Principles and Practice of Clinical Electrophysiology of Vision

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A Year Book Medical Publishers imprint of Mosby-Year Book, Inc.

Mosby-Year Book, Inc.
11830 Westline Industrial Drive
St. Louis, MO 63146

1 2 3 4 5 6 7 8 9 0 CL CL MV 95 94 93 92 91

Library of Congress Cataloging-in-Publication Data
Principles and practice of visual electrophysiology / [edited by] John R. Heckenlively, Geoffrey B. Arden.
p. cm.
Includes bibliographical references.
Includes index.
ISBN 0-8151-4290-0
1. Electroretinography. 2. Electrooculography. 3. Visual evoked response. I. Heckenlively, John R. II. Arden, Geoffrey B. (Geoffrey Bernard)
[DNLM: 1. Electrooculography. 2. Electrophysiology. 3. Electroretinography. 4. Evoked Potentials, Visual. 5. Vision Disorders—physiopathology. WW 270 P957]
RE79.E4P75 1991 91-13378
617.7 1547—dc20 CIP
DNLM/DLC
for Library of Congress

PART I

History of Visual Electrophysiology

Introduction: A Personal Memoir

Ragnar Granit

It is of some interest to note that the electroretinogram (ERG) was discovered in two independent laboratories and that in both cases it emerged from different but false assumptions. The Uppsala physiologist Professor Frithiof Holmgren was inspired by his famous teacher, DuBois-Reymond of Berlin, who discovered the electrical nature of the nerve impulse, then known as "the negative variation," as elicited by an electrical shock to a nerve.[1] With better recording instruments available in the early 20th century the more precise term "action potential" came to be used. Holmgren's question was "Could the negative variation also be obtained when a natural stimulus such as light was used?"

To this end he placed recording electrodes on the front and at the back of a frog eye and was rewarded by observing a response to a light flash. At the time (1865) he thought that he had recorded an electrical mass discharge from the optic nerve, thus confirming DuBois-Reymond's discovery. I assume that Holmgren must have been worried by the fact that he also saw another electrical response at cessation of illumination, or why otherwise would he have started shifting his electrodes around the bulb to conclude in 1870 that the current distribution required the observed responses to have arisen in the retina itself? The date of understanding what he had recorded is thus 1870, the real birth date of the ERG.

Responsible for an independent discovery of the ERG were two young Scotsmen, Dewar and McKendrick.[1] The former later became the brilliant physicist Sir James Dewar, head of the Royal Institution in London, the latter ultimately professor of physiology at the University of Glasgow. The year was 1873, and in that year photoconductivity in selenium had been first reported in Great Britain by Willoughby Smith.[1] The Edinburgh scientists, not knowing about Holmgren's findings, wondered whether some similar photoelectric effect initiated the activity in the retina.

To make a long story short, I quote the greater part of a letter from McKendrick to Holmgren:

> Sir, I send along with this letter a number of papers of which I respectfully beg your acceptance. Among these you will find a Memoir by Mr. James Dewar and myself on the physiological action of Light, in which we give details regarding an experimental research we made as to the specific action of light on the retina. This research was begun, carried on and concluded, and the Memoir was actually printed, before we were aware of your most admirable work as published in the *Upsala Journal*. You will observe that at the end of the Memoir we have added an Appendix in which we at once acknowledge your priority in the discovery. We have had your papers translated from Swedish, and it is satisfactory to know that our independent work corroborates yours in almost every particular. . . . Meantime with every sentiment for you and in admiration of your work.[1]

Dewar also succeeded in recording from the human eye, and so 1877 became the year of birth of the ERG of man.

The slow galvanometers of that period prevented further development. Actually the first author to describe the full phasic display of the ERG was Gotch[1] in 1903, who used the capillary electrometer and a frog eye, which as we know now, is a more complex structure than that of mammals because it has to operate at a level of precision that the mammals only can achieve by recourse to cortical centers. But in that same year Einthoven developed his string galvanometer, fast and sensitive enough for the record-

ing of both ERGs and electrocardiograms (ECGs), the latter Einthoven's main interest. It came to dominate instrumentation in electrophysiology for some 20 years, or until electronic amplification became available, and soon was applied everywhere. The first amplifiers for ERG were developed by the American physicist Chaffee and his team in 1923.[1] Again the frog eye was their preparation. And from that time on, after sufficient amplification, any fast recording instrument could be used in neurophysiological experimentation, the most popular being at first the Matthews oscillograph, later the cathode ray.[1]

The pioneer Dewar was followed some 45 years later by Kahn and Löwenstein (1924)[1] and Hartline (1925).[2] The former pair realized that the Einthoven string galvanometer made recording of human ERGs possible. Their aim was clinical, but they concluded that the technique was too difficult for clinical purposes. Hartline, in the course of recording ERGs from different animals, also included man. He had some good records but never returned to ERG because he became permanently fascinated by the single-fiber preparation. I have followed his scientific development in the *Biographical Memoirs of Fellows of the Royal Society*.[2]

In the early 1930s I was engaged in the Oxford laboratory of Sir Charles Sherrington in an analysis of the obviously complex ERG. For this end I employed the more compact and sturdy Edelmann permanent magnetic string galvanometer with which the risk of breaking strings was greatly reduced. It was used with a homemade amplifier based on a circuit I had received from Hartline, who, I believe, had it from K.S. Cole. E.D. Adrian had given me good advice in the choice of vacuum tubes. Two of my Oxford friends, Sybil Cooper and R.S. Creed,[1] collaborated to make an attempt at the human ERG, and we had records with b-waves on the order of 0.35 mV alike in the central and peripheral vision. At about the same time some records were published by Sachs (1929) and Gröppel, Haass, and Kohlrausch (1938).[1] In 1940 and 1941, Bernhard,[1] in the course of electroencephalographic (EEG) work, also recorded ERGs from some subjects. Perhaps the advent of EEG contributed to making clinically minded scientists less afraid of electrically based techniques. This development synchronized happily with the advent of more robust and easily handled commercial EEGs.

The long latency of the clinical application of ERG, after recording had been shown feasible around 1925, depended partly upon technical difficulties. It certainly had to await the advent of electronic amplification. But then, why did not I, for instance, try to mobilize ophthalmologists in Stockholm to come to my laboratory for the necessary instructions for clinical application? Actually, when Gösta Karpe[1] in 1944 did just that, I tended to be skeptical about the outcome. It seemed to me that there might well be significant information within the virtually monophasic human ERG, but it would be difficult to extract in comparison with what I had been able to do with the ERGs of cats and frogs 10 years earlier. But Karpe was insistent and of course received the necessary elementary advice from our laboratory. The work itself was carried out at the Ophthalmological Department of Karolinska Institutet. So, by dint of hard work Karpe became the first to prove that clinical ERG was both possible and worth doing. Thus a new field of approach to ocular disease had been opened, and soon it was developed in many directions. We did not know at the time that during the war the able American psychologist Lorrin Riggs[1] had designed a contact lens electrode for the recording of ERG in man. Karpe designed one independently.

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