

Rayner Grant

First exemplar on
denna bok. Det autörade den
15 april 1947.

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Oxford University Press
Press Road
Neasden
London, N.W.10

SENSORY MECHANISMS OF THE RETINA

WITH AN APPENDIX ON
ELECTRORETINOGRAPHY

By

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GEOFFREY CUMBERLEGE
OXFORD UNIVERSITY PRESS
London New York Toronto

1947

OXFORD UNIVERSITY PRESS
AMEN HOUSE, E.C.4
London Edinburgh Glasgow New York
Toronto Melbourne Cape Town Bombay
Calcutta Madras
GEOFFREY CUMBERLEGE
PUBLISHER TO THE UNIVERSITY

Printed in Great Britain

5845 · 6449

PREFACE

This book, begun in the summer 1941 and completed in 1943, is primarily a presentation of facts. It contains very little theory, and I have tried to indicate the limitations of the theories and generalizations, used in developing the experimental work described. At the same time the book is written from a definite point of view which should suggest several correlations to those interested in the broader field of neurophysiology, but the text would have become too burdensome for many other prospective readers had the correlations always been discussed.

The foundations for this book were laid twenty years ago, when its author—then a beginner in physiology—made acquaintance with Sir Charles Sherrington's classical work, *The Integrative Action of the Nervous System*. In his work Sherrington emphasized several parallels between visual phenomena and reflex behaviour. To the young reader the subject of vision suddenly became vitalized and embodied with a deeper significance than psychophysics alone could provide. Ramon y Cajal's great histological work on the retina as a 'true nervous centre' later consolidated my desire to study the retina itself from this point of view. A beginning was made with psychophysical methods, first at Helsingfors, later at Oxford. Then came Adrian's brilliant papers on the discharge from sensory end organs, and at the Eldridge R. Johnson Foundation of Pennsylvania University, Philadelphia, U.S.A. I made an attempt with the aid of the flicker method to translate some of his most important results, combined with those of the Oxford school into the language of psychophysics.

However, Adrian's work had clearly established the great value of the electrophysiological approach. So after some further time spent in practising this technique at Helsingfors my work was transferred to Oxford for the second time and begun in earnest. I cherish the memories from the years in Sir Charles Sherrington's laboratory at Oxford as imperishable treasures

which increase in value with the lengthening perspective of age.

To many friends and collaborators as well as to disciples from later years I owe a debt of gratitude. If I only mention by name Dr. C. G. Bernhard and Dr. C. R. Skoglund, Lecturers at the Caroline Institute, and Dr. P. O. Therman, Lecturer at Helsingfors University, it is because they have been my nearest colleagues for so many years. Their many and independent contributions to this field and their eager discussions of all phases of the work has been a constant stimulus of immense value. The credit for solving the many physical problems encountered in the final development of the work must be given to my friend and physicist collaborator since 1937, Mr. K. T. Helme, Mag.Phil. I remember many others with feelings of gratitude and affection. I am indebted to Miss Barbro Holmgren for her care in typing the manuscript and checking the references, and to her father, Professor Israel Holmgren, Stockholm, for permission to publish some letters of historical interest sent to his father, the late Professor Frithiof Holmgren, the discoverer of the retinal electrical response to illumination.

Economic support has been given generously for over a decade by the Rockefeller Foundation; at Helsingfors also by the 'Ella och Georg Ehrnrooths Stiftelse', at Stockholm by the 'Knut och Alice Wallenbergs Stiftelse' and the Caroline Institute which together created this Research Institute.

Dr. Katharine Tansley (Mrs. R. J. Lythgoe), Reader in Special Senses at Birmingham University, kindly undertook to revise the manuscript of the book. In a most unselfish manner and with scrupulous care she has devoted herself to the task of interpreting and clarifying the text of the original manuscript. Dr. Tansley's contribution to the final result is of the greatest value and places me in debt to her in a way that makes me, more than ever, wish that I had been able to produce the same result without causing her so much trouble and labour.

Several English friends and colleagues have been kind enough to sacrifice time and patience in order to study my manuscript and suggest improvements and corrections. Dr. W. D. Wright (Imperial College of Science and Technology, London), Dr. W. A. H. Rushton (Trinity College, Cambridge), Professor F. R. Winton (University College, London) have all read sections of the book and I wish to express my sincerest thanks for their

interest and valuable co-operation. Finally the whole manuscript was read by Dr. E. G. T. Liddell (Waynflete Professor in Physiology, Magdalene College, Oxford) who took a great deal of care in preparing it for publication and mediating contact with the Publisher when communications with England were not very easy. All this help from my English friends was given during the war at a time when extra work entailed a considerable sacrifice of time and energy, a fact which makes their friendly services particularly valuable to me.

The delay in publication since the book was completed is due to post-war conditions beyond my control. I have added references to later work from my own laboratory and a few recent papers from other countries have been mentioned in footnotes. Otherwise the text is unchanged.

RAGNAR GRANIT

Stockholm

June 1946

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INTRODUCTION

‘It would be of great importance to devise a method by means of which it were possible to find an objective expression for the effect of light upon the retina. The following contains an attempt to solve this problem.’—FRITHIOF HOLMGREN in the Introduction to his first paper on the retinal electrical response (*Upsala Läkareförenings Förhandlingar*, 1865-66, I, 177-91).

‘No doubt a great many questions concerning physiological optics may be treated according to this method, and among them are such as can hardly be solved in any other way now known to us. Among these I count, for instance, the problem of the time course of excitation in the retina.’—FRITHIOF HOLMGREN, *Upsala Läkareförenings Förhandlingar*, 1870-71, VI, 419-55. (Translated from the original Swedish.)

The retinal currents were independently discovered by Dewar (Sir James Dewar of the Royal Institution, London) and McKendrick (later Professor of Physiology at Glasgow) who, in a letter to Professor Holmgren, wrote:

Physiological Laboratory,
University of Edinburgh.
20th April, 1874.

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 being 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. You will observe, by reading the Memoir, the points which we have especially investigated. It would be very gratifying to Mr. Dewar and myself if you would write me a few

lines in reply to this letter. Meantime with every sentiment of respect for you and in admiration of your work,

I am, Sir, Yours truly,

JOHN G. MCKENDRICK.

Of the methods known to us at the present time, the electrophysiological one alone has enough sensitivity, speed, and precision to be really useful in the analysis of the fast retinal processes that mediate our sensations of light. Chemical methods have, so far, yielded very little information, photochemical work on the light-sensitive substances of the retina somewhat more, but the results have been concerned with the static rather than the dynamic factors in the receptive mechanisms. In order to learn whether a given photosensitive substance, extracted from the eye, has any sensory significance, its reaction to light must be shown to bear some simple relation to the discharge of impulses in the optic nerve. Many substances found in an eye may be photosensitive, but this property as such does not necessarily imply mediation of sensations of light. In the end, therefore, we have to fall back on recording the electrical activity of the light-sensitive end-organ or the impulses set up in its nerve to discover whether the reactions of an extracted substance were actually represented in the message carried to the brain. In man, sensations, and in animals, reflex reactions may, in this particular case, provide us with a substitute, but the electrophysiological method reaches farther. By micro-dissection the electrical activity of single or a limited number of sensory units can be isolated and recorded and the complex message, integrated by the brain as colour, or pattern can be split up into the letters, words, and sentences of its language.

The electrophysiology of the retina is a venerable field for research with traditions dating from the middle of the last century when DuBois Reymond's discovery of the 'negative variation' in nerves and of the resting potential of the eye (1849) prompted the Swedish physiologist, Frithiof Holmgren, to apply electrodes to an eye. His galvanometer gave a deflexion when the eye was illuminated and another when the light was cut off. Holmgren described what is now known as the electroretinogram (see e.g. Fig. 28) in a paper published in 1865 in Swedish and republished, probably at the request of

scientific colleagues, in Kühne's reports from the Heidelberg Institute of Physiology in 1880. The electroretinogram was independently discovered by Dewar and McKendrick (1873-7) in Scotland. In a note to their paper (1873) they state that they later became acquainted with Holmgren's work. Since those days our knowledge in this field has 'proceeded hand in hand with the development of electrophysiology in general. The history of the striking progress in electrical recording is briefly summarized in the literature relating to "retinal action currents"' (Granit, 1933), as they were then called. Gotch (1903-4) was the first to use a sufficiently fast instrument (the capillary electrometer) and with it he obtained the first electroretinograms which embodied all the features now known to us. Later, v. Brücke and Garten (1907) and Piper (1911) showed, in an extensive series of investigations with Einthoven's string galvanometer, that the electrical responses to light of various vertebrate eyes are alike. This conclusion could in fact have been drawn from the unjustly neglected work of Dewar (1876) (see p. 44). Then electroretinograms began to appear in textbooks of physiology, albeit chiefly as learned curiosities rather than as an aid to our understanding of the sensory mechanisms of the retina.

Thanks to the development of valve amplification, electrophysiology has made great strides in the course of the last two decades, and the retina was the first sense organ to be analysed (by Chaffee, Bovie, and Hampson in 1923) with the new technique. Although the vacuum tube amplifier increased the precision with which an electroretinogram could be obtained this was not its most important contribution to the electrophysiology of the sense organs. It was the increased range of sensitivity that it gave to instruments fast enough to follow the rapid action potentials in the nerve from an end-organ which really made the difference. In Adrian's hands (1928) the new instrument was responsible for the now well-known discovery that every sense organ reacts to an adequate stimulus by discharging a series of brief action potentials (action currents) of constant size—a series of repeated negative variations, to use DuBois Reymond's expression—through its nerve fibre. (Such action potentials, impulses or 'spikes' recorded from single fibres of the optic nerve can be seen in Figs. 11, 17, 58, 61 and 65.)

Variations in the frequency of these discharges reflect variations in the 'intensity' of the stimulus, so that the nerve fibre responds to an increase in the stimulus with an increased *rate* but not *size* of discharge.

Together with R. Matthews, Adrian early (1927-8) included work on the optic nerve in his pioneer research programme. To be exact, this was not the first time that anyone had placed the optic nerve across a pair of electrodes. Kühne and Steiner had done so in 1881, recording the results with the slow type of galvanometer which had to be used in those days in order to obtain enough sensitivity, and Ishihara (1906) and Wester-

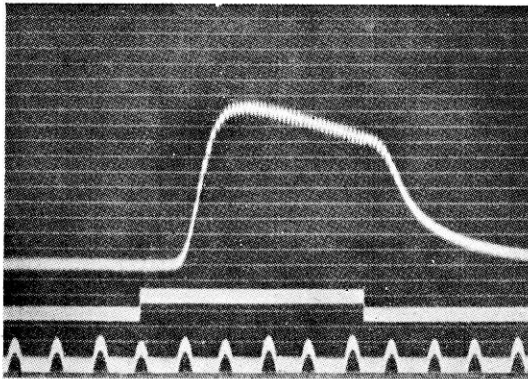


FIGURE 1. Electroretinogram of *Eledone moschata*. Time marking: $1/5$ sec. (Fröhlich, 1913, *Z. Sinnesphysiol.* 48)

lund (1912) both used the string galvanometer in an attempt to obtain records from the optic nerve. These workers all saw the nerve respond both to the onset and to the cessation of illumination of the attached eye. In the light of what we know to-day it is probable, however, that what they recorded was the actual impulse activity in the nerve *plus* what is now called the electrotonic potential (p. 64) and, in some cases, electrical leakage from the retina as well. Further, without themselves realizing its significance, Gotch (1903), Einthoven, and Jolly (1908), and Chaffee, Bovie, and Hampson (1923) had actually seen the effect of grouped impulses from the optic nerve in the shape of small extra wavelets superimposed on the much

slower electroretinogram. The oscillatory character of these wavelets is particularly obvious in the records published by Einthoven and Jolly. Fröhlich (1914, 1921), who obtained particularly good oscillations (see Fig. 1) superimposed on the electroretinogram of the cephalopod *Eledone moschata*, noted their increased frequency with increase in the intensity of the stimulating light and concluded that they represented a second type of retinal response distinct from the slow, smooth potential change of the electroretinogram. He believed that this second type of response was transmitted through the *neruli optici* of the eye. Fröhlich did not understand that these rhythmic changes were really the well-known action currents of the nerve and it was left to Adrian (1928) to demonstrate the true nature of the rhythmic discharge of sense organs and to suggest the correct explanation of Fröhlich's results.

Even though Holmgren and Dewar, hampered by the slow type of instrument available at the end of the last century, could not analyse the complex, polyphasic response of the retina to light, they were able to make the important observation that the vertebrate retina responds both to the onset and the cessation of illumination. The reality of the off-effect in vertebrates has since been confirmed by all workers in the field, including those studying the activity of the nerve alone. During the period following its discovery research was mainly devoted to establishing the precise form of the electroretinogram, but partly, also, to attempts to split it into its components and to study its relation to various types of alteration of the stimulus. The reactions of the eye to alteration of the intensity area, duration and wave-length of the stimulating light, as well as the variations of these reactions due to its state of adaptation were examined. We shall return to a study of these contributions under their proper headings later. The amplifier was not essential for work on the retina alone, although it made the experiments easier and the results more reliable, but by making the *nerve* available for research it did pave the way for the advance with which this book deals, that is, the transformation of the study of the electrical responses of the eye into a scientific method capable of analysing the intricate sensory mechanisms of the retina.

Before one can understand the details of the retinal mechan-

isms it is necessary to know what happens in the nerve when certain potential changes occur in the retina. As we shall see later, not every potential change in the retina is accompanied by the transmission of impulses through the nerve, for one component of the complex electroretinogram has no direct relationship to activity in the nerve and another seems to be very closely related to inhibition. Thus, in order to interpret the retinal process, it is necessary to be able to record the nervous discharge. On the other hand, the analysed electroretinogram is equally necessary for an understanding of what takes place in the nerve. When, for instance, the vertebrate optic nerve responds to the cessation of illumination with a burst of impulses it is certain that this is but a reflexion of the retinal process responsible for the off-effect in the electroretinogram even though the latter is so very different. Somehow the electrical changes must reflect the events in the retina which are responsible for those in the nerve. Indeed, the first problem of the physiology of the sensory mechanisms of the retina is that of how these can generate and, as we shall see, also inhibit the discharge of impulses in the nerve. Even if the activity in the nerve were not actually produced by the potential changes in the retina, the electroretinogram is, nevertheless, the only measurable index of what takes place in the retina in response to changes in illumination.

The correlations between the processes in retina and optic nerve, therefore, comprise a great and important group of problems associated with another set of correlations connecting the peripheral mechanisms with our sensory experiences. Some electrophysiological facts can easily be translated into the language of our visual sense, notably those concerned with flicker phenomena, dark adaptation and the perception of brightness or colour, while for others there is, as yet, no corresponding place in the pattern of our sensory experience. It is to be hoped that systematic comparative experiments in which the creation of similar situations for sensory and electrical recording is attempted will become a natural line of development in this field and that in this way some of the gaps, which are so obvious to one now engaged in summarizing our present knowledge, will be closed. There are, for instance, a large number of electrophysiological discoveries concerned with ex-

citation and inhibition in the retina which cannot, as yet, be related to the results of experiments on visual sensations, experiments which are still chiefly of the type developed at the end of the last century.

Another group of problems is concerned with the correlation of photochemical facts with those derived from a study of electrophysiological phenomena. Photochemical information which is reliable enough to serve as a background for such work is, at present, practically limited to visual purple and visual violet. However, electrophysiological measurements of the spectral sensitivity of various types of eye are gradually supplying the sort of information which could guide photochemical work on other substances which may mediate the visual reactions to light. Here also is a line of research along which we can look forward to interesting developments in the near future, hoping that the knowledge accumulated by electrophysiology may direct as well as interpret the results of accurate chemical and photochemical analyses made possible by the great resources which are to-day available.

In reviewing the present position of our knowledge of the sensory mechanisms of the retina I do not intend to present the results in their historical order although all important work will be referred to in its proper place. It has seemed better to deal with the results in the order which corresponds best to my own mental picture. In the chronological sense this has meant beginning at the end since I have chosen to start with a consideration of that recent work on the artificial generation of trains of nervous impulses which has occupied the centre of interest in this laboratory for the last three years. In consequence this book does not begin with a consideration of the retina at all, but instead with a brief reference to some work on the peripheral nerve as a model sense organ.