Principles and Practice of Clinical Electrophysiology of Vision

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History of the Electroretinogram

A.F. de Rouck

EARLY DISCOVERIES

In 1849, DuBois-Reymond[27] discovered in excised tench (fish) eyes a potential of about 6 mV when using an electrode placed behind the eye and a similar electrode placed on the surface of the cornea. He found that the cornea was positive with respect to the posterior pole of the eye. The existence of this standing potential was soon confirmed by other authors.

In 1865, Holmgren[39] discovered that an excised frog eye showed an electrical response to light, and in 1880 he found by removing the anterior segment of the eye and placing the corneal electrode directly on the retinal surface that the retina itself was the source of the response.[38, 40]

About the same time, Dewar and McKendrick[26] independently reported the discovery of "action currents" with illumination of the eye; they concluded that there was a relationship between the amplitude of the electrical response and the logarithm of the stimulus intensity. Wavelengths that appeared brightest to the human eye evoked the largest amplitude response.

In 1877 Dewar[25] showed that electrical potentials could be recorded from an intact animal eye by applying the second (reference) electrode on the abraded skin. He also reported the first successful recording of a human electroretinogram (ERG). For this purpose, he used an elaborate instrumental setup.

> A small trough of clay or paraffin was constructed around the margin of the orbit, so as to contain a quantity of salt solution, when the body was placed horizontally and the head properly secured. The terminal of a non-polarizable electrode was introduced into this solution and in order to complete the circuit, the other elecrode was connected with a large gutta-percha trough containing salt solution, into which one of the hands was inserted.

The two electrodes were connected to a sensitive Thomson galvanometer. The resulting curves, however, were not published.

In 1880, Kuhne and Steiner,[47] working on isolated frog and fish retinas, claimed that the light-induced action currents originated in the receptor layer and not in the ganglion cell layer.

EARLY RECORDING

The electrical measuring devices at the time, slow galvanometers, were unable to measure rapid changes in potential accurately. The responses were often practically invisible. Brücke and Garten[18] connected many eyes in series to construct a living battery to obtain more power. In an extensive series of investigations, they showed that the electrical responses of various vertebrate eyes were similar.

Gotch[32] described a capillary electrometer that allowed him to determine that there was a response in the frog eye at both the onset and cessation of the light stimulus. He was the first to call the latter wave the "off-effect" and to note the early negative portion of the response. He was able to produce accurate measurements of the latent period and to show that it decreases when the intensity of stimulation increases.

Einthoven and Jolly[28] obtained excellent detailed records of the frog eye by using a string galvanometer. They were the first to designate several portions of the ERG by letters (Fig 2–1); an initial negative

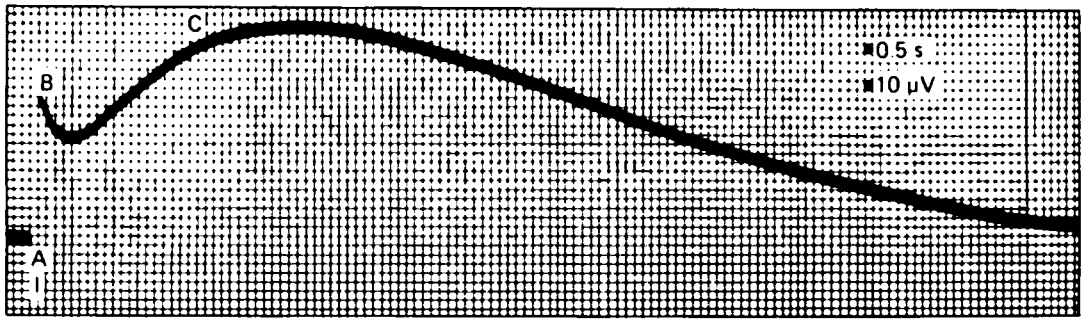

FIG 2–1.
ERG recorded by Einthoven and Jolly (1908). The a-, b- and c-waves are designated. (From Einthoven W, Jolly W: *J Exp Physiol* 1908; 1:373–416.)

segment, the a-wave, is followed by a larger positive defection, the b-wave, and later, by another slower positive potential, the c-wave. When the light stopped, the d-wave, or off-effect, appeared. The authors stated that the electrical potential is in fact an integrated mass response made up of a number of independent components.

Piper[55] realized that there are two main types of retinas; he found that eyes with large a-waves showed a good off-effect whereas those with small a-waves had poor off-effects. Piper's analysis of the ERG into three components, based partly on the work of Waller,[72] was also accepted by Kohlrausch.[46]

THE FIRST PUBLISHED HUMAN ELECTRORETINOGRAM

Kahn and Löwenstein[43] published the first human ERG curve (Fig 2–2) by employing a string galvanometer and leads from the cornea and a distal temporal point of an anesthetized eyeball. They attempted to use the ERG as part of the clinical examination of the human eye but concluded that the practical difficulties of their method made it unsuitable in the clinical setting.

About this same time, Hartline[36] used moist thread electrodes and saline-filled goggles to make contact with the eyes. Since this was uncomfortable for the patient, another method was developed. A simple cotton wick was applied to the cornea after local anesthesia, and the reference electrode was placed in the mouth. The string galvanometer revealed the same components as previously obtained in animal records. In 1929 Sachs[60] showed that the human ERG was dependent on the scotopic visual system of the retina.

In 1933, Cooper and associates[21] recorded the human ERG with a string galvanometer and a direct-coupled amplifier. They obtained good waves on single and multiple flash stimulation. Leads were taken from anesthetized conjunctiva and the mouth.

Gröppel et al.[35] used a nonpolarizable zinc elec-

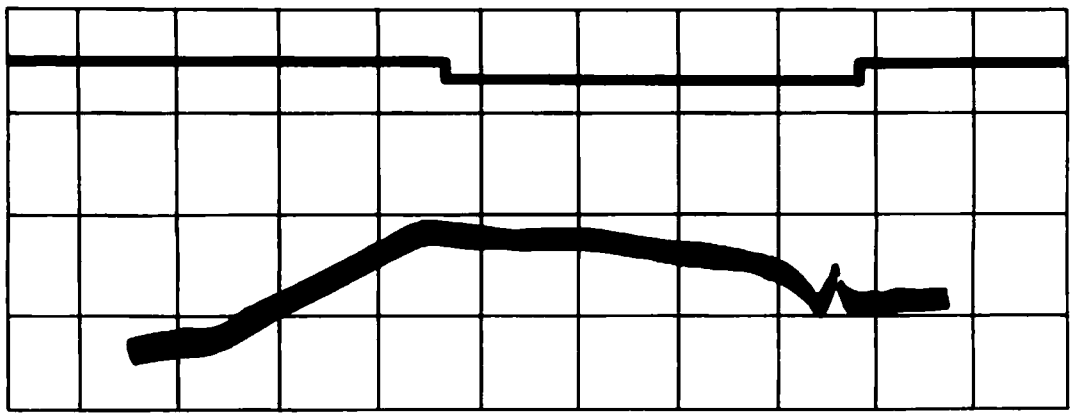

FIG 2–2.
First human ERG (Kahn and Löwenstein). The curves are to be read from right to left (*squares:* 500 μV, 1.2 seconds). (From Kahn R, Löwenstein A: *Graefes Arch Ophthalmol* 1924; 114:304–325.)

trode consisting of a short glass tube that contained an amalgamated zinc rod in a concentrated watery solution of zinc sulfate. The part near the eye was filled with Ringer's gelatin in which a small cotton wick was inserted. The reference electrode consisted of a glass funnel that was placed on the temple and a zinc electrode in Ringer's gelatin. The electrical potentials were magnified by a direct-coupled amplifier and photographically registered by a string galvanometer.

The development of the vacuum tube amplifier increased the precision with which an ERG could be obtained. The measuring instruments became fast enough to follow the rapid action potentials in nerves.

ELECTRORETINOGRAM COMPONENTS

Granit's (1933 to 1947) extensive investigations with improved techniques led to the analysis that is still in use.[34] By the use of chemical agents he was able to modify the ERG in ways that could be interpreted by postulating the existence of three processes (or potentials) that he called PI, PII, and PIII, named for the sequence of disappearance under ether anesthesia. The properties of these processes were summarized by Riggs (Table 2–1).[58]

Granit's analysis indicated that the fast-developing corneal negative PIII forms the a-wave. The corneal positive PII (which is much larger) then develops, and the resultant of the PIII and PII produces the b-wave. As PII decreases, PI grows slowly and thus produces the c-wave.

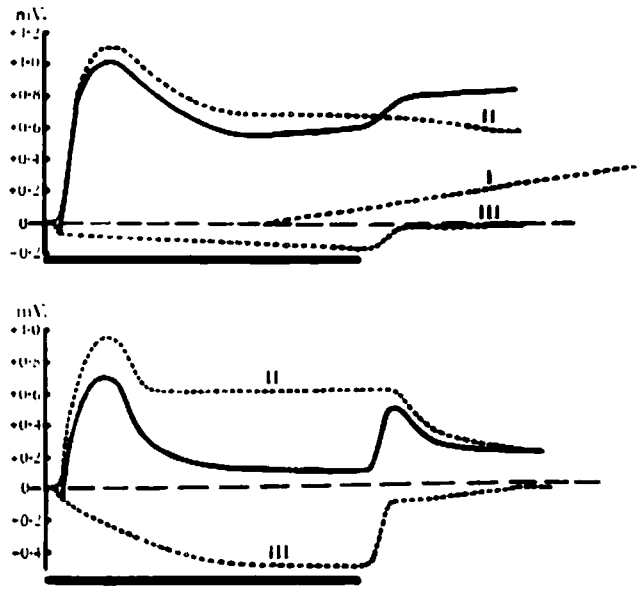

FIG 2–3.
Analysis of the I-ERG (frog): *upper,* dark-adapted; *lower,* light-adapted; duration of stimulus, 2 seconds. (From Granit R, Riddell HA: *J Physiol* 1933; 77:207–240. Used by permission.)

Granit believed that PII originated in the neural

TABLE 2–1.
A Summary of the Properties of Electroretinograms and Their Relation to PI, PII, and PIII as Described by Granit*

	Process		
Property	PI	PII	PIII
Latency	Long	Medium	Short
Polarity	Positive	Positive	Negative
Electroretinogram wave accounted for	c-Wave	b-Wave	a- and d-Waves
Effect on nerve impulses	"Sensitizes" PII	Excitatory	Inhibitory
Result of light adaptation	Usually abolished	Greatly reduced	Not much change
Probable site of origin	?	Bipolar cells?	Rod and cone cells
Effect of asphyxia	Moderately susceptible	Very susceptible	Highly resistant
Effect of ether	Abolished first (reversible)	Abolished second (reversible)	Abolished last (irreversible)
Intensity of light to stimulate	High	Low	High
Effect of alcohol	?	Enhances	Diminishes
Effect of adrenalin	Enhances and prolongs	Diminishes and prolongs	?
Effect of KCl	None	Abolishes	Enhances, then inhibits

*Adapted from Riggs LA: Electrical phenomenon in vision, in Hollaender A (ed): *Radiation Biology,* vol 3. New York, McGraw-Hill International Book Co, 1956, pp 581–619.

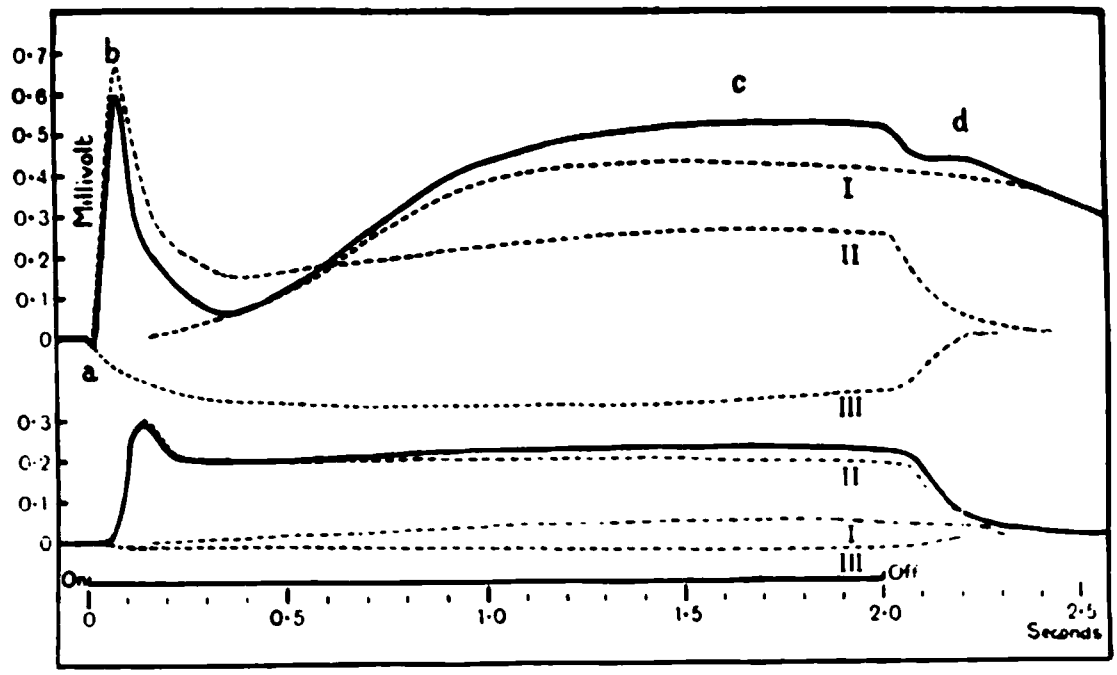

FIG 2–4.
Analysis of the E-ERG (cat) at two intensities: *upper*, 14 mL; *lower*, 0.14 mL. The a-wave has been broadened slightly out of proportion to demonstrate its derivation more clearly. (From Granit R: *J Physiol* 1934; 81:1–28. Used by permission.)

pathway between the receptors and the ganglion cells and was correlated with optic nerve activity. A possibility suggested by Bartley[11] was that it arose in the bipolar cell layer. The short latency of PIII indicated that it developed very early in the chain of events constituting retinal activity, probably in the receptors themselves.

The ERG off-response coincided with the end of PIII and the off-response in the optic nerve, and Granit suggested that PIII might represent a "central inhibitory state," release from which was associated with optic nerve discharge. He also showed that retinas dominated by cones respond to photic stimulation by generating a large a-wave (I retinas, "inhibitory" type, Fig 2–3), whereas those dominated by rods generate large positive waves (E retinas, excitatory type, Fig 2–4). The E-retina response in flickering light is characterized by a rather low fusion frequency, and the wavelets consist primarily of b-waves. The I retina responds with a series of a- and b-waves and has a much higher fusion frequency. However, rod (E) and cone (I) systems possess the same components, but their relative size may vary a great deal from species to species.

Noell[51–53] extensively studied the relationship of the cellular elements of the retina to ERG components and was the first to record both the slow and rapid changes associated with retinal illumination. He used three substances, sodium azide, iodoacetate, and sodium iodate, each of which had a specific effect upon the ERG and on the transretinal potential. Sodium azide increases both the transretinal potential and the c-wave, but not after the use of sodium iodate, which causes damage to this layer while leaving the remaining ERG components relatively unaffected. He concluded that the retinal pigment epithelium (RPE) develops the c-wave and the transretinal potential. The negative PIII could be differentiated into an early and late component with different time constants, with the faster arising from the receptors. The b-wave arose from a region lying between the inner portion of the receptors and the inner nuclear layer.

MICROELECTRODES

Intraretinal microelectrodes were first used to analyze the ERG by Tomita[68] and by Brindley.[14] The former discovered the subdivisions of Granit's PIII, while the latter documented the presence of the highly resistive R membrane formed by the tight junctions of the pigmented epithelium. These groups worked on amphibia, but Brown and Wiesel[15–17] and

later Brown with a number of collaborators used Kuffler's closed-eye preparation to investigate the ERG of cats and primates.

Brown identified the "landmarks" encountered by a penetrating extracellular microelectrode and was thus able to judge the position of its tip relative to the RPE and the internal limiting membrane (ILM). He took advantage of the dual blood supply of the retina and by blocking the central retinal artery was able to demonstrate that PIII was produced by the receptor layer. He utilized the anatomy of the foveola, which contains only photoreceptors, to further identify PIII and to distinguish between rod and cone receptor responses.

The generators of the b-wave were sought by recording amplitude/depth characteristics of the responses. However, no clear distinction was made between voltage and current gradients, and the significance of the change in gradient was not understood; this was unfortunate since the published results clearly demonstrate that the b-wave is generated by a cell that extends from the outer to the inner limiting membranes, the significance of which was first detailed by Faber[29] who recognized the b-wave as a glial potential, which was confirmed the following year by Miller and Dowling,[48] who recorded intracellular Müller cell responses from mud puppy retinas and confirmed the localization by staining and identifying the cells.

Brown's group saw a number of other minor ERG components that were later described by others and, in particular, discovered the early receptor potential, a charge displacement in the outer limb due to the chemical changes in rhodopsin that occur in the first milliseconds after bleaching.

Following this work, intracellular recordings from individual retinal neurons[13, 48, 69, 70] clarified the nature between extracellular and intracellular recordings and laid the foundation for the present spate of work on transduction, the mechanisms of the generation of photoreceptor potentials, and the interactions and synaptology of retinal neurons. The first of these, the discovery of the eponymously named S-potential by Svaetichin, remained for some years little understood; in fact, only since the recent developments of intravital staining and analysis of cultured cell recordings are we beginning to obtain quantitative estimates of retinal synaptic function.

Steinberg et al.,[65] in Brown's laboratory, investigated the slower responses from the RPE and demonstrated the mechanisms of production of the c-wave, fast oscillation, and the light peak. The microelectrode experiments also proved the site of origin of the c-wave and showed that it was caused by a reduction in potassium ion concentration in the subretinal space, which causes apical polarization of the RPE.

CLINICAL ELECTRORETINOGRAPHY

The development of clinical electroretinography was the consequence of a better understanding of the major components of the ERG, progress in the recording devices, and the introduction of the haptic (scleral) contact lens electrode by Riggs[33, 57, 62]; this consisted of a silver disk cemented into a hole in the contact lens. A fine flexible wire supported by beeswax was employed as a lead from the electrode. When the lens was inserted into the eyes, the silver made contact with the isotonic sodium chloride solution between it and the cornea.

The contact lens minimized the influence of irrelevant eye movements and reflex blinks. Even untrained patients could wear it because it allowed long experimental sessions without discomfort for the subject. Another advantage was that the potentials were larger than those recorded with previous types of electrodes.

Karpe and Tansley[45] used a direct-coupled amplifier that was connected to an oscillograph with a camera. Later they used a condenser-coupled amplifier with a time constant of approximately 1.5 seconds. The records were made on moving photographic film.

Karpe[44] introduced ERG as a routine method in the ophthalmology clinic and used a similar electrode consisting of a silver rod screwed into a bottle neck in a plastic contact lens. The tube was filled with isotonic sodium chloride solution, and the reference electrode was a chlorided silver plate applied to the patient's forehead. Since then many models have been proposed, including those of Burian and Allen,[19] Jacobson,[41] Henkes and Van Balen,[37] and Sundmark.[66] In recent years, however, other types of corneal or scleral electrodes have been introduced that are generally more comfortable for the patient; these include soft contact lenses by Galloway[31] and Sole, et al.,[64] a gold foil electrode by Arden et al.,[5] and a DTL microfiber electrode by Dawson, Trick, and Litzkow.[23]

Karpe[44] emphasized the importance of the ERG as an objective record of the function of the retina, one that is not dependent on the function of the optic nerve or the optic pathways and is minimally modified by clouding of the optic media (Fig 2–5). He

FIG 2–5.
Contact lens electrode (Riggs).

stressed the need for standardized procedures and established a normal range of response amplitudes as a function of age. With his technique the light-adapted ERG was sometimes too small to measure. It was merely possible to state whether the a-wave was present or absent. The dark-adapted ERG was much larger and dominated by the b-wave. Changes in amplitude were found to be clinically useful. Although this technique was important in the detection of some retinal diseases such as metallosis, tapetoretinal degenerations, vascular disturbances, and congenital functional anomalies, the early restriction of the human ERG to scotopic visual processes was a serious handicap for both clinical and experimental work.[59] This deficiency was remedied by Johnson and Bartlett[42] and Alpern and Faris,[4] who introduced intense short stimulus flashes that yielded photopic responses with durations well below those that gave maximal scotopic ones.

Another method of distinguishing cone from rod responses was pioneered by Motokawa and Mita,[49] who discovered a smaller positive deflection preceding the b-wave of the ERG in a moderately light-adapted human eye. They called it an x-wave but gave no interpretation of it.

Adrian[3] rediscovered the phenomenon independently (Fig 2–6) and established that the scotopic b-wave was absent in red light and in a state of light adaptation, that it could be isolated in blue light, and that it was augmented considerably by dark adaptation. On the other hand, the x-wave (called "photopic response"), characterized by a shorter implicit time, was absent in blue light, could be isolated by red light, and did not increase during the later part of dark adaptation.[10] Adrian[3] showed that it is best developed in animals with a rich cone population (monkey, pigeon) and not in animals with few or no cones (cat, rabbit, guinea pig). Armington[7] demonstrated that the x-wave was augmented during the first minute of dark adaptation. Its spectral sensitivity did not correspond to the subjective scotopic or photopic curves, but had a maximum of 630 nm. Armington and Thiede[9] showed that either the x-wave or the b-wave may be selectively reduced in amplitude if the eye was adapted to light for which one component or the other possessed greater sensitivity.

Later studies[30] have shown that cone responses to red light were absent or severely reduced in protanopia and congenital achromatopsia and that cone

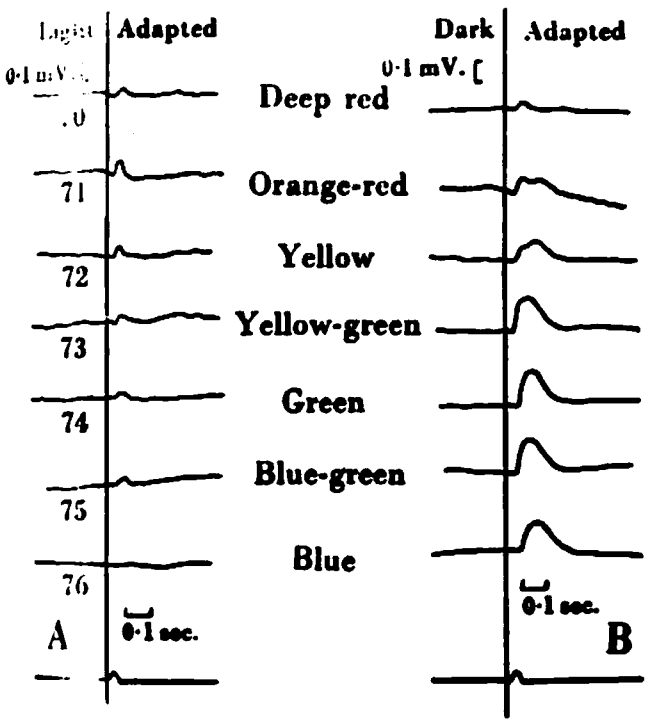

FIG 2–6.
Human ERG responses to various wavelengths of light in the light-adapted **(A)** and dark-adapted state **(B).** (From Adrian ED: *J Physiol (Lond)* 1945; 104:84–104. Used by permission.)

responses to green light could be obtained as well.[33, 56] The spectral sensitivity curve, determined by the method of flicker ERG, showed sensitivity losses at appropriate wavelengths for protanopes and deuteranopes.[22, 24, 54, 59] Blue cone responses could only be isolated with more complex techniques.[61, 71]

In 1954, Cobb and Morton[20] described rhythmic wavelets, now known as oscillatory potentials, on the ascending limb of the b-wave that appeared when bright flashes were used. Yonemura et al.[73] proved their clinical importance. They were absent in disturbances of the superficial retinal layers and often selectively reduced in circulatory disturbances and diabetic retinopathy.

In the last two decades, clinical developments have included an analysis of the timings of ERG components in disease[12]; an analysis of sensitivity from the voltage/log light intensity function[6, 50]; and the use of computer averaging techniques to obtain small responses and to reduce the effect of noise, which allowed for the development of the visual evoked cortical potential and the pattern ERG and ultimately culminated in the recording of the "scotopic threshold response."[63] In addition, technical developments have led to the possibility of recording focal responses, pattern responses, and the slow c-wave in clinical situations; these topics are treated in separate sections of this book.

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