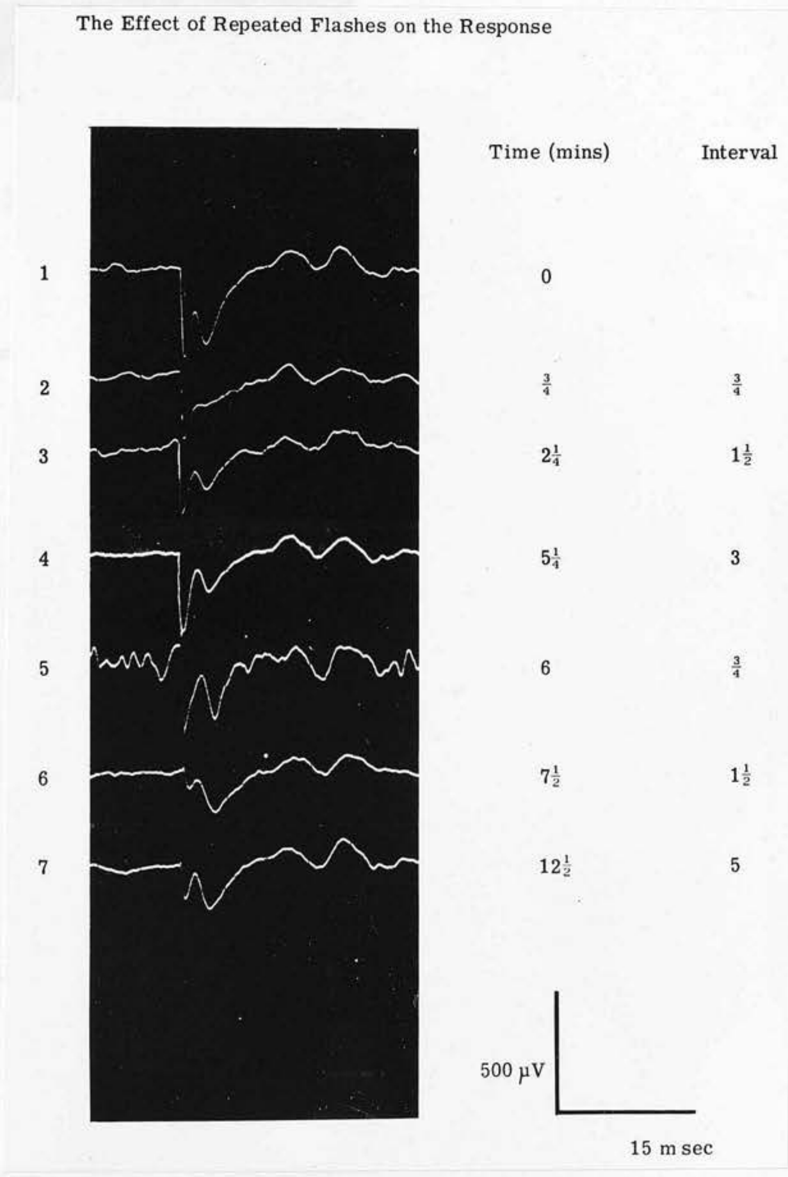


Fig. 2

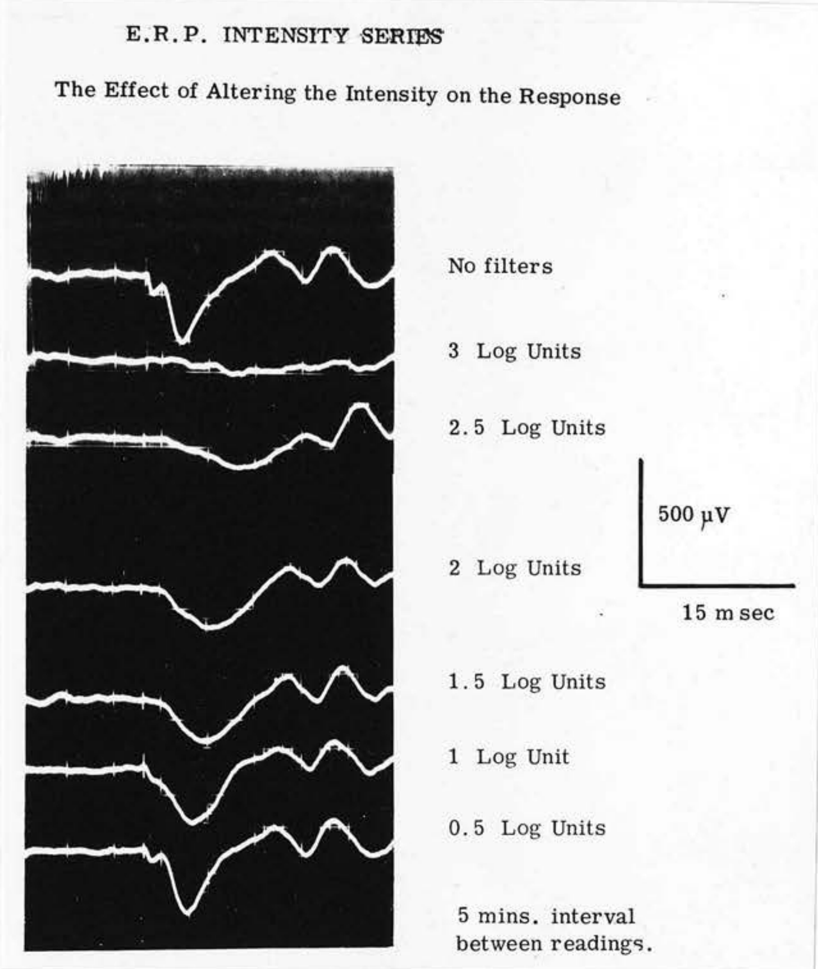

E.R.P. INTENSITY SERIES
The Effect of Altering the Intensity on the Response
No filters
3 Log Units
2.5 Log Units
500 µV
15 m sec
2 Log Units
1.5 Log Units
1 Log Unit
0.5 Log Units
5 mins. interval between readings.

Fig. 3.

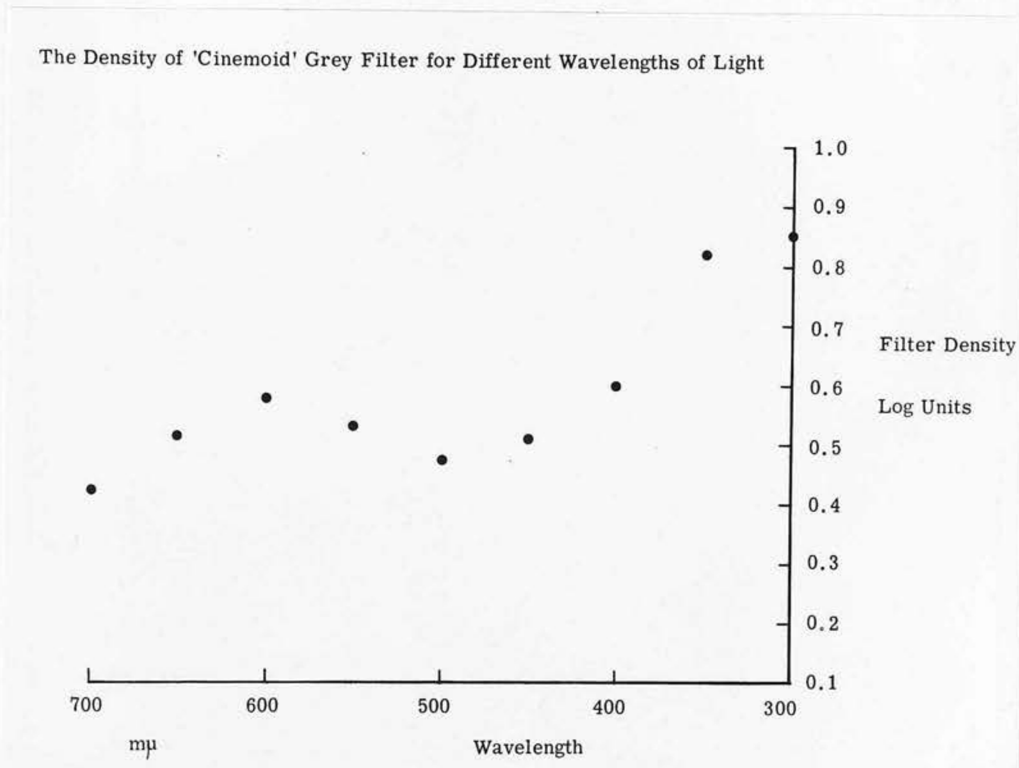

The Density of 'Cinemoid' Grey Filter for Different Wavelengths of Light
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
Filter Density
Log Units
700
600
500
400
300
mµ
Wavelength

Fig 3.

THE NORMAL RESPONSE.

(b) The effect of varying the intensity of the light source.

The intensity of the flash was varied by inserting neutral density filters in front of the light guide. Each filter was taken to be one half log unit. The density of this material ('Cinemoid') is shown for different wavelengths in Fig 3.

Readings were taken at five minute intervals. The first response was obtained with no filters in position. After five minutes the flash was repeated but this time with six filters (3 log units) interposed between the flash and the eye. By gradually reducing the number of filters a gradually increasing response was obtained until a near normal trace was produced with a $\frac{1}{2}$ log unit filter. The Early Receptor Potential was only present however when less than 1 log unit of filters were present. (See Fig. 3.)

Effect of Dark Adaptation on the Response

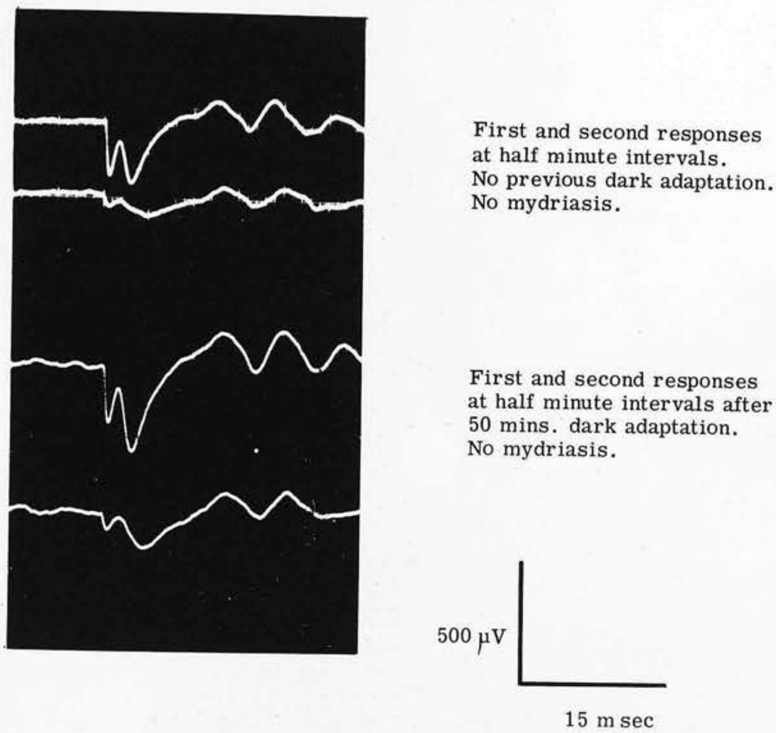


Fig. 4

THE NORMAL RESPONSE.

(c) The effect of mydriasis and dark adaptation.

Fig. 4 shows the result obtained with no previous dark adaptation and no mydriasis. That is to say the test was performed in a rountine way except that the pupils were not dilated. A second flash was then applied after half a minute.

The lower two traces demonstrate the result of the same experiment when performed after 50 mins. dark adaptation. The result shows that dark adaptation is probably unnecessary for routine clinical use when time with each patient is limited. It can be seen that both first and second responses are rather larger after fifty minutes of adaptation although the size of the Early Receptor Potential is not very different.

If one compares these results with those obtained with a dilated pupil (see Fig. 1) one can see that there is not a great difference between the two. Since the test is carried out in the dark, the pupils tend to be dilated in any case and the stimulus and response occur before the pupil has time to react. However, because the pupils of elderly subjects do not always dilate well in the dark, all future tests were performed after the instillation of a mydriatic.

THE NORMAL RESPONSE.

(d) The effect of altering the alignment of the light guide.

Because of the possibility of the light guide not being exactly aligned with the eye being tested, it was felt necessary to test the response when the stimulus was applied from an oblique angle. In Fig. 5 can be seen the results obtained with the light guide at 45^{o} to either side of the optical axis of the eye. Quite a good response was obtained in either case although the E.R.P. appeared to be larger when the light was directed onto the temporal side of the retina.

The Effect of Altering the Alignment of the Light Guide

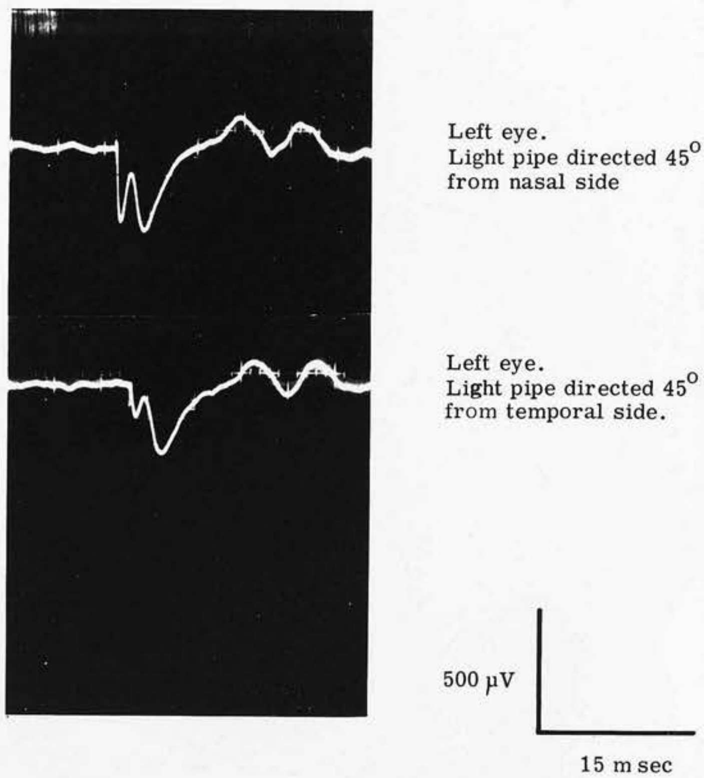


Fig. 5.

THE NORMAL RESPONSE.

(e) The effect of coloured filters on the response.

When a red filter was placed in front of the eye to be tested the 'a' wave was delayed and reduced in size. The E.R.P. was present but small. When a blue green filter was placed in front of the eye, the E.R.P. disappeared but the 'a' wave was larger than that produced with the red filter. The lowest pair of traces shows the effect of adding a neutral density filter to the blue green filter so that the size of the 'a' wave is comparable with that obtained using the red filter. In the figure each record was followed by a normal response taken from the other eye for comparison.

The Effect of Coloured Filters on the Response

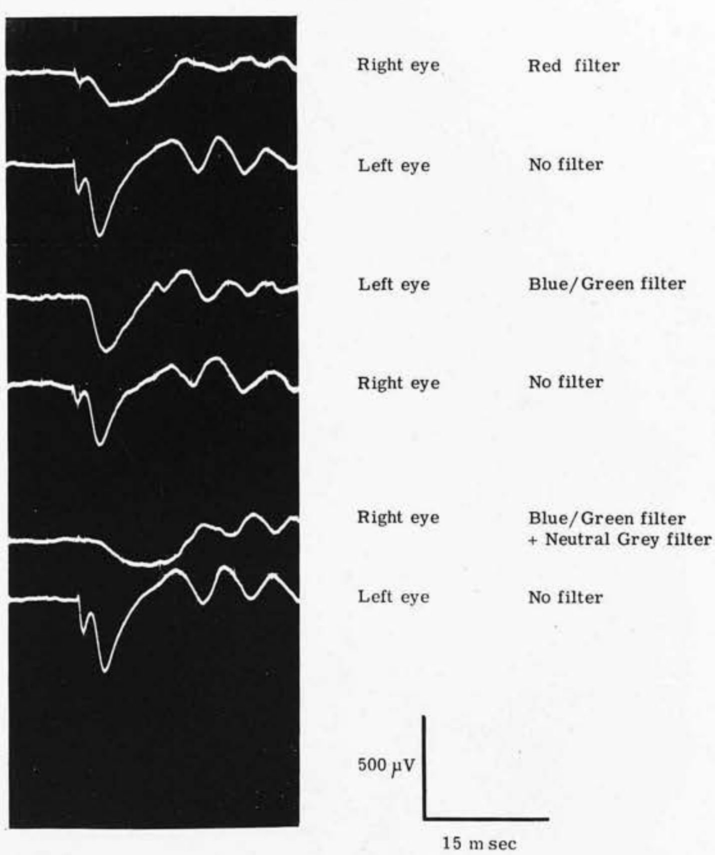


Fig. 6.

THE NORMAL RESPONSE.

(f) The relation of the E.R.P. to the subjective response.

Whenthe stimulus flash occurs, a bright flash followed by a series of after images are seen. The final after image remains for a variable time but is noticeable for about one minute. During the first quarter minute after the flash, the central vision is largely obscured by the after image. This period of time corresponds with the recovery time of the E.R.P. A second flash occurring when the dense after image is still present produces only a very small electrical response.

Data obtained from normal series

Table 1.

Age	Eye	E.R.P. µV	b_1 latency cm (1 cm = 5 m sec)	'a' wave µV	a+b µV
26	L	117	2.6	342	288
23		300	3.0	72	168
19-		60	3.0	360	240
21		270	2.3	252	360
19		90	2.3	198	261
19		90	2.5	234	243
19		90	2.6	333	396
19		144	2.5	270	288
20		234	2.6	363	405
30		185	2.5	351	270
19		180	2.5	342	117
19		210	2.5	300	210
20		216	2.5	300	216
19		300	2.4	210	252
30		400	2.6	320	460
19		460	2.3	240	400
29		400	2.5	380	400
20		400	2.3	550	500
22		300	2.4	520	460
17		297	2.4	315	225
58		315	2.7	495	378
26		108	2.6	324	279
52		198	2.5	306	261
22	R	240	2.5	420	320
	L	108	2.5	215	234
40	R	220	2.2	300	380
	L	260	2.3	340	440
20		400	2.5	560	320
22	R	300	2.4	420	320
	L	360	2.5	500	400
56		160	2.3	300	400
24		240	2.4	380	500
23	R	220	2.2	240	340
	L	100	2.4	240	360
30	L	160	2.4	300	400
	R	160	2.3	240	300
40		140	2.3	400	500
18		135	2.5	270	288
26		140	2.2	280	360
59		200	2.2	260	380

The oscillatory potential was present in all cases.

Frequency Distribution of Different Components

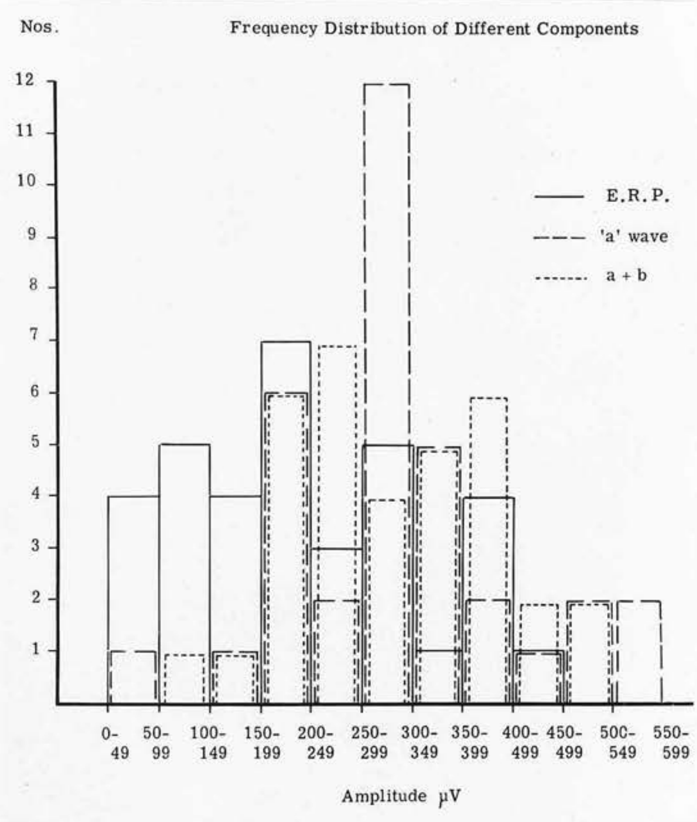


Fig. 7

THE NORMAL RESPONSE.

2. Data Obtained from a Normal Series of Subjects.

Measurements were made on forty normal eyes. Fifteen of these were in medical students and each student had one eye tested only. Ocular or systemic disease was excluded by taking a history and by examination with the ophthalmoscope and slit lamp. The other normal subjects were hospital staff as well as one or two patients who had suffered unilateral eye injuries and where there was no reason to suspect involvement of the other eye.

In table 1 can be seen the results obtained. The frequency distribution diagram (Fig. 7) shows that the amplitudes have a Gaussian distribution although the E.R.P. amplitudes were skewed to the left. Some of the early records had rather small E.R.P.'s but better results were obtained if extra care was taken in positioning the contact lens.

All the results showed two and usually three oscillatory wavelets on the 'b' wave. These decreased in size progressively so that the third wavelet was sometimes confused in the background noise.

Statistical analysis of the table gives the following results:

Early Receptor Potential	Mean Amplitude	222.7μV
	Variance	10743.3
	Standard Deviation	103.6
	Standard Error	16.4
Latency of 'b_i'	Mean	12.0 msecs.
	Standard Deviation	2.05
	Standard Error	0.3

Normal Series (Continued).

'a' wave Amplitude	Mean	326.1μV
	Standard Deviation	101.4
	Standard Error	16.1
Amplitude 'a' + 'b'	Mean	332.9μV
	Standard Deviation	93.4
	Standard Error	14.8
Ages	Mean	26.8 years
	Standard Deviation	13.2
	Youngest	18 years
	Oldest	59 years

There was no significant correlation between age and amplitude in the series presumably because of the predominance of younger subjects.

THE NORMAL RESPONSE.

Discussion.

The electrical response obtained using this apparatus shows the following features which distinguish it from previously recorded responses from the human eye; the 'a' wave is preceded by a negative wave of undetectable latency which appears to be identical with the Early Receptor Potential described by Brown and Murakami in monkeys; the oscillatory potential is consistently present and well defined; the 'a' wave is large compared with the 'b' wave.

The Early Receptor Potential.

These experiments reveal that when the flash was repeated after half a minute, the response was usually less than half its original value but the recovery was nearly always complete after a few minutes. On the other hand, a slightly larger response could be obtained after dark adapting for fifty minutes than when the eye was adapted to ordinary room lighting. If repeated flashes were applied, some exhaustion occurred in that the recovery time became delayed. Mydriasis or alteration of the alignment of the light guide did not greatly alter the response. The resulting variation in size of the E.R.P. was no greater than from subject to subject in the normal series.

Consistency of the response.

In the forty eyes examined, the mean E.R.P. was 222.7µV, the mean 'a' wave 326.1µV and the mean a-b difference was 332.9µV. The most constant reading was the latent period of the 'b_i' peak at about 12 msecs. It will be seen that the standard deviation of all the amplitudes is large; this is an unfortunate feature of clinical electrical measurements on the eye which has limited the clinician to qualitative rather than quantitative observations. The possible causes of the large variation in response are as follows:

(1) Recording technique.

(a) Good contact of electrodes with eye or skin not achieved.

(b) Variation of intensity of flash.

(c) Alignment of light guide poorly adjusted.

(2) True variations in the response.

(a) Diurnal variation. The size of this is unknown.

(b) The state of dark adaptation.

(c) The age of the patient.

(d) The psycho galvanic reflex.

In the above series every attempt was made to eliminate these factors where possible. For example the tests were carried out at about the same time of day. The state of dark adaptation was controlled and the experiments on a single subject were carried out on different days to avoid the possible effects of previous flashes.

THE ABNORMAL RESPONSE

THE ABNORMAL RESPONSE.

Introduction.

The aim of this part of the study was to use the same technique to investigate a wide spectrum of eye diseases. In addition a special study was made of a series of cases of retinal detachment and a series of patients with heriditary retinal degenerations.

For the clinical test the method was modified however in that each patient was exposed to two flashes at a half minute interval. (See experiment on dark adaptation, Fig.4). The reason for this was to gain some idea of the regeneration time of the response in different conditions.

Where possible measurementswere made alongside other electrodiagnostic tests. In most cases the electroretinogram was also measured using the standard stimulus light and recording with a penwriter and in addition electro-oculography was also performed.

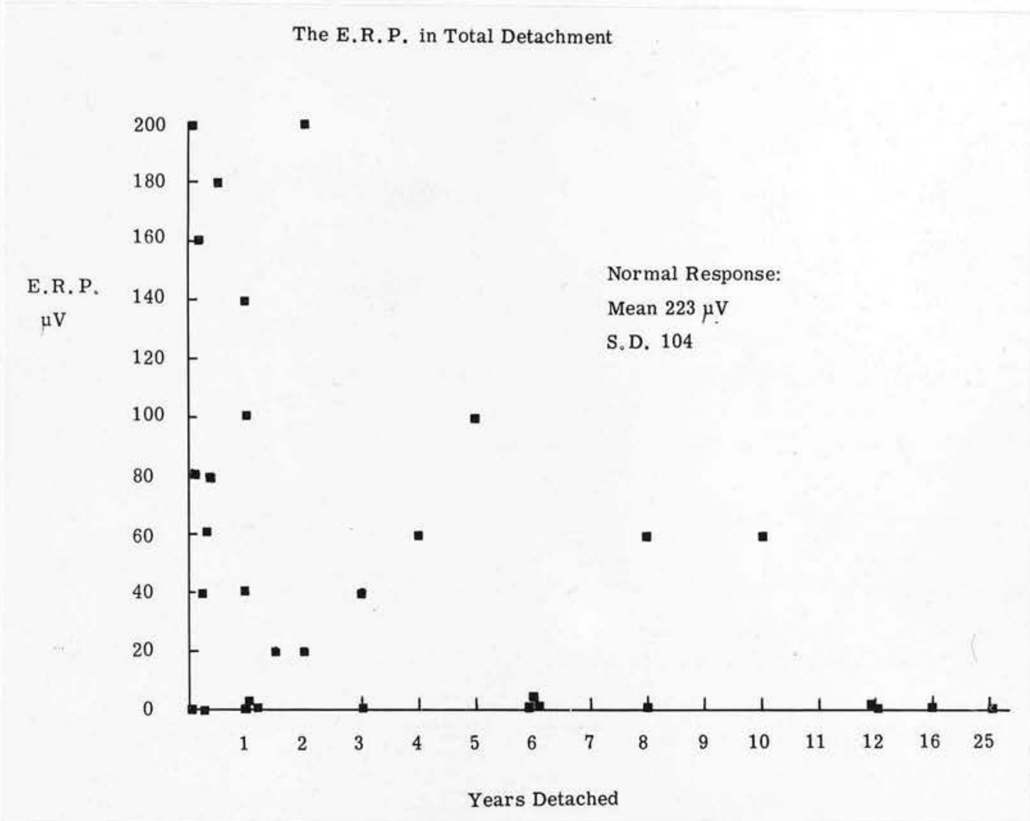

The E.R.P. in Total Detachment
E.R.P.
μV
200
180
160
140
120
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
12
16
25
Years Detached
Normal Response:
Mean 223 μV
S.D. 104

Fig 1

THE ABNORMAL RESPONSE

1 Retinal Detachment

Selection of Cases.

Patients from the retina unit at Moorfields Eye Hospital High Holborn were referred if (1) the retina had been detached for a long period and there was doubt about the value of surgery or (2) the diagnosis of retinal detachment was in doubt due to the presence of opacities in the media.

Results.

Table 1 and Fig. 1 show the results obtained. It can be seen that the Early Receptor Potential is present in many of these cases but appears to decay over a period of two to three years. Of the thirteen eyes with no response, nine had had a retinal detachment for three years or more. However an absent response was obtained in one recent detachment which had been present for 10 days before the test was carried out.

In Fig. 1, the reduction in size of the E.R.P. with time is illustrated in cases with total detachments.

The age incidence of these cases is similar to the age incidence obtained from blind registration statistics for cases of retinal detachment in this country. The incidence gradually increases from childhood to reach a peak in the 50 to 60 year age group, (Sorsby, 1966).

When the retina was totally detached the other components of the electroretinogram, that is the 'a' and 'b' waves were abolished. This is in accordance with previous work (Blach and Behrman, 1967). Even in recent detachments the 'a' and 'b' waves were absent when the detachment was a total one. The amplitude of the E.R.P. was below the mean value in all cases.

Table I.

Age.	E.R.P. size.	Length of time detached.	Extent of detachment.	Case No.
51	0	10 days	total	1641
50	0	7 weeks	total	1619
50	0	25 years	total	1619
59	40	3 months	total	1532
59	0	1 year	total	1532
40	100	1 year	total	1558
47	20	6 months	total	1606
47	10	1 year	total	1606
20	60	10 years	total	1613
50	80	10 weeks	total	1399
26	60	1 month	total	1400
	120	8 years	3/4	1420
16	180	7 weeks	1/4	1478
64	140	1 year	total	1492
64	40	3 years	total	1492
21	160	3 weeks	lower 1/2	1320
60	0	1 year	total	1337
26	0	16 years	total	1352
50	200	2 years	total	1364
61	0	3 years	total	0416
33	200	1 week	total	1529
69	160	1 month	total	1370
50	60	4 months	total	1533
18	20	2 years	total	1375
26	0	12 years	total	1197
59	40	1 year	total	1262
60	0	6 years	total	1290

Age.	E.R.P. size.	Length of time detached.	Extent of detachment.	Case No.
60	0	6 years	total	1290
14	120	6 months	total	1294
38	0	12 years	total	1177
44	80	4 months	total	1553
42	40	2 years	lower 1/2	1608
13	0	6 years	total	1356
33	0	8 years	total	1529

Partial Retinal Detachments.

In the past it has been conclusively shown that the electrical activity of the retina is markedly impaired as soon as a retinal detachment occurs and that the depression of the response is related to the extent of the detachment, (Jayle et al., 1965). Although this series was concerned mainly with total detachments, four patients with partial detachments were referred and the results are shown in the table.

All the four E.R.P.s were well below the mean value obtained from the normal series, but comparison with the total detachment series (see Fig.2.) shows that they do not indicate the extent of the detachment; that is to say the E.R.P. appears relatively well preserved in recent cases of retinal detachment irrespective of the extent of the detachment.

The E.R.P. in Partial Detachment of the Retina

Case No.	Duration of Detachment	Extent of Detachment	E.R.P.	a wave	a-b diff.
1420	8 yrs.	3/4	60 µV	100 µV	no b wave
1320	3/52	1/2	160 µV	140 µV	80 µV
1608	2 yrs.	1/2	40 µV	none	none
1478	7/52	1/4	180 µV	160 µV	180 µV

Fig. 2.

The Response After Successful Surgery

Case No.	Age	E.R.P.	a wave	a-b diff.	time elapsed since surgery
1399	50	100 µV	80 µV	100 µV	1 mnth.
1364	50	180 µV	140 µV	200 µV	1 yr.
1250	37	0	0	0	4 mnths.
1574	38	R 60 µV	180 µV	240 µV	2 yrs.
		L 120 µV	80 µV	80 µV	1 yr.

Table II.

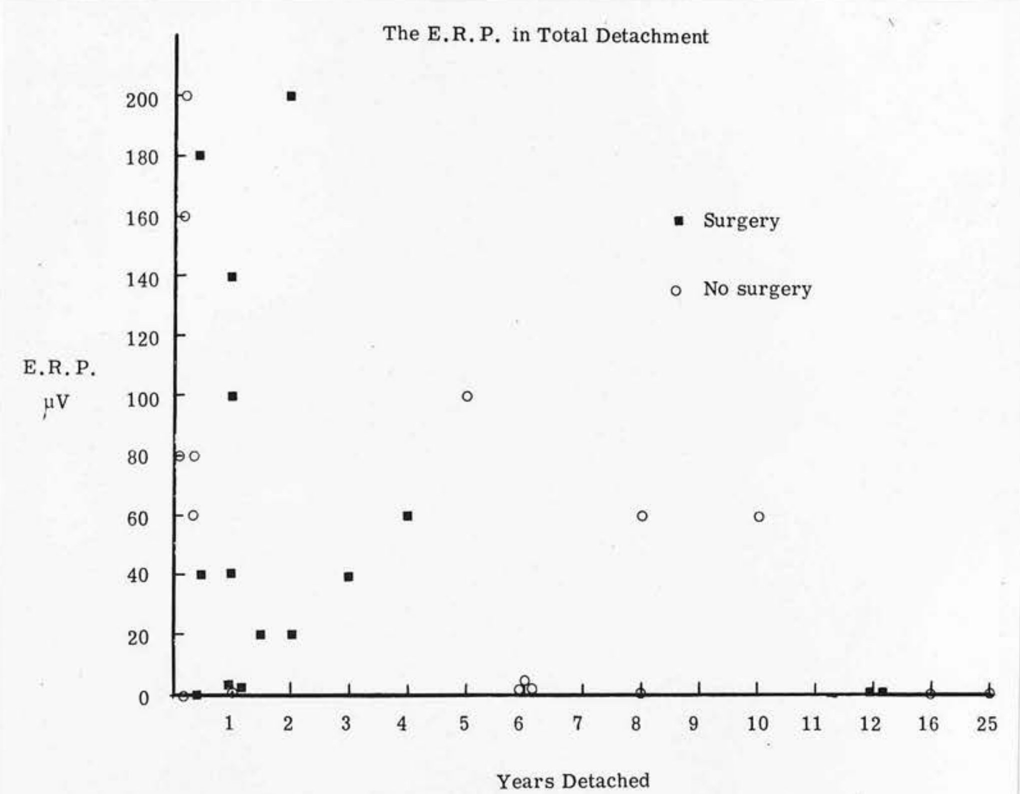


Fig. 3.

The Effect of Successful Surgery on the Response.

Four patients were examined who had had successful detachment surgery and details of these are listed in table II.

All Patients except no. 1574 had undergone encircling operations for their detachments and the figures indicate considerable recovery of the electrical response. The exception to this was case 1250. This patient had a detachment which had been present for about three years; a preoperative test showed no response. When examined four months after successful surgery, the peripheral field had been restored but a large central scotoma was present in spite of the flat retina. The visual acuity of this eye was limited to counting fingers but the patient was able to see his way about the room whereas preoperatively he had been virtually blind in this eye. The absent response in this case was a surprising finding and will be considered in the discussion. Traces recorded from case 1574 are shown as examples in Fig. 3 .

The Effect of Unsuccessful Surgery on the Response.

Surgery per se did not appear to influence the size of the E.R.P. and electroretinogram. Sixteen patients in the series of total detachments had had surgery of some kind. This usually entailed an encircling operation (Schepens et al., 1957) or plombage (Custodis, 1956) with silicone rubber. As has been shown the more recent detachments tended to give better responses whether or not surgery had been undertaken. (See Fig. 3).

Comparison of these findings with those obtained by electro-oculography.

Electro-oculography was carried out as a supplementary investigation in sixteen cases.

No light rise was present in any of the cases tested. A small E.R.P. was present in seven of these and in addition a small 'a' wave was present in two cases. In these last two cases the detachment was subtotal whereas in the other cases the retina was completely detached.

In one patient who had had successful surgery, the E.R.P. and E.R.G. showed considerable post operative recovery but the light rise of the electro-oculogram did not reappear.

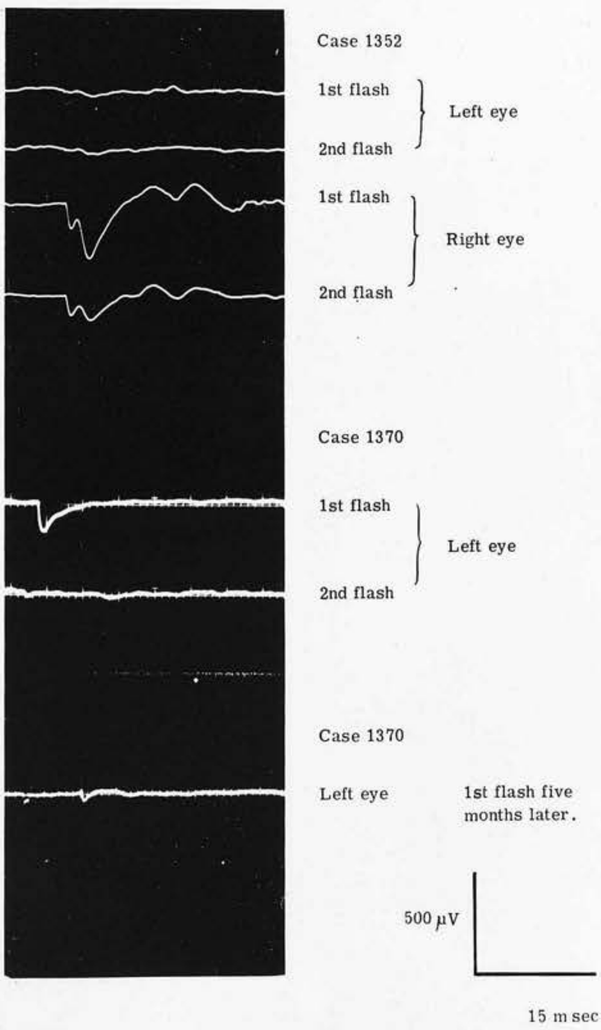
The Electro-oculogram was therefore more severely affected in these cases than any of the other responses which were measured.

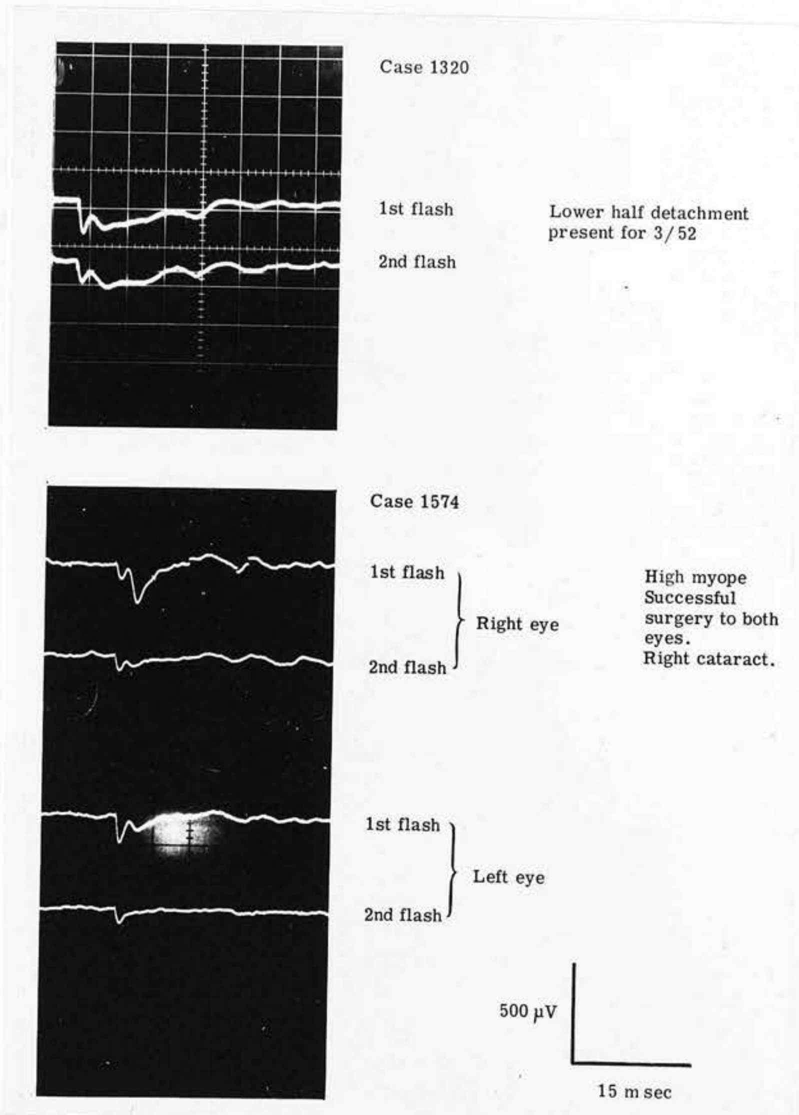
Illustrative Cases.

Case 1352. This illustrates the response in a 26 year old patient who had suffered a catapult injury to the left eye 16 years previously. The left retina was totally detached. The lower two traces were taken from his normal right eye for comparison.

Case 1370. The traces are from a 69 year old patient with a subtotal retinal detachment in the left eye and a history of chronic bilateral uveitis. The retina became detached one month before the first reading was taken and one can see that the response appears to have deteriorated further in the ensuing five months.

Illustrative Cases

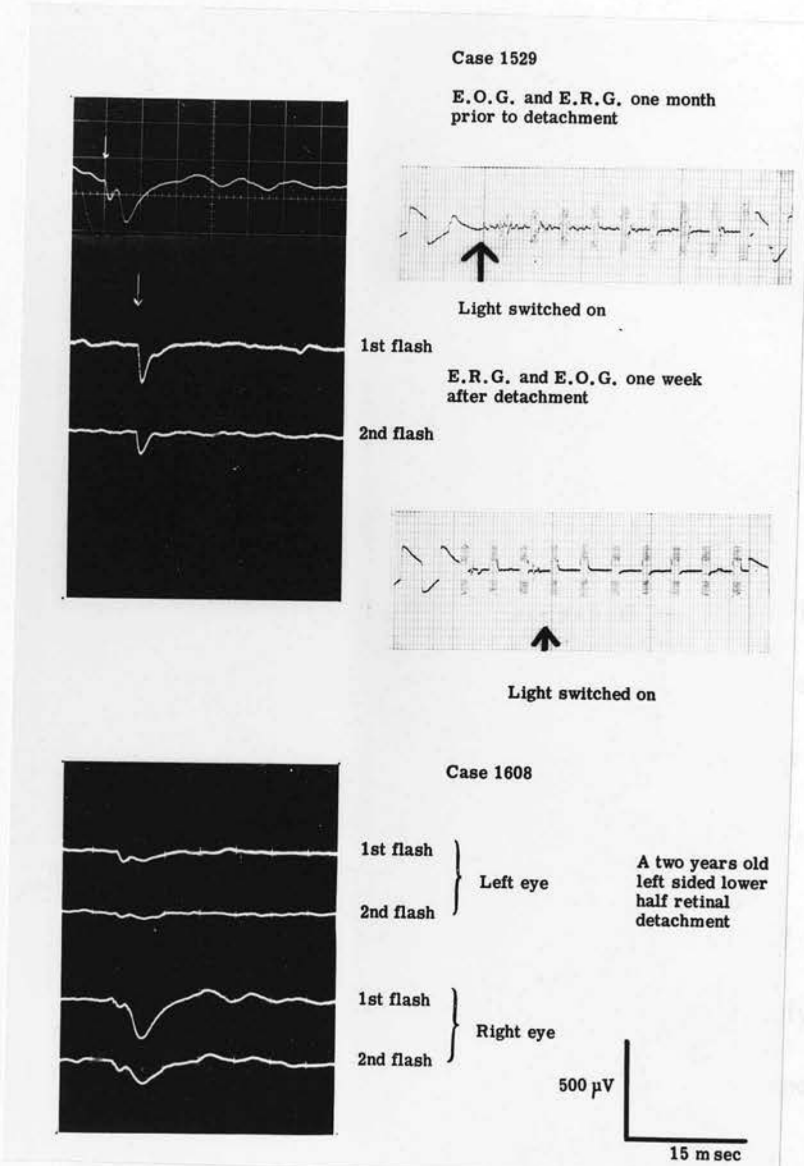



Case 1320
1st flash
2nd flash
Lower half detachment present for 3/52
Case 1574
1st flash
2nd flash
Right eye
High myope
Successful surgery to both eyes.
Right cataract.
1st flash
2nd flash
Left eye
500 µV
15 m sec

Illustrative Cases.

Case 1320. This trace is shown to demonstrate the persistence of the later components of the electroretinogram, namely the 'a' wave, 'b' wave and oscillatory potential in a patient with a lower half detachment. This had been present for three weeks.

Case 1574. This patient had had successful detachment surgery to both eyes. Both retinae were in good position but the patient was a high myope and the left visual acuity was limited to 6/60. The right visual acuity was limited to perception of light with good projection and a dense cataract was present on that side. The right eye had had detachment surgery 2 years before the test and the left eye one year before.


Case 1529
E.O.G. and E.R.G. one month prior to detachment
Light switched on
1st flash
E.R.G. and E.O.G. one week after detachment
2nd flash
Light switched on
Case 1608
1st flash
2nd flash
Left eye
A two years old left sided lower half retinal detachment
1st flash
2nd flash
Right eye
500 µV
15 m sec

Illustrative Cases.

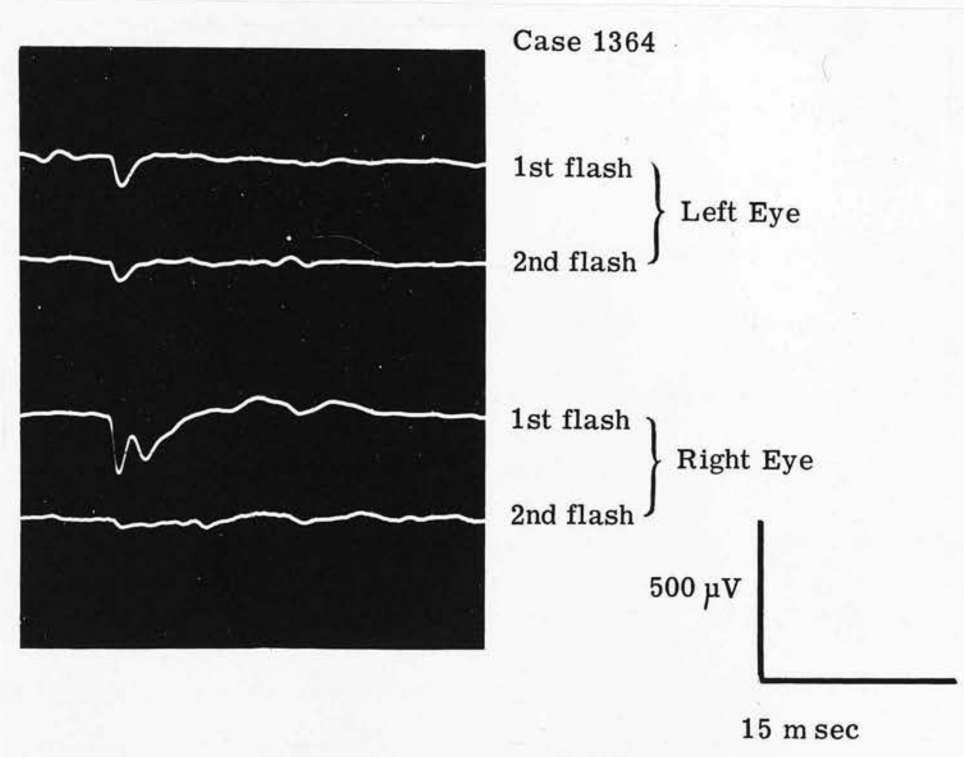
Case 1529. This case is of interest because the electroretinogram was measured one month before and one week after the patient suffered a retinal detachment. The patient was initially examined because of a longstanding detachment in the other eye. When seen one month after, he gave the history of sudden loss of vision in his remaining eye one week previously. The result of the electro-oculogram is also shown for comparison. Note that the first electro-oculogram shows a normal light rise, whereas the second shows no light rise.

The filmed traces show a normal response prior to the deatchment; the E.R.P. and other components are all visible though somewhat reduced in size. The response after the detachment is limited to a single negative peak, the E.R.P.

Case 1608. A two year old detachment of the lower half of the retina. Unsuccessful surgery had been carried out shortly after the detachment occurred. The traces from the normal right eye are shown below.

Illustrative Cases.

Case 1364. This patient had bilateral retinal detachments. Surgery to the right eye (lower trace) was successful but his left retina detached again postoperatively. The response from the left eye shows a small Early Receptor Potential. On the right side the trace shows a good recovery of all components but the second response after half a minute is severely impaired.



Discussion.

The prime aim of the above investigations was to observe the changes in the EarlyReceptor Potential in eyes which had suffered a detachment of the retina. The secondary aim was to assess any possible future clinical applications of this type of measurement. The changes in the E.R.P. have now been described and a discussion follows on the prognostic value of the response and its possible site of origin.

The Prognostic Value of the Response.

It has already been shown by several authors that the E.R.G. is abolished in cases of total detachment and that the size of the E.R.G. is related to the extent of the detachment (Rendahl, 1957). The prognostic value of the E.R.G. has been disputed (Jacobson et al., 1958; Francois, J. and De Rouck, 1955). The results of detachment surgery depend on many things; the amount of permanent damage suffered by the retina, the type of operation performed, the skill of the surgeon, the number and the extent of the tears in the retina and presumably a number of as yet unknown factors. It would therefore be highly presumptious to expect that by making an electrical measurement on a patient, one could predict the outcome of surgery. However, one might expect the E.R.G. to provide information about the amount of permanent damage suffered by the retina. This information could then be considered alongside the other factors in making a prognosis.

The difficulty encountered with the standard method of electroretinography is that the response is abolished altogether in total detachments irrespective of the residual function of the retina. However, as has been shown, the E.R.P.

is still present but gradually decays over a period of years. Future studies may show that this component does have some prognostic value.

The Site of origin of the E.R.P.

It is important to consider the possible relationship between these electrophysiological findings and the histological changes which occur in retinal detachment. The changes which occur in the human retina following a detachment have not been fully described because of the difficulty in obtaining pathologic material but recently a detailed study of these changes has been made in the owl monkey (Machemar et al., 1968). The findings show that in this animal whose eye is very similar to the human eye, the outer segments of the rods and cones undergo early degenerative changes; the ganglion cells and nerve fibre layer survived undamaged and the pigment epithelium remained intact although some of the cells were altered in appearance. It has also been shown that the degenerative changes can be reversed by reattaching the retina surgically, (Machemar, 1968).

These findings seem to conflict with the idea that the E.R.P. is produced in the outer segments of the receptors. This idea is based on the following information:

(1) The extremely short latency of the response.

(2) The agreement of its action spectrum with that of rhodopsin.

(3) The direct proportionality of its amplitude to the energy of the stimulus.

(4) The persistence of the 'vitreous positive' peak at very low temperatures.

(Cone, R.A., 1964: Pak and Ebrey, 1965).

Is it possible for a histologically degenerate layer of outer segments to produce an Early Receptor Potential? If not then its site of origin must be elsewhere.

Brindley and Gardner Medwin (Brindley, G.S. and Gardner Medwin, A.R.) suggest that the E.R.P. is associated with displacements of charge within the monolayers of visual pigment which are thought to lie within the 'disks' which can be seen in the outer segments of the receptors in electron micrographs. These displacements of charge are brought about by the sequence of chemical changes which occur with the absorption of light. They base their hypothesis on a series of experiments carried out using microelectrodes on the isolated retina of the frog.

One must next consider the possibility of these human recordings being something different from the Early Receptor Potential recorded in animals. In animal experiments it has been shown that this rapid potential is complex and made up of at least five different components which may be separated by such measures as reducing the temperature, altering the state of light adaptation or by altering the stimulus wavelength (Arden et al., 1966). The pigment epithelium itself is responsible for a fast component which has been termed the eyecup potential (Brown, 1965). In fact a variety of tissues produce an E.R.P. like response when exposed to a bright flash, the essential common feature of these tissues, being the presence of melanin (Arden et al., 1966). These responses do not however show the property of light adaptation and in this respect they differ from the true E.R.P. which can be recorded from the isolated retina using microelectrodes (Cone, 1964).

When the E.R.P. was measured in this series, the eye was exposed to two flashes at a half minute interval. In all cases the second response was either absent or much smaller than the first. This would indicate that the eyecup potential has not been accounting for any significant part of the recorded potential. One might in fact deduce that this is a true retinal potential in spite of the histological evidence of severe damage to the receptors in a relatively recent detachment.

The question arises as to whether the E.R.P. arises from any particular receptor, that is either the rods or the cones or both. It was not possible to carry out accurate spectral sensitivity measurements with this apparatus because the amplitude of the response was too severely reduced by any filters. However one of the detachment cases is of interest in this respect, (case 1250). This patient had had the detached retina successfully replaced by surgery but although the peripheral field was restored, a dense central scotoma remained. The patient was not able to read any of the letters on the Snellen chart even with a suitable spectacle correction. No E.R.P. could be recorded from this eye and one might be led to think that the E.R.P. could be a cone potential since most of the cones in this patient's eye must have been permanently damaged. However other factors must be considered. In the next section it will be seen that the reverse situation can be found clinically. In some advanced cases of retinitis pigmentosa the peripheral fields are grossly constricted. The patient may be able to read the Snellen chart to the 6/6 line, viewing the chart as it were through a tunnel. In such a case, the E.R.P. was also abolished (See 1638). These findings would suggest that the E.R.P. is not specifically related to rod or cone function but that the response disappears if a sufficiently large number of receptors are damaged.

Summary.

The Early Receptor Potential can be recorded from an eye when the retina is totally detached. It differs in this respect from the 'a' and 'b' waves of the electroretinogram and from the electro-oculogram. The size of the E.R.P. appears to diminish over a period of years. The bearing these findings have on the theories of origin of the E.R.P. is discussed. Evidence is also presented to show that the E.R.P. recorded in humans is not specifically a rod or a cone response.

THE ABNORMAL RESPONSE.

2. Retinitis Pigmentosa.

Selection of cases.

Out of the twenty-one cases that were examined by this technique suffering from retinitis pigmentosa or related disorders, ten were selected because the appearance of the fundus and the presenting history fitted the classical description of the disease. All ten showed a waxy pallor of the optic disc, attenuation of the retinal arteries and bone spicule pigmentation distributed around the equatorial retina.

In the remaining cases, a diagnosis of 'tapeto retinal degeneration' had been made.

Results.

These are tabulated in table 3 . In many of the patients it was difficult to establish how long the eyes had been involved since the abnormal fundi had been noticed during a routine eye test. It was therefore felt that any assessment of the duration of the disease might be misleading.

In six of the eyes the E.R.P. was abolished and in all these cases the 'a' and 'b' waves of the E.R.G. were also absent. However in one case the E.R.P. was preserved when the rest of the E.R.G. had been abolished. In the total series of twenty-one cases there were several instances of this late preservation of the E.R.P. but in no instance was the E.R.P. abolished and the 'a' and 'b' waves preserved.

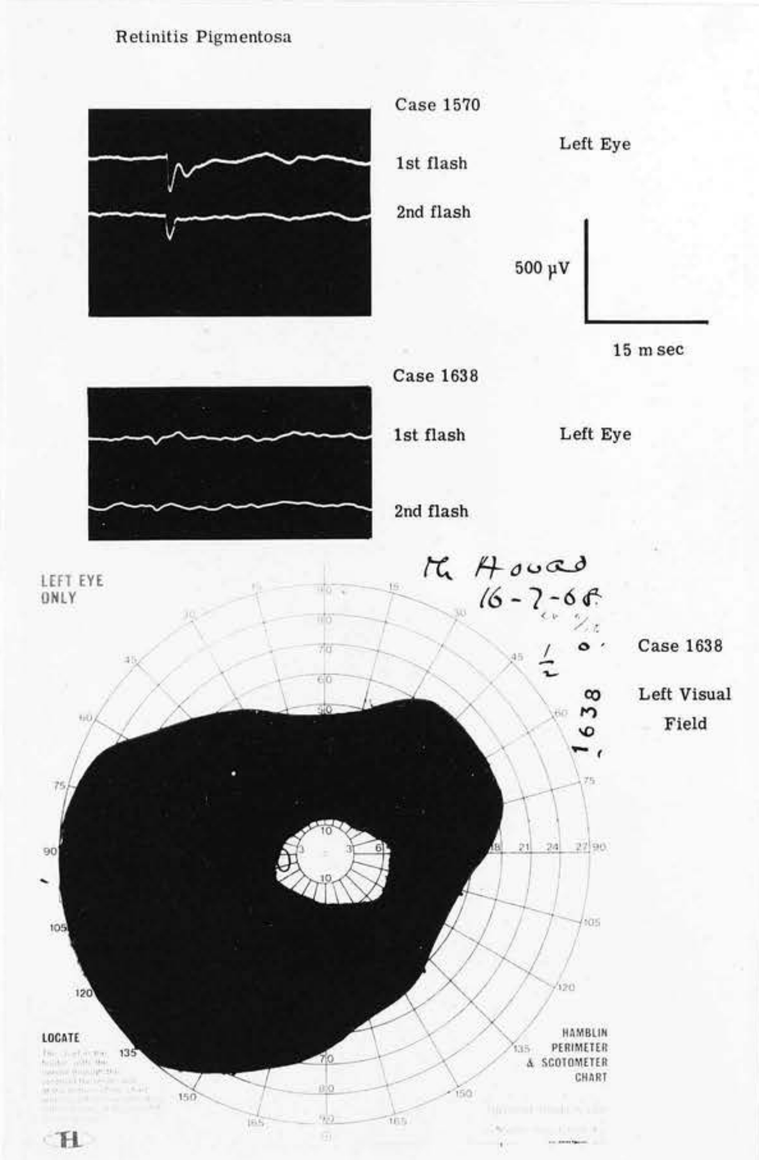
In two cases the electro-oculogram showed no light rise and yet the

E.R.G. was present although reduced. In no case was a light rise in the electro-oculogram accompanied by an absent E.R.G.

Table 3 .

Retinitis Pigmentosa.

Case No.	Age.	Clinical Presentation.	Vision. R.	L.	E.R.P.	a & b wave.	E.O.G.	Family History
1300	76	'Typical'	6/12	6/9	220	reduced a no b		yes
1289	54	'Typical'			120	reduced a no b	flat	no
1223	57	'Typical' + macular changes	6/9	6/9	0	absent	flat	no
1174	20	'Typical'	6/18	6/18	80	absent	flat	no
1167	28	'Typical'	6/9	6/9	R360 L200	normal reduced a absent b	flat	no
1638	25	'Typical'	6/12	6/18	0	absent		
1588		'Typical'	6/6	6/6	0	absent		no
1570	57	'Typical'	6/12	6/9	180	reduced a and b	250% R. & L.	no
1576	21	'Typical'	6/12	6/9	0	absent	flat	yes
1565	36	'Typical'			0	absent		nystagmus in family


Retinitis Pigmentosa
Case 1570
1st flash
2nd flash
Left Eye
500 µV
15 m sec
Case 1638
1st flash
2nd flash
Left Eye
LEFT EYE
ONLY
Case 1638
Left Visual
Field
LOCATE
HAMBLIN
PERIMETER
& SCOTOMETER
CHART

Illustrative Cases.

Case 1570. This patient, a male aged 57 years, sought an ophthalmological opinion several months before having had electrodiagnostic studies carried out. He was complaining of frontal headaches but these were thought to be unconnected with his eye condition. He had suffered from rheumatoid arthritis since the age of fourteen years. On examination he was found to have the fundus appearance of retinitis pigmentosa and some peripheral defect in both visual fields. The electro-oculogram gave a normal result in both eyes (Light Rise 250% R. & L.). The E.R.G. for a bright flash can be seen in Fig. of case. The 'a' and 'b' waves are both markedly reduced. This case is unusual in that the E.O.G. has been well preserved compared with the E.R.G.

Case 1638. This patient had advanced retinitis pigmentosa with the typical fundus appearance. The right visual acuity was 6/12 and the left 6/18. The visual field and trace are shown.

Discussion.

It is well recognised that the E.R.G. becomes severely affected at an early stage in patients with retinitis pigmentosa, (Karpe, 1954). However it has also been shown that small E.R.G.s are detectable even in the more advanced cases (Henkes, 1956). It would appear that the electro-oculogram tends to be more severely affected than the E.R.G. (Arden and Fojas, 1962) although the scotopic component of the E.R.G. also shows very early changes (Gouras and Carr, 1964). In this series the early disappearance of the light rise of the electro-oculogram is confirmed although there was one striking exception. (See case no. 1570). The persistence of the E.R.G. in some more advanced cases is also shown.

The series demonstrates that the E.R.P. is reduced to a lesser extent than the 'a' and 'b' waves and the electro-oculogram. In some cases the E.R.P. was still present when the other responses had disappeared. In advanced cases the E.R.P. was abolished.

Relation to Histology.

Histological examination of the eye in patients with retinitis pigmentosa reveals that the earliest change is destruction and disappearance of the neuro-epithelium. The first structures to be involved are the rods in the equatorial region. The pigment epithelium also shows degenerative changes. The last structures to be affected are the ganglion cells and the nerve fibre layer. There is considerable glial proliferation and this especially applies to the fibres of Muller. There may be associated thickening of the internal limiting membrane (Verhoeff, 1931) : (Bourne et al., 1938; Hogan and Zimmerman, 1962).

At first sight one might attempt to relate the different components of the electrical response to different layers of the retina in the order in which they are affected during the progress of the disease. However as is the case with retinal detachment, this could be misleading. It is well known that the central vision in retinitis pigmentosa is usually preserved to a late stage in the disease, and therefore some rods and cones must remain; it could be as has been previously claimed (Arden and Fojas, 1962) that the poor electrical response is not related to the degenerative process but to the presence of some insulating barrier for example the thickened internal limiting membrane described by Verhoeff.

Work on the E.R.P. in animals has suggested that this part of the response arises in the receptors (see above pp 60-62).The late disappearance of the E.R.P. in retinitis pigmentosa might be considered to contradict a receptor origin. On the other hand the remaining receptors could account for the response even though considerably reduced in numbers.

It would seem in the light of present evidence, that the E.R.P. could arise in the structures which remain intact to a late stage in the disease, that is the nerve fibre layer and the ganglion cells. However these structures are transparent and do not absorb light. As in the patients with retinal detachments, the E.R.P.s in advanced cases of retinitis pigmentosa showed light adaptation; the second response after half a minute was absent or reduced. It is therefore likely that these traces were not produced by the eyecup potential. (See discussion on retinal detachments).

Summary.

The technique described was applied to the eyes of a series of patients with retinitis pigmentosa. The marked reduction of the response in these cases was confirmed but it was found that the Early Receptor Potential persists to a late stage of the disease. In very advanced cases it was abolished.

Table 1

	Eye No.	Side	Age	Grade of haemorrhage	Associated disease
Grcup I	1	L	34		n.a.d
Normal	2	L	56		"
Eyes	3	L	60		"
	4	R	49		"
	5	L	20		"
Group II	6	L	32		Eales disease
Abnormal	7	L	58		Chronic glaucoma
Eyes with	8	R	40		Eales disease
clear vitreous	9	R	74		Peripheral pigmentary degeneration
Group III	10	L	40	II	Eales disease
Vitreous	11	L	49	I	Retinal tear successfully treated
haemorrhages	12	R	20	I	Injury
with normal	13	R	32	II	Eales disease
responses	14	L	65	I	Detachment successfully treated
Group IV	15	L	43	I	Proliferative diabetic retinopathy
Vitreous	16	R	43	II	" " "
haemorrhages	17	R	58	II	Chronic simple glaucoma
with abnormal	18	R	34	II	?
responses	19	R	65	II	? detachment
	20	L	74	II	? detachment
	21	R	56	II	? traumatic detachment
	22	R	60	II	?
	23	R	57	II	? detachment

Table 2

	Eye No.	ERP amplitude uV	a wave amplitude uV	b, wave latency m sec	a - b, uV	oscillatory potential
Group I	1	320	350	12.5	390	reduced amplitude
Normal	2	160	300	11.5	400	normal
Eyes	3	460	460	12.0	380	"
	4	300	420	12.0	320	"
	5	260	240	11.5	300	"
Group II	6	140	200	12.0	300	normal
Abnormal	7	200	222	12.0	240	"
Eyes with	8	160	320	11.5	360	"
clear vitreous	9	50	200	undetermined	-	absent
Group III	10	60	340	11.5	400	normal
Vitreous	11	390	500	12.5	400	"
haemorrhages	12	320	260	12.0	360	"
with normal	13	160	200	12.0	300	"
responses	14	200	280	11.5	320	"
Group IV	15	160	200	undetermined	280	absent
Vitreous	16	60	120	"	140	"
haemorrhages	17	60	140	"	160	"
with abnormal	18	150	260	"	300	"
responses	19	80	0	"	0	"
	20	0	0	"	0	"
	21	80	0	"	0	"
	22	300	460	"	460	"
	23	100	80	"	80	"

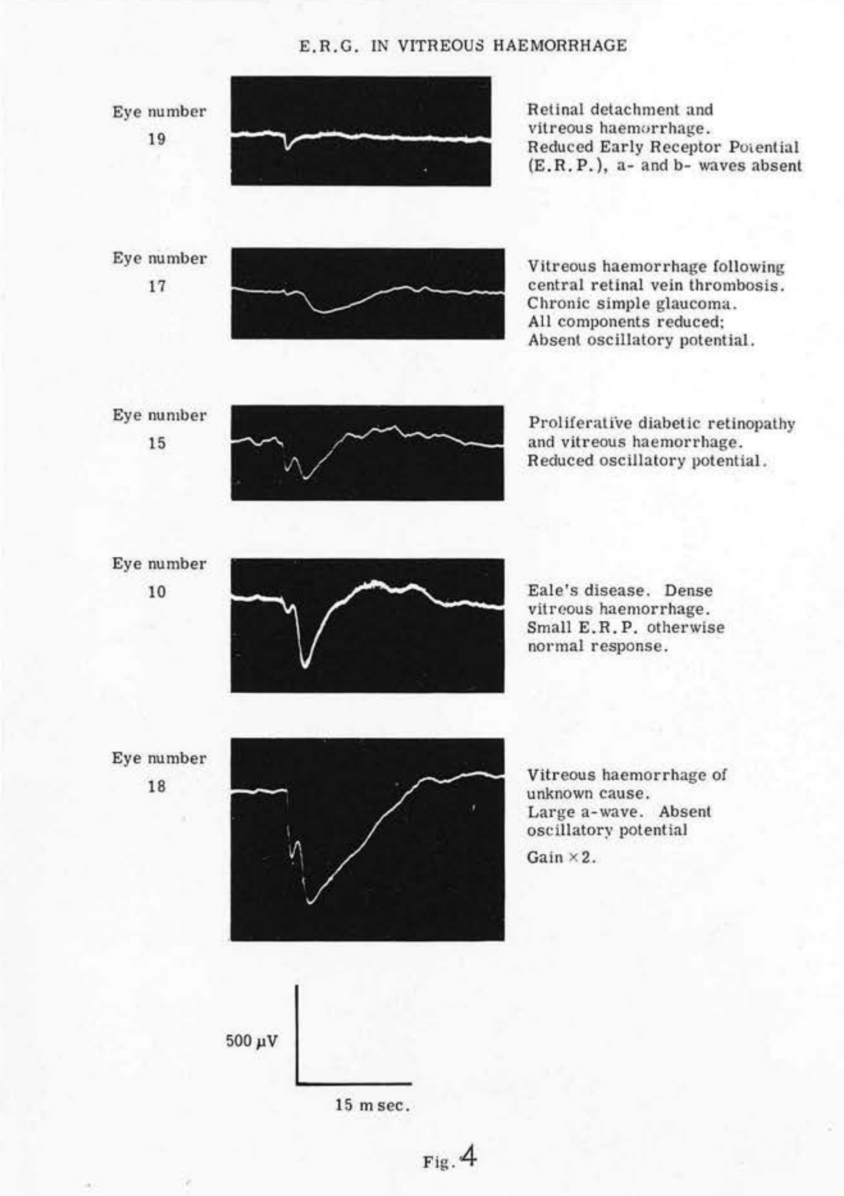

E.R.G. IN VITREOUS HAEMORRHAGE
Eye number 19
Retinal detachment and vitreous haemorrhage. Reduced Early Receptor Potential (E.R.P.), a- and b- waves absent
Eye number 17
Vitreous haemorrhage following central retinal vein thrombosis. Chronic simple glaucoma. All components reduced; Absent oscillatory potential.
Eye number 15
Proliferative diabetic retinopathy and vitreous haemorrhage. Reduced oscillatory potential.
Eye number 10
Eale's disease. Dense vitreous haemorrhage. Small E.R.P. otherwise normal response.
Eye number 18
Vitreous haemorrhage of unknown cause. Large a-wave. Absent oscillatory potential
Gain ×2.
500 μV
15 m sec.

Fig. 4

Fig. 4.

THE ABNORMAL RESPONSE.

3. Miscellaneous Cases.

(a) Vitreous Haemorrhages.

The results in 23 eyes from 12 patients suffering from vitreous haemorrhages were analysed. For convenience the individual eyes were grouped as follows:

Group 1. Clinically Normal Eyes.

Group 2. Clinically abnormal eyes with clear vitreous.

Group 3. Eyes with vitreous haemorrhages and normal response.

Group 4. Eyes with vitreous haemorrhage and abnormal response.

The density of the vitreous haemorrhage was graded as either "some fundus details visible" (Grade 1) or "fundus details not visible" (Grade 2). In table 1 can be seen a list of the relevent clinical data, the eyes being numbered from 1 to 23. The eyes can be paired by referring to the age column. Table 2 shows a quantitative analysis of the electrical response in each of these eyes.

The vitreous haemorrhage was bilateral in only two of the cases. The most significant finding was in eye no. 13 where a normal response was obtained in spite of a dense haemorrhage. This would indicate that the response is not modified by a vitreous opacity and that information about retinal function can be obtained in spite of the haemorrhage. A search of the literature has revealed no previous confirmation of this. Examples of some of the traces are shown in Fig. 4 .

Discussion.

In clinical ophthalmology it is sometimes important to be able to assess retinal function when no view of the fundus can be obtained with the ophthalmoscope. Formerly this applied largely to cases of cataract where the surgeon wished to have some idea of the chances of successful surgery. The same factors are now beginning to apply to patients with vitreous haemorrhage since some success has been achieved with vitreous replacement surgery in recent years. In addition a retinal detachment may sometimes present as a vitreous haemorrhage and in fact the diagnosis is sometimes missed for this reason. An electrodiagnostic examination of the eye could avoid such an error.

The results show that with our present knowledge, this test can give some indication of retinal function although an abnormal result cannot pinpoint the exact pathology. On the other hand a normal result can be of much greater value since it excludes the presence of a retinal detachment.

A final point should be mentioned here; in recent years there has been considerable interest in the state of the retina before a detachment occurs. Various types of degenerative change can cause the retinal tears which cause the retinal detachment. In the next section it will be shown that extensive peripheral retinal degeneration may affect the oscillatory potential. It is possible that in future years this technique could be used not only to diagnose a detachment behind a vitreous haemorrhage but also to diagnose retinal degeneration.

THE ABNORMAL RESPONSE.

Miscellaneous Cases.

(b) Cases with Selective Loss of the Oscillatory Potential.

Although the oscillatory potential was described in 1954, very little is known about the origin or the clinical applications of this component of the electroretinogram. Amongst the miscellaneous cases eleven patients were noted to have selective loss of the oscillatory potential and they are grouped together and analysed in this section.

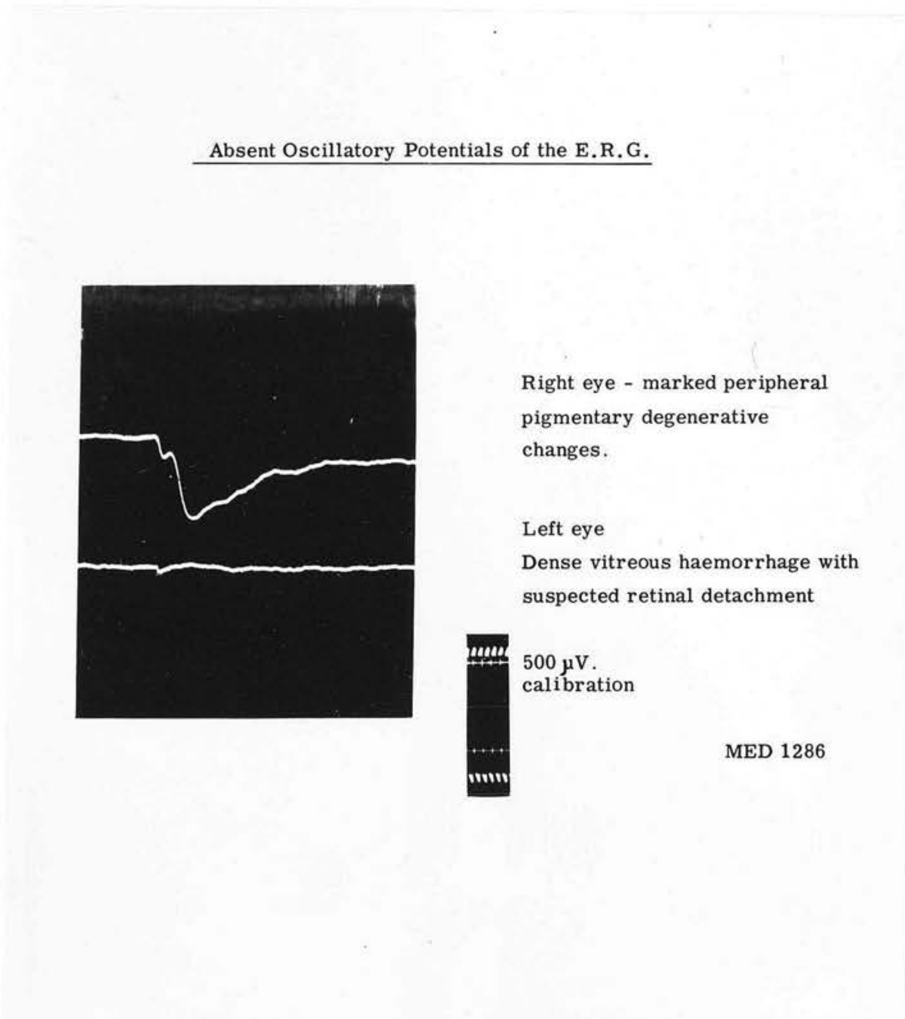
Table 1 gives a list of the cases together with the age and clinical diagnosis in each instance.

Case	Age	Diagnosis
1	29	Choroiditis.
2	64	Tobacco Amblyopia.
3	74	Peripheral Retinal Degeneration.
4	38	Chronic Simple Glaucoma. Retinal Arteriosclerosis.
5	60	Vitreous Haemorrhage and Cataract.
6	34	Vitreous Haemorrhage of unknown cause.
7	40	Sickle Cell Disease. Choroiditis.
8	43	Diabetes.
9	50	Traumatic vitreous haemorrhage.
10	50	Retinal Arteriosclerosis.
11	20	Central Retinal Artery Occlusion.

Absent Oscillatory Potential.

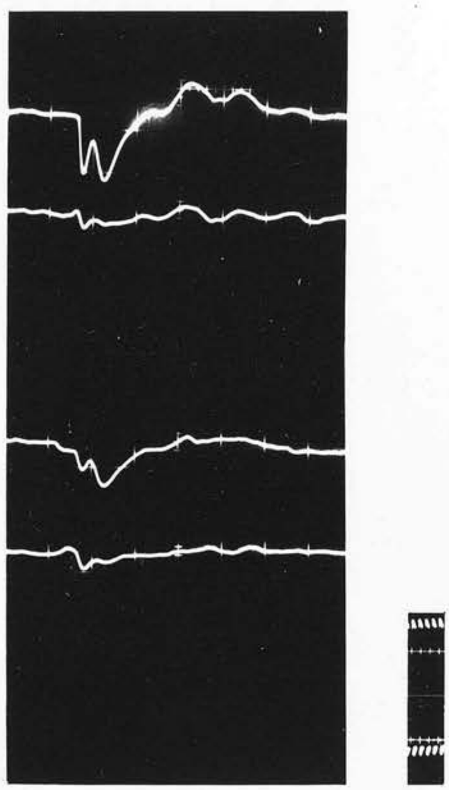
Illustrative Cases.

Case 3. Age 74. Marked peripheral 'paving stone' degeneration in the right eye. Fundus otherwise normal for age. Left vitreous haemorrhage.



Case 5. Aged 60yr. Sudden loss of vision in right eye two years previously. On examination dense right cataract. A vitreous haemorrhage was noted prior to the formation of the cataract.

Absent Oscillatory Potentials of the E.R.G.



Left eye
No abnormality

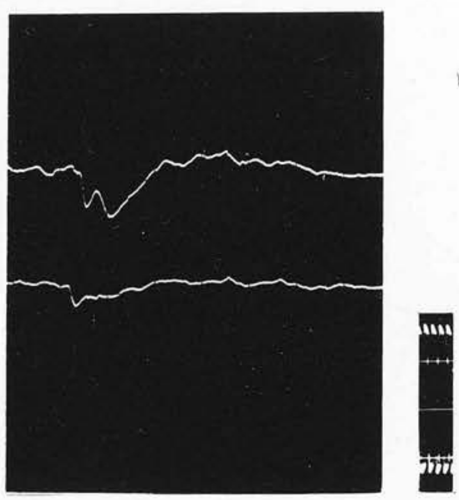
Right eye
Cataract and vitreous haemorrhage

500 µV calibration
50 c/s

MED 1338

Case 8. Aged 43 yr. A known diabetic for two and a half years. Controlled on moderate dose of insulin. Fundi showed early retinitis proliferans in each eye with considerable impairment of visual acuity.

Reduced Oscillatory Potentials of the E.R.G.



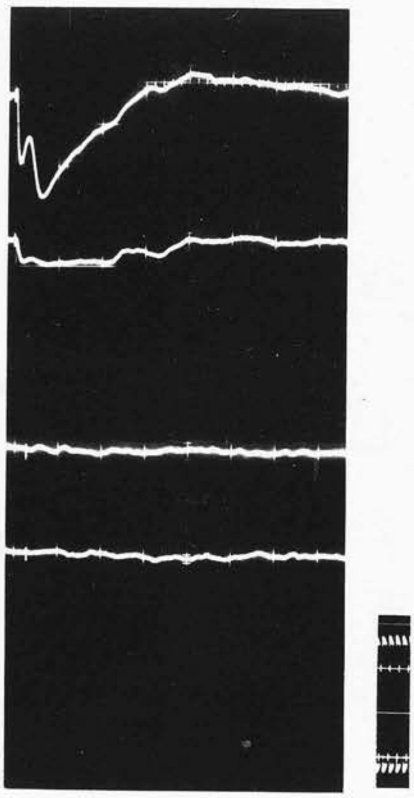
Left Eye
1st & 2nd flashes
Diabetic retinopathy with early proliferative changes.

500 μV calibration

MED 1542

Case 10. Age 66 yr.

Retinal Detachment and Arteriosclerosis



Left eye

Arteriosclerosis of the retinal arterioles.

2nd flash

Right eye

Total detachment following cataract extraction

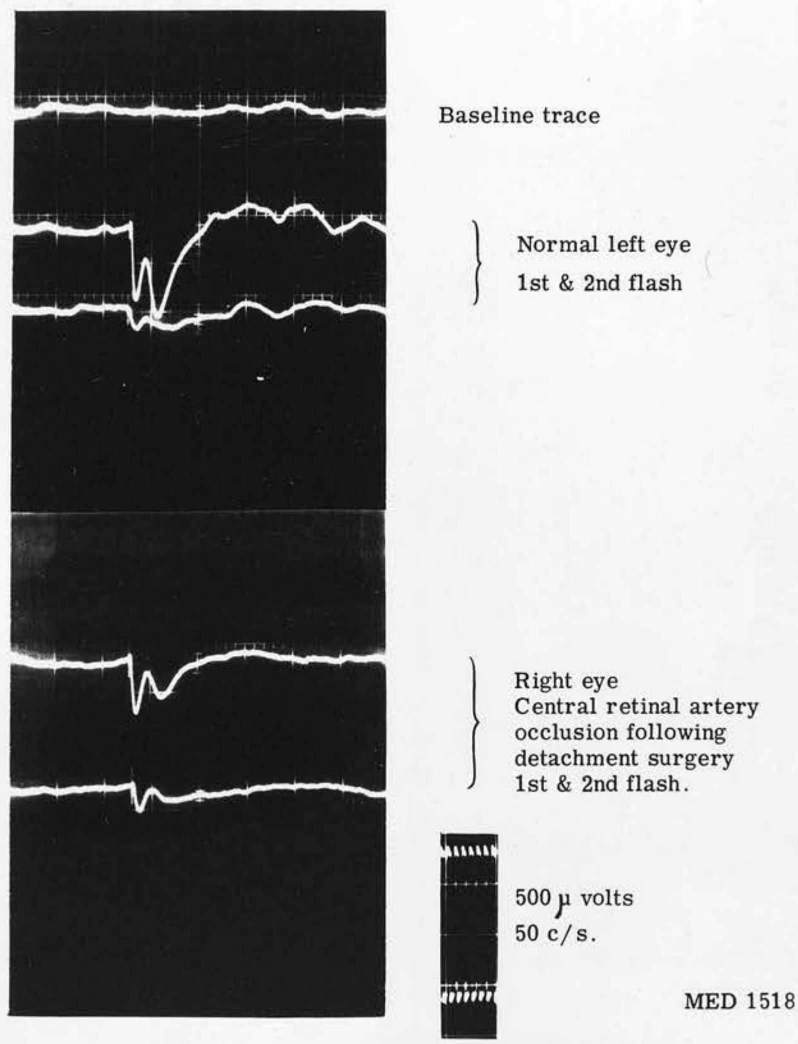
2nd flash

500 μ volts

MED 1386

Case 11. Age 20 yr. This patient suffered a unilateral retinal detachment. The retina was replaced surgically but his vision failed to improve in spite of this. On examination the right fundus showed optic atrophy and attenuation of the retinal arteries.

Absent Oscillatory Potentials of the E.R.G.



Discussion.

The oscillatory potential was described in man in 1954 by Cobb and Morton (Cobb and Morton, 1954) although a similar response was described as long ago as 1914 by Frohlich (Frohlich, 1914) in the Cephalopod. Heck and Rendahl observed these wavelets in 1958 and considered that they were altered in colour blind subjects. Jacobsen, Suzuki and Stephens (Jacobsen et al., 1963) also claimed that there was a reduction in size of the wavelets in certain types of colour blindness. They postulated that the individual wavelets might be produced by different groups of receptors. Steriade (Steriade, 1968) has shown that the oscillations are progressively enhanced by increasing the flash duration up to 50 - 110 msecs. They may also be augmented by repeating flashes at about 5 per second.

There is some evidence against the likelihood of the origin of these wavelets being in the colour receptors. For example, they are present in the rat which has an exclusively rod retina (Steriade, 1968). Doty and Kimura have claimed that the wavelets arise in the ganglion cells from their work on cats and monkeys, (Doty and Kimura, 1963). An investigation of unit discharges in the optic nerve has revealed that bursts of activity occur following a flash which correspond in time with the oscillatory potential (Steinburg 1966).

In 1966, Kurachi et al described a series of diabetics with absent or reduced oscillatory potentials. They had 22 cases of early diabetic retinopathy. Of these five had no O.P.s and thirteen had reduced O.P.s. The O.P. was diminished or absent in 24 out of 43 patients with diabetes but no visible fundus change, (Kurachi et al., 1966).

The present series of cases indicate that the oscillatory potential can be impaired by a wide variety of conditions apart from diabetes. In fact it is difficult to find any common link between the cases which might throw some light on the origin of the wavelets. A large proportion of these patients were suffering from disease of the retinal vessels and possibly this is the common factor. The retinal artery supplies the inner half of the retina, the receptors and outer part of the bipolars being nourished by the choroid. Impairment of the flow in the retinal vessels leads to damage to the ganglion cells and bipolars. Case 11 shows the electrical response from a retina where the central retinal artery has been completely occluded.

From the results obtained in this series of cases the following conclusions can be drawn:

(1) The Oscillatory Potential is consistently present in normal traces.

(2) It is selectively abolished at a relatively early stage in a wide variety of diseases of the eye.

(3) Amongst other diseases, those primarily affecting the retinal vasculature appear to play an important part.

REFERENCES

RENDAHL, I. (1952) The E.R.G. in detachment of the Retina Arch. Ophthal. Chicago. 57, 566-576. (1952).

JACOBSON, J.H., BASAR, D., CARROL, J., STEPHENS, G. and SAFIR, A. (1958) The E.R.G. as a prognostic aid in Retinal Detachment. Arch. Ophthal. Chicago. 59, 515 - 520. (1958).

FRANCOIS, J. and De ROUCK, A. (1955) L'electroretinographie dans la Myopic et les Decollements Myopigenes de la Retine. Acta. Ophthal. Kobenhavn. 33, 131-155. (1955).

MACHEMAR, R. (1968) Experimental Retinal Detachment in the Owl Monkey II Histology of Retina and Pigment Epithelium. Amer. J. Ophthal. 66, 396-410. (1968).

MACHEMAR, R. (1968) Experimental Retinal Detachment in the Own Monkey IV The Reattached Retina. Amer. J. Ophthal. 66, 1075-1091. (1968).

CONE, R.A. (1964) The Early Receptor Potential of the Vertebrate Retina. Nature, London. 204, 736-739. (1964)

PAK, W.L. and EBREY, T.G. (1965) Visual Receptor Potential Observed at Subzero Temperatures. Nature, London. 205, 484-486. (1965).

BRINDLEY, G.S. and GARDNER MEDWIN, A.R. (1966) J. Physiol. 182, 185-194. (1966).

ARDEN, G.B., IKEDA, H. and SIEGEL, I.M. (1966) New Components of the Mammalian Receptor Potential and their relation to Visual Photochemistry. Vision Research, Vol. 6, p. 373-384. (1966).

BROWN, K.T. (1965) An Early Potential Evoked by Light from the Pigment Epithelium Choroid Complex of the Toad Eye. Nature, London. 201, 626-628. (1965).

REFERENCES

KARPE, G. (1954) The Basis of Clinical Electroretinography. Acta. Ophthal. Kobenhaven Suppl. 24. 23, 1-116. (1954)

HENKES, H., Van der TWEEL, L.H. & Van der GON, J.D. (1956) Selective Amplification of the Electroretinogram. Ophthalmologica 132, 140-150. (1956).

ARDEN, G.B. & FOJAS, M.P. (1962) Electrophysiological Abnormalities in Pigmentary Degenerations of the Retina. Arch. Ophthal. 68, 369-389. (1962).

GOWAS, P. & CARR, R.E. (1964) Electrophysiological Studies in Early Retinitis Pigmentosa. Arch. Ophthal. 72, 104-109. (1964).

VERHOEFF, F.H. (1931) Microscopic observations in a Case of Retinitis Pigmentosa. Arch. Ophthal. (Chicago). 5, 392. (1931).

BOURNE, M.C., CAMPBELL, D.R. & TANSLEY, K. (1938) Retinitis Pigmentosa in Rats. Trans. Ophthal. Soc. of U.K. 58, 234. (1938).

HOGAN, M.J. & ZIMMERMAN, L.E. (1962) Ophthalmic Pathology. W.B. Saunders & Co., Philadelphia. p. 544 (1962).

REFERENCES

COBB, W.A. & MORTON, H.B. (1954) A New Component of the Human E.R.G. J. Physiol. (London) 123, 36p. (1954).

FROHLICH, F.W. (1914) Beitrage zur Allgemeinen Physiologie der Sinnesorgane. Z. Psychol. Physiol. Sinnesorg., II Abt. Sinnesphysiol. 48, 28-164. (1914).

JACOBSEN, J.H., SUZUKI, T. & STEPHENS, G. (1963) The E.R.G. obtained by Computer Techniques in Colour Deficient Humans. Arch. Ophth. (Chicago). 69, 424-435. (1963).

STERIADE, M. (1968) The Flash Evoked after Discharge. Brain Research. 9, 169-212. (1968).

DOTY, R.W. & KIMURA, D.S. (1963) Oscillatory Potentials in the Visual System of Cats and Monkeys. J. Physiol. (London). 168, 205-218. (1963).

STEINBERG, R.H. (1966) Oscillatory Activity in the Optic Tract of the Cat. J. Neurophysiol. 29, 139-156. (1966).

KURACHI, Y., YONEMURA, D., HATTA, M. TSUCHIDA, Y. & YAMADA, Y. (1966) Folia Ophthal. Japan. 17, 375. (1966).