eye became painful and glaucomatous some weeks later and was trephined 4 months after the original operation on the left eye. It was enucleated a month later.

Microscopical Sections.—This eye is the only one of the series which shows all the characteristics recognized as peculiar to advanced sympathetic disease in an exciting eye. The whole of the uveal tract is a mass of granulation tissue in which all types of inflammatory cell are seen, and which shows nodules containing epithelioid and giant cells. The central vessels, optic disc, and the nerve sheath, as well as the ciliary vessels and nerves, are infiltrated with lymphocytes. The lens capsule is ruptured, but in this case the rupture may have occurred when the operation for the relief of secondary glaucoma was performed.

THE OFF/ON-RATIO OF THE ISOLATED ON-OFF-ELEMENTS IN THE MAMMALIAN EYE

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IN this communication I would like to draw attention to some aspects of the micro-electrode work with the retina of the dark adapted decerebrate cat which have come to the fore after the appearance of my (very much delayed) summary in 1947. Some new results and concepts have emerged from the further analysis of several hundred isolated fibres in this retina and it is possible that there is something in this work that may interest the clinician also. It is not my intention to review experiments published elsewhere, except in so far as they are necessary for this discussion of concepts and principles.*

The retinal elements are either *on-elements, off-elements* or *on-off-elements*. The on-elements respond to light with a stream of impulses, the off-elements with a discharge at the cessation of illumination and the on-off-elements combine these two properties. For the discrimination of light and colours the on-off-elements must be the most important ones. In the cat's eye they are also the most numerous ones; there Miss Tansley and I found 80 per cent. on-off-elements. The on-elements turned up in 16 per cent. of our total of 164 elements. We have reasons to believe them to be pure rod-elements. The on-off-elements may differ in colour sensitivity at " on " and " off." For this reason it is impossible to assume that the on and off-components are set up by identical

* The original papers will be found in the *Jl. Physiol.*, and *Jl. Neuro-Physiol.*, for 1947. The latest one is due to appear in the latter Journal within a few months. The summary referred to is " Sensory Mechanisms of the Retina," Oxford Univ. Press, 1947.

receptors. Hence the on-off-element is a complex structure to which receptors of different properties have contributed. Some of them must have arrived over internuncial channels involving the retinal synapses. One of the first tasks in retinal physiology is to find out how internuncial activity modifies the primary receptor response. (The latter probably appears in a relatively pure state in the simple on-elements.) For this analytical work it is necessary to develop methods and concepts.

One of the fundamental new concepts is the off/on-ratio. Miss Tansley and I discovered this variation in the properties of the on-off-elements. We increased the strength of the light gradually and found that sometimes the on-, sometimes the off-component of an on-off-element turned up first. An on-off-element is thus relatively more on-sensitive *or* relatively more off-sensitive. Sometimes the on- and off-components were equally light-sensitive at the threshold and then the off/on-ratio obviously is 1·0. Dr. Gernandt and I have since, independently and together, measured the off/on-ratios for a large number of on/off-elements, stimulating with different wave-lengths. One obtains statistical distribution curves showing that the majority of the elements have off/on-ratios varying from 0·1 to 10·0 but that the extremes of the curve are represented by variations as large as 1000 and 0·001. This, of course, is an amazing variation and one may well ask what purpose it serves.

In a general way one can say that the variation in the off/on-ratios improves discrimination. Most acts of discrimination presuppose a moving eye for which the off-discharge is just as important as the on-discharge. A wide range of variation in the off/on-ratio increases the local variability necessary for discrimination.

In his extensive material Gernandt (unpublished) also has measurements for red (0·650 μ), green (0·510 μ) and blue (0·460 μ) light. Any wave-length may have any off/on-ratio but the probability that the maximum would be in the green was only 0·18 as against 0·39 for the blue and 0·47 for the red light. This means that there are several elements which become relatively more off-sensitive towards either or both ends of the spectrum. Others have a constant off/on-ratio throughout the spectral range. This, of course, is a very interesting finding. My measurements of the spectral sensitivity of dark adapted cats were always carried out with the on-components, when on-off-elements were localized by the micro-electrode. They gave, when averaged, roughly the visual purple distribution of spectral sensitivity (as again confirmed in this laboratory). The off-components (which at present are being measured) cannot do so unless the element is of the type for which the off/on-ratio is constant throughout the spectral range. Other receptors than those activated by visual purple must therefore contribute relatively more to some off-components. These apparently contain a greater number of cones than the on-components. This conclusion was also reached by Miss Tansley and myself who found that red-sensitivity tended to increase with off-sensitivity.

Another of Gernandt's results was still more interesting. He found, as I had done before, that different on-off-elements are differentially sensitive to adaptation with red, green or blue light. But to this he added the important observation, that, in general, selective adaptation of an on-off-element tended to depress the more sensitive component relatively more, so that if the element was more off-sensitive, the off-component was relatively more depressed and, *vice versa,* if it was more on-sensitive. What this means is best understood with the aid of an example. Assume that the eye be stimulated with a blue stimulus. Then, during illumination, all the specific blue-sensitive on- and off-components become depressed. The off-discharge that follows upon cessation of stimulation will therefore be favoured in off-sensitive elements containing other components than blue ones. This is precisely the kind of arrangement that would facilitate a contrast mechanism operating with on-off-elements.

Let us now consider why the off/on-ratio varies as it does. The fact itself seems rather remarkable. All receptors are working at their maximum capacity because the eye is fully dark adapted. How then is it possible for some to be a 1,000 times less sensitive than others? The on-component may be 1,000 times more sensitive than the off-component and, *vice versa,* the off-component 1,000 times more sensitive than the on-component. The off/on-ratio may thus vary from 1000 to 0·001. This occurs despite the fact that hardly any elements are likely to be *pure* cone-elements. There is always a great deal of convergence of rods and cones towards the ganglion cell from which the micro-electrode picks up the response. The rods will dominate in dark adaptation.

Nevertheless the assumption that the variation in the off/on-ratio really expresses a variation in the cone/rod-ratio deserves to be examined. If true it would mean that the less sensitive component is dominated by cones. Thus, when the off/on-ratio is high, the on-component would contain the cones, when the off/on-ratio is low the cones would be in the off-component. Available evidence does not support this simple explanation. On the contrary, the higher the off/on-ratio, the greater, on an average, the relative sensitivity to red light (0·650μ) for *both* the on- and the off-component. This was found by Miss Tansley and myself with 61 on/off-elements. At the wave-length 0·650μ the photosensitivity of visual purple is of the order of 0·3 per cent. of its maximum around 0·500μ so that a positive correlation between off/on-ratio and red-sensitivity can only mean that the higher the off/on-ratio the more likely that cones participate in the response.

There is another very potent argument against the idea that the off/on-ratio would be a variable illustrating merely the relative contribution of cones to the on- and off-components of the elements. This presupposes that the off/on-ratio would be constant but actually it is only constant just at the threshold and, above it, and is subject to great fluctuations under the influence of light-stimuli. Electrical stimulation of the eye also changes the off/on-ratio at the threshold. Now this is not surprising. Stimulation with light produces differences of electrical potential across the retina so that if this influences the off/on-ratio, direct electrical stimulation must do so too. The curves illustrating impulse frequency against stimulus intensity also demonstrate variations in the off/on-ratio. Sometimes the on-effect is inhibited within a certain range of intensity, sometimes the off-effect (Granit, *Jl. Physiol.,* 1944, Vol. CIII, p.103). Impulse frequency is by no means a simple function of stimulus intensity when one records from a single fibre *after* the effect has passed through a nervous centre. The optic nerve, of course, is really a central tract and this accounts for the difficulties in interpreting the message. It has already become highly differentiated. The frequency-intensity function has become modulated in the retinal centre.

With these facts at our disposal we can readily understand that the variation in the off/on-ratio at the threshold represents the selection of one particular state of balance between the forces of excitation and inhibition (or suppression) in the retina. This conclusion leads to the novel and somewhat radical concept that an element, already at the absolute threshold, is subject to " internal tension " exerted by forces of facilitation and depression. The synaptic organization maintaining the element in a resting retina (at the absolute threshold) cannot be regarded merely as an anatomical distribution pattern of the paths of various receptors, bipolars, amacrines and horizontals but it is also a structure using energy in order to suppress the activity of certain cells and, perhaps, heighten that of others. The threshold variations in the off/on-ratio demonstrate how this semi-stationary state of balance of forces within an on-off-element is organized at one particular level of intensity.

It would not surprise me if the extremes represented less probable labile states. I have seen several on-off-elements with off/on-ratios of the order of 0·001 under the influence of electrical polarization acquire an off/on-ratio of around 1·0. This change has been in the nature of a release of the suppressed component under the influence of the electrical stimulus. The latter has been delivered from electrodes on opposite sides of the bulb.

Long ago Dr. L. A. Riddell and I myself (*Jl. Physiol.*, 1934, Vol. LXXXI. p. 1) noted with the frog's eye that a light adapted retina was a relatively more negative retina (inside more negative to outside of bulb) and pointed out that light adaptation involved slow electrical changes altering the " state " of the retina. In a later summary I spoke of " electro-adaptation." It will now be necessary to return to similar problems with the mammalian eye.

It is highly probable that the slow electrical changes induced by light determine the off/on-ratio because electrical stimulation strongly affects this relationship. But recent observations from experiments now in progress have led me to suspect that we are allowing ourselves to be too dogmatic when tacitly assuming that the anatomical organization is fixed and unchangeable. I believe that we must seriously consider the possibility that the " boutons " at the synapses expand or contract so as to alter the contact surface. In certain types of on/off-elements I find that stimulation with light induces large changes of electrical threshold. These often return very slowly and sometimes the responses to anodal and cathodal currents and those to illumination at " on " and " off," shift relative to one another in such a manner that one must raise the question as to whether one really is dealing with the same anatomical organization.

On the whole I feel that one should not be afraid of putting radical views to the test of an experiment. It seems to me a greater mistake to assume that a new technique, such as the micro-electrode technique, must necessarily answer questions suggested by the very different psychophysical method of approach. If we frame our questions on the basis of old findings the new technique may refuse to answer them. Our aim must be to put the right questions to the micro-electrode.