Physiological Basis of Flicker Electroretinography as Applied in Clinical Work.

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In speaking to this audience it is my first pleasant task to express my deep gratitude for your decision to make me the recipient of your quinquennial Donders Medal. Being a physiologist rather than an ophthalmologist, I appreciate it all the more. We laboratory men may well be happy in our own world of experiments and deductions. Nevertheless, when our clinical fellow workers by an act of this kind indicate that our results have been of some significance for them in their attempts to understand disease and to relieve suffering, this creates special delight and ministers to that need most of us feel—secretly or openly—for criteria by means of which our usefulness to mankind might somehow be established. Donders, who had the strength and talent of two men, as all of us know, was equally successful in physiology and ophthalmology and I am happy and proud of being thus associated with his name.

In choosing for my theme the flicker method and its prospects as a clinical test, let me begin by emphasizing that there is a natural cleft between electroretinographic or optic nerve data on the one hand and psychophysical observation on the other. The ophthalmologist must of necessity be interested in psychophysical measurements, say, of dark adaptation or visual acuity, because they provide the indicators by which he judges visual functions directly and these, of course, are relevant to the patient. Yet much of what the physiologists of to-day are engaged in, such as work on retinal receptive fields, on-off-discharges, spontaneous impulse activity, spectral sensitivity distributions, retinal microelectrodes, cannot be directly translated into sensory terms useful for the purposes of the ophthalmologist. This is why in our arsenal of methods those are likely to become particularly valuable which in some way bring psychophysics and electrophysiology together.
Perhaps this statement requires further qualification. Consider, for instance, electroretinography so useful nowadays for many clinical purposes ever since Karpe (1945) first developed and applied this method in ophthalmology. The electroretinogram contains slow or static electrical components of opposite sign as well as fast dynamic changes at onset and cessation of light, the on- and off-effects. Yet though we know that the optic nerve also responds to “on” and “off”, we cannot say what is perceived at “off” nor can we in sensory terms evaluate the slower EEG-components. The clinical usefulness of the method is largely based on empirical correlations and comparisons with normal subjects, at the moment chiefly evaluated by means of the dynamic change at onset of illumination, the so-called b-wave. The electrophysiological work leaves no doubt about the fact that the optic nerve responds twice to a flash, once at onset and once at cessation of illumination. We likewise know very well that the two dynamic changes, “on” as well as “off”, are the ones by which the retina responds to intermittent or flickering light. What is more, we possess both psychophysical as well as electrophysiological analyses of the flickering response. The question I shall raise to-day is therefore: what particular information are we entitled to expect from systematic application of the flicker method in electroretinography? Far be it from me to claim that I can give a final and complete answer to this question. However, I shall go over the ground from this point of view, discuss the facts and reach some conclusions which may serve as a stepping-stone for further work. Flicker as measured in terms of fusion frequency with the aid of perception, has been proved to reproduce some of the essential properties of electroretinographic flicker fusion. This crucial fact may prove helpful, and for the very reason I have given, namely because it provides a common basis for psychophysics and electrophysiology.

To an earlier mode of thinking about vision in more static or, perhaps, in photochemical terms, it may have seemed an odd and unintelligible fact that the optic nerve should respond to both onset and cessation of light and that it, indeed, discharges but slowly and irregularly during steady illumination. In many animals, as e.g. the frog, next to nothing is visible between “on” and “off” (see below) but one only has to pass a pencil quickly through the light beam to get an immediate reply in terms of impulses. In mammals somewhat more is seen while the light is shining but
adaptation soon suppresses this discharge to a very low frequency which even may get lost in the spontaneous discharge independent of light. This strong effect of adaptation to a light source has long been well known in the clinic. It was studied at an early date by the Norwegian ophthalmologist Holth (1896) who spoke of “stirred-blindness” or “fixation blindness”, meaning that small objects in the peripheral visual field disappear during fixation. To move the test spot in perimetry is part of the ophthalmological routine.

However, not until recently has it become possible to do accurate psychophysical work with small so-called stopped images and thus to avoid all varieties of eye movement. The image is projected into a viewing screen by a mirror fixed to a contact lens. From there it is allowed to enter the pupil after having passed through a compensating path by means of which any small angular rotation of the bulb gives the image viewed an opposite shift of the same magnitude as the eye movement. This method of automatic compensation of eye movements was first considered by Ratliff (1952), then developed by Riggs, Ratliff, Cornsweet and Cornsweet (1953) and, apparently independently, by Ditchburn and Ginsborg (1953). Such stopped images just disappear, fade out after some seconds, and can be re-evoked by a slight eye movement. When fixation time exceeds half a second, the eye movements may be 2 min. of arc, while the cone diameter is only about 25 sec. of arc. An early advocate for the role of eye movements in perception was Weymouth (1928) followed by many others, but when the electrophysiological studies of the on- and off-discharges became available (see below), it seemed obvious that the dynamic components in vision must serve to light up contours with brief on-off-oscillations and that this process must be an important source of information for the higher centres (see e.g. Wright and Granit, 1938; Granit, 1947, p. 168).

There is, for instance, a continuous tremor of the eye at rates up to 90 per sec. (generally less) of the order of 10-20 sec. of arc. The on-off-fluctuations, so far from being unintelligible, to this dynamic view of vision appear as highly essential components of the organized structure interpreting the visual world. Clearly, since flicker is an approach to the dynamic aspects of vision, it is worth while spending some time on a more detailed discussion of such problems.

An extra-retinal factor should at first be recalled, i.e. the eye-muscles, to which Donders devoted so much important work.
These differ from skeletal muscles in the high frequencies at which they discharge. It is uncommon to find in ordinary striate muscles discharge frequencies above 50 per sec. (Adrian and Bronk, 1929), and the persistent or tonic activity rarely exceeds 20 (Denny-Brown, 1929; Granit, Phillips, Skoglund and Steg, 1957). But in cat (Reid, 1949) as well as in man (Björk and Kugelberg, 1953) the highest frequencies observed by electromyography in eye muscles run up to 200 per sec. which may not be the limit.

Commonly the values are around 50-100 and at 50 per sec. one is near the threshold of just visible contraction. As in other striate muscles, so in these also, the spindle organs sensitive to minute stretch are kept under control from higher centres by special nerve fibres (Cooper, Daniel and Whitteridge, 1955; Cooper and Daniel, 1957), but for the eye muscles the full significance of this sensitivity modulation is not yet understood, nor do we know how, if at all, it determines motor output, if by setting up stretch reflexes or only by variations of output frequency around a mean. The electromyographical work on eye muscles proves, however, that these organs are eminently suited for the tremor, saccadic movements and rapid flicks the eyes perform in addition to the slow adjusted movements. The small eye movements that to an earlier epoch must have seemed an example of "faulty design" we now know to be the consequence of properties specifically developed for eye muscles and calculated to give them the high-frequency spectrum necessary for quick action.

If we want to analyse flicker by electroretinigraphy, surely the simplest beginning will be to repeat a second light flash at lengthening intervals from its predecessor, alternatively, to keep the eye illuminated and interrupt this light at varying intervals. This means that re-illumination will be superimposed on the off-effect left by the first flash. It is well-known nowadays that the retinogram begins with a negative a-wave (Fig. 2), then follows the positive b-wave and ultimately, at cessation of illumination, the off-effect or d-wave.

Fig. 2 demonstrates this with the frog’s eye and an intermittent light above the fusion point (thus on the Talbot-Plateau law equivalent to a steady light at half the intensity).

Einthoven and Jolly (1908) in this country, when occasionally re-illuminating the frog’s eye had noted particularly large a-waves. They did not, however, pursue the subject by systematic analysis. We see in Fig. 1 some experiments on the eyes of frog,
pigeon, owl and cat on lengthening intervals of re-illumination and note the large a-waves in the first three cases as against no a-waves in the cat. Pigeon, owl and frog have a considerable number of cones whilst the cat has a smaller number. In general one finds rod eyes behaving in this respect like the eye of the cat. A consequence would be that rod eyes should tend to flicker with repeated positive b-waves, b-b-b, whilst cone eyes ought to flicker with a negative-positive sequence a-b-a-b.

Most eyes are mixed, and so must show a shift in their pattern of response to intermittent illumination with state of adaptation, provided that either type of receptor system is present in sufficient density to emerge at all in an average response such as the electroretinogram. The frog, which has rods and cones in about the same proportion, is an excellent preparation for a test of this proposition and, as we shall see, the human eye has a sufficient number of cones to behave like the frog eye.

The records in Fig. 2 refer to the frog's eye. The experiment begins in the dark-adapted state (record A) in which the retina refuses to flicker at the rate of intermittent stimulation, indicated by the black oblongs below the record. After this the eye is left exposed to the same stimulus for 5 min. which suffices to bring about a complete change of behaviour. In record B it now flickers at a very much faster rate than the one used in A. In order to demonstrate that this flicker is of the type a-b-a-b, record C has been taken. The record begins with the off-effect. When intermittent stimulation starts, the response begins with an a-wave. But the off-effect is held ready to swing back, like a Jack-in-the-box, and does so after the first flash together with the b-wave.
In this way the process goes on. Strictly speaking then, cone flicker is not only a-b-a-b, but into the positive b-component enters part of the off-effect or d-wave, which is so difficult to demonstrate in single electroretinograms of eyes dominated by rods. From the point of view of reception we conclude that the frog retina in the dark-adapted state is a sluggish instrument compared with its mode of behaviour in light-adaptation. In the latter state it makes far better use of the dynamic components at onset and cessation of illumination to increase its speed of performance. It is therefore likely that flicker at high intensities and fast frequencies of intermittence would provide an ideal method of getting at the cone responses by electroretinography, a major ophthalmological aim of present-day research by this method.

The ophthalmologist who in the first instance is a student of the human eye will now be interested in a repetition of the same type of experiment in man. This is shown in Fig. 3 from a paper by Döllt (1952). Flicker begins at a slow rate with the pure b-waves, known to dominate the retinogram of our eye which, after all, with 125 million rods as against the 4-7 million cones must
be dominated by rod properties. But, since in this experiment a high intensity of light has been used, the flicker gradually changes its character: the a-waves turn up, followed by the off-effect and the b-wave. These two combine to increase the deflexions beyond the original size until ultimately the rate of stimulation becomes too fast and the deflexions again diminish. Large flickering wavelets at intermediate rates of intermittence have also been described in man by Best and Bohnen (1957). It is clear that with two positive events, the b-wave and the off-effect, encroaching upon each other, there must be a frequency at which the individual wavelets have a maximum size. This maximum has been seen by Dodt and Wirth (1953) also with the pigeon’s retina, dominated by cones, in which, besides, the fusion frequency is as high as 150 flashes per sec., while in man the maximum is of the order of 70.

We may legitimately ask: is this phase of superposition of b-wave and off-effect at a certain rate of flicker a purely algebraical phenomenon: I mean, a mere summation of potentials without visual significance or is there an equivalent rise of sensation? If so, this would amount to particularly bright and violent flicker at a certain frequency. We do not yet know the answer. But it should be recalled that Brücke (1864) long ago pointed out that at certain rates of flicker, around 17-18 per sec., the sensation was one of maximum brightness. This matter should be taken up again by those nowadays working on flicker in man. It should be possible quantitatively to compare the electroretinographic picture with perception.

Let us finally enquire into the cause of the change-over, as we
have said, from rod-flicker to cone-flicker, obtained by maintaining intermittent illumination with a strong light in an originally dark-adapted eye. Is it wholly due to the transition from rods to cones with light-adaptation or is the electrical response of either element in itself speeded up by illumination? A general effect of light-adaptation is undoubtedly to make the phasic components faster than before (Granit and Riddell, 1934). One could, however, object against these experiments that they were carried out with mixed eyes. In the last five years the genus of squirrels has been found to provide species suitable for the study of mammalian pure cone eyes. Arden and Tansley’s work, as reported by Tansley (1957) at the Hamburg Symposium on Electroretinography shows that at a certain level of high intensity the b-wave becomes sharply pointed. Thus it would be able to follow faster rates of intermittent stimulation. Nevertheless there are reasons left for ascribing the greater part of the transition from slow to fast flicker with increasing light-adaptation to a real shift from rod properties to cone properties. (Cf. Dodt and Heck, 1954.) There seems to be no escape from the conclusion that cone-eyes as such are capable of following faster flicker than rod-eyes. Relatively low fusion frequencies are always obtained from rod eyes of various animals by comparison with cone eyes. Thus it is impossible to force the retina of the guinea-pig that has very few cones to follow as fast rates of flicker as the cat’s retina with a larger number of cones, whatever the light intensity (Dodt and Enroth, 1953; Dodt and Wirth, 1953).

The absolute maximum of the fusion frequency in guinea-pigs is of the order of 30-40 flashes per sec., for which intensities around 10,000 lux have to be used, that of the cat of the order of 60-70 flashes per sec. But, as stated, the pigeon’s cone-retina follows up to 150 flashes per sec. (see below, Fig. 11). Patients with primary total colour blindness have maxima around 20-25 flashes per sec., whilst the corresponding value in normal man is around 70 (Dodt and Wadensten, 1954).

Now cones are far more important for discrimination than rods which seem to be designed for integration of feeble stimuli, as also suggested by the large number of rods per nerve fibre (around a million nerve fibres in man). I began by pointing out that for discriminatory tasks small fast eye movements are essential, unless time of exposure is cut down below a tenth of a sec., and that this mechanism would be useless unless the visual appa-
ratus had high differentiation velocity (= fast dynamic components). Therefore, in using flicker electoretinography, the ophthalmologist has at his disposal an objective method of studying an essential factor in discrimination as performed by the cone system, provided that he uses high intensity and rather rapid rates of intermittence. In addition the method brings out the off-effect of the human electoretinogram (Dodt, 1952), which so far has been neglected by the electoretinographers. Perhaps, at this stage, I should mention one more reason why I now have devoted so much time to these phenomena of transition from rod-flicker to cone-flicker. The electoretinogram is a mass event, requiring a large area of illumination (as measured in cats by Wirth and Zetterström, 1954) and it is impossible in man to measure the size of the generative surface of the retina with any degree of precision. The change with state of adaptation and the shift from rods to cones serve to improve definition by shifting the field of investigation from the periphery to the macular region. I doubt whether ordinary retinography ever can become useful in precise perimetry (see discussion, Granit, 1955, Ch. V; Karpe, 1945; Wirth, 1950).

While the electoretinogram is an average response, the discharge of impulses from retinal ganglion cells or optic nerve fibres provides the necessary detail. This is the message delivered to the brain for interpretation. The act of interpretation itself we can hardly approach except through psychophysics but the optic nerve data help us to understand the electoretinogram in flicker. Together, however, the three modes of approach, retina, optic nerve and perception, might be said to carry us further on the way of understanding a retino-neural event than any other method of studying the sensory processes in the human eye. We can neglect the old attempts to analyse the optic nerve response with the slow instruments then available. The pioneer work with the modern technique of vacuum tube amplification was carried out by Adrian and Matthews (1927a, b; 1928). Using the whole optic nerve of the Conger eel they found the fusion frequency to increase with an increase in the intensity of the stimulating light, as also noted with the mammalian electoretinogram (Creed and Granit, 1933). I believe the first to notice the similar relationship in perception was Schafhautl (1855) who also realized that brightness for this reason could be measured by using the fusion frequency as an index. For this purpose, Schafhautl built an instrument with a pendulum swinging behind a hole in a screen letting through
the light beam. Frequency was varied by changing the length of the pendulum. But it remained for Ferry (1892) to show that fusion frequency actually measures brightness alone and not colour as such. We know this to be true for electroretinographic flicker also, at least in a general way. All recent work in electroretinography indicates that the dynamic changes at onset and cessation of light contain components of different rates of rise which depend upon wave-length and so there must be specific effects of wave-length on flicker though probably not of an order of magnitude sufficient to disturb the average relationship that we have discussed. (For work on such components of the b- and d-wave see, e.g., Motokawa and Mita, 1942; Adrian, 1945; Granit, 1947; Armington, 1953; Bornschein, 1953; Ronchi and Grazi, 1956; Wirth, 1956; Ronchi and Bittini, 1957; Heck and Rendahl, 1957.)

The next step on the perceptual side was taken by Porter (1898, 1902) who found the fusion frequency to be proportional to the logarithm of the brightness of the stimulus. This relationship is known as the Ferry-Porter law and we shall return to it below. This problem has a large subsequent literature (cf. Landis, 1954). However, the Ferry-Porter law is a good enough approximation for most purposes.

Returning after this digression to the average response of the optic nerve, let us consider what happens when the experiment on re-illumination on top of the off-effect of the frog’s retina is repeated with electrodes on the nerve instead of on the retina. What, in particular, corresponds to the large a-waves that were found to initiate the response to re-illumination after a brief interruption? This experiment we had on the programme in 1934 (Granit and Therman, 1934, 1935) and I can still remember the excitement with which we noted that the off-discharge in the optic nerve was inhibited during that phase after re-illumination which corresponded to the a-wave of the electroretinogram.

This is shown in Fig. 4. At the time this kind of work was still new and, though I had postulated the existence of inhibition in the retina (Granit, 1933), I doubt whether any one then was prepared to believe that light not only could elicit impulses but also stop them. This experiment has since been repeated in so many laboratories that very few people to-day will understand why it caused such a thrill to the young experimenter of the year 1934. Now it simply is part of the general stock of knowledge. From the point of view of flicker it means that, inasmuch as flicker
also is an off-flicker, it will be an alternation between excitation and inhibition, as since studied in detail in single optic nerve ganglions in the retina of the cat by Enroth (1952). (Historical exposition by Granit, 1952).

At that time my colleague and very good friend H. K. Hartline working at the Johnson Foundation of the University of Pennsylvania had perfected his beautiful technique of recording from single fibres in the frog's retina by lifting them onto electrodes at the point where they emerge fan-like from the blind spot. The results were published in full in 1938 (preliminarily in 1935). Apart from confirming the inhibition of the off-discharge by renewed illumination they brought the exciting information that the diversity of response pattern in single fibres of the optic nerve was more striking than one might have expected. Hartline found fibres that responded merely to onset of illumination, on-fibres, others that merely responded at "off", off-fibres, but most of them (50%) responded to both onset and cessation of illumination, i.e., they were the on/off-fibres that the records from the whole nerve had made one expect. Most fibres specialized on these dynamic components; a few were found that gave a maintained discharge. The types were stable over a considerable range. I need not now enter upon the subsequent development of micro-electrode work that confirmed and expanded Hartline's results and brought the mammalian retina into the picture, having re-
viewed it elsewhere in considerable detail (Granit, 1947, 1955). I intend merely to pick the facts that are relevant to our present theme of flicker. In every eye studied we have found on-, off- and on/off-elements in different proportions but the common laboratory mammals seem to differ from the frog by (i) having mostly on/off-elements; (ii) in the lesser stability of their responses, i.e., depending upon intensity and state of adapting many elements change type; (iii) in possessing a larger number of fibres with some sustained discharge during illumination. (iv) There also seems to be more spontaneous activity in the mammalian retina. We have every reason to assume our own retina also to show plasticity of response type, at least in the periphery. The foveal responses may well be more stable. From the point of view of flicker, plasticity of type means that a very diversiform pattern of on- and off-responses is being delivered up the optic nerve for interpretation, Fig. 5 shows patterns of response from the cat's retina. At this stage it is possible to introduce a simplification, unexpected in the sense that it emerged gradually from work carried out over many years and ultimately maturing into a generalization that could be tested. This generalization was that the on- and off-components of an on/off-discharge were mutually exclusive. In flicker this would mean that, as the rate of intermittent illumination grows faster, the on/off-elements, which are the

![Figure 5](image)

*Fig. 5. Diagram shows discharge types in cat's retinal ganglion cells. These, as stated in text, vary within anyone cell with changes in state of adaptation and stimulus intensity (Enroth: Acta physiol. scand. 27: Suppl. 100 [1952].)*
overwhelming majority in mammalian eyes, could not flicker at both “on” and “off”, but would be forced to make a choice. This notion was put to a test based on the simple expedient of shortening the exposure of the flash systematically while recording from single on-off-elements in the cat’s retina (Granit, 1951). The discharges at onset and cessation of illumination are drawn-out events compared with the length of exposures used in this test, and so ultimately a flash duration was reached at which the on- and off-discharges were found to clash. The question then arose of whether the two would add to produce a higher discharge frequency than either could deliver by itself. This proved not to be the case. The stronger discharge, independently of whether it was “on” or “off”, took the lead and the weaker was ousted from participation. In such experiments the conclusion was reached that the on- and off-components of the discharge from an individual ganglion cell really are mutually antagonistic. This was soon confirmed by Kuffler (1953) by a technique of micro-illumination in which two light spots in the retina converging individually to produce in the same ganglion cell on- and off-discharges respectively, were pitted against each other (a more detailed presentation in Granit, 1955, pp. 67-78). Again the stronger discharge took the lead.

Though this conclusion that the on- and off-components of a ganglion cell are mutually antagonistic did not rise above the experimental horizon with the dramatic suddenness of many other retinal findings from the last twenty years, it nevertheless, on consideration, seems to me one of the most essential facts in retinal neurology. The intraretinal events building up an on-discharge for any given ganglion cell inhibit those setting up an off-discharge and vice versa. We cannot now discuss this neural mechanism but from the point of view of discrimination it means that the individual ganglion cells will be forced to produce different patterns (the variable on/off-ratios studied by, e.g., Granit and Tansley, 1948) according to changing gradients of illumination and depending also upon eye movements. Overlapping fields of reception is a fundamental principle of sensory organization, both in the retina and in the brain (cf. Granit, 1955), and so discrimination can only arise out of differentiation by the changes of on/off-pattern created by the mechanism discussed. From the point of view of flicker it means that, depending upon relative strength of the on- and off-components of an on/off-
element, the element will approach the fusion point either as an on- or as an off-discharge, even though at lower frequencies it responded by on-off.

The most extensive analysis of flicker in individual retinal elements that we possess was carried out by Enroth (1952, 1953). It is of some interest, in view of the inhibition of the off-discharge by re-illumination to reproduce as Fig. 6 a record of a good off-discharge (A) after a flash lasting 100 msec. Flicker in the records B shows how this off-discharge every time is inhibited by the re-appearing flash until, in B3, the rate of stimulation becomes so fast that "fusion" takes place which for an off-discharge means silence, because it is inhibited by light. When, at the end of B3, flicker is interrupted by closing the shutter altogether, the off-discharge again appears and, if it had been reproduced in full, would have taken the time course of record A.

![Figure 6](image)

*Fig. 6. Off-response to an isolated single flash compared with flicker response. A: vigorous response to a single flash of 100 msec. duration. B: consecutive records of an accelerating flicker. Response to a similar flash to that in A, marked with arrow. The latency is shorter than in A, and the volley curtailed. On-off-element at 910 x off-threshold. Light indicated by horizontal lines above bottom trace. Time 50 c./sec. faintly on bottom trace, and two intervals of 100 msec. marked by arrows. (Enroth: Acta physiol. scand. 27: Suppl. 100 [1952].)*

The on-discharges fell naturally into two types, sustained ones and non-sustained ones. As Fig. 7 is reproduced a sustained type of on-discharge for which also the frequency of intermittent stimulation is carried beyond the rate necessary for fusion. The details of Enroth's analysis cannot be taken up here. It seems clear, however, in view of the instability of types in the mammalian eye, that at any one intensity, state of adaptation and frequency,
Fig. 7. "Sustained" on-discharge of slowly adapting type showing persistent asynchronous discharge at frequencies above fusion. Fusion frequency, marked by arrow, 22.1 flashes/sec. Signal indicates light upwards. Time 50 c./sec. The records are consecutive. Intensity 1.5 × threshold, no off-discharge seen at any intensity. (Enroth: Acta physiol. scand. 27: Suppl. 100 [1952].)

A pattern will be delivered up the optic nerve in which various response types are represented. Only sustained discharges are likely to be able to sustain the steady state that corresponds to steady homogeneous illumination of extended parts of the eye. It is difficult to assume the higher centres to split up into flicker a discharge fused in the optic nerve. On the contrary, the brain may for various reasons (and at least in pathological states) be incapable of resolving the optic nerve message or, indeed, the ganglion cells may in themselves be incapable of resolving the flickering pattern set up nearer towards or within the receptor layer. Best and Bohnen (1957) find the perceived frequency to lie below the electroretinographic value if very strong lights are used. Some very simple relation between them must nevertheless exist —judging by the experience we have of the cat's retina—though the question merits investigation with simultaneous records from retina and optic nerve. If in pathological states perceived fusion frequency falls below the value set by the retina, it is reasonable to ascribe the cause to these states, e.g., synaptic depression at one or several sites within the path from the bipolar up to the striate area. It should be well known that psychophysical
flicker fusion nowadays is recorded in a variety of diseases and drug afflictions as an indicator of depressions (see the summary by Landis, 1954). However, at the optic nerve level it is possible to make comparisons between flicker fusion in individual ganglion cells or optic nerve fibres on the one hand and the perceived fusion frequency on the other by falling back upon the Ferry-Porter law. This problem was studied by Enroth (1952, 1953). From Adrian’s (1928) work onwards all electrophysiological analyses of sensation go to show that the factor of quantity in perception, which in vision is called brightness, is determined by impulse frequency (and number of cells engaged). Now, since fusion frequency (on the Ferry-Porter law) is a measure of brightness, it should be determined by impulse frequency. Thus, the higher the fusion frequency of any one ganglion cell to any defined stimulus intensity, the greater should be the impulse frequency measured at the moment just before fusion takes place. The individual cells, as we have seen, may present an exceedingly variable pattern but this does not matter as long as for any one cell, however tested, there is this relation between the impulse frequency it delivers and the flicker frequency at which it shows fusion. Enroth’s experiments (1952, 1953) covered both light- and dark-adaptation and a large variety of cell types, on- as well as off-discharges, illuminated at different intensities so that they behaved in many different ways.

Nevertheless, when, as in Fig. 8, the impulse frequencies were measured at the moment just before fusion took place, they proved to be directly proportional to fusion frequency. This remarkable result explains the Ferry-Porter law. It also shows how necessary it is, in discussing perception, to consider the average statistical behaviour of an assembly. All of the ganglion cells responding to flicker frequency \(a\), perceived as fusion, do not have this fusion frequency. Some may have \(a + b\) and others \(a - b\), where \(b\) is some fraction of \(a\) because, as we have seen, the ganglion cells, so far from being standardized in behaviour, tend to vary a great deal. But apparently, at fusion frequency \(a\), a sufficient number of the cells deliver spikes at frequencies which force them to flicker fusion. The ones that discharge at higher frequencies and so could fuse at higher rates will be too few to be able to interfere.

Thus this elegant method of measuring average impulse frequency in the optic nerve by means of studying flicker fusion is presented to the ophthalmological world in two versions, one
Fig. 8. Relation between fusion frequency and initial impulse frequency under varying conditions, as described in text. **Point in circle:** on-discharge; **crossed circle:** off-discharge; **open circle:** unidentified discharge. *(Enroth: Acta physiol. scand., 29: 19 [1953].)*

electroretinographic, the other psychophysical. I know that the psychophysical version on the whole has failed to appeal to the clinician because in the early thirties I tried—without much success—to sponsor it. I had at the time been interested in studying the effects of stimulus intensity and size of illuminated area by the psychophysical approach, a series of papers reviewed in 1936 *(Granit and Harper, 1930; Granit, 1936).* Some interesting papers on clinical application were published by Teräskeli *(1934), Phillips*(1933) and E. Enroth and Werner *(1936)* and in Holland by Hylkema *(1942, 1943 a, b).* The reward was by no means disappointing but the method appeared to be too difficult for the patients to cope with. Also, as stated, a fall in fusion frequency in a given case could, of course, have central as well as peripheral causes. Now the situation is different. We can measure the average electroretinographic response and thus rid ourselves of the complications that arise out of pathological states in the upper part of the visual pathway. The work on animals shows that electroretinographic flicker, at least to a first approximation, determines the events in the optic nerve and optic nerve fusion measures average spike frequency which, being the message delivered for interpretation, is a most essential item of information. The modern electronic arrangements for amplification and control make it possible to study individual flickering wavelets by locking them to the visual stimuli. Thus one should be able to follow in detail how the flicker response changes with the dramatic changes in the
differentiation velocity of the retina accompanying transition from dark- to light-adaptation or vice versa. This, too, is reproduced in perception. Schaternikow (1902), working in the laboratory of von Kries, was the first to point out that during dark-adaptation the fusion frequency fell although the subjective brightness rose. Lythgoe and Tansley (1929) made a thorough psychophysical analysis of these changes and E. Enroth and Werner (1936) reported some interesting results from a study of them in patients (cf. Weekers and Roussel, 1948).

![Graph](image)

*Fig. 9. Double logarithmic plot of fusion frequency (FFF) against light intensity (lux), as determined by electroretinography. Open circles: individual readings of 8 observers. Filled and crossed circles: averages for 3 observers of readings during one or several months. Pupil dilated with homatropin. (Dodt and Wadensten: Acta ophthalm. Kbh. 32: 165 [1954].)*

Fig. 9 from Dodt and Wadensten (1954) shows in double logarithmic plotting the electroretinographic relation between fusion frequency and stimulus intensity in man. The two branches of the curve were known already to Porter. Von Kries (1903) who published a psychophysical analysis of a totally colour-blind observer found only the lower branch preserved. Fig. 10 shows the two branches in a set of psychophysical measurements by Enroth (1952). As stated above, the Ferry-Porter law is good enough to a first approximation over much of the range, if separate constants are chosen for the low-intensity values, ascribed to rods, and the high-intensity range ascribed to cones, according to the interpretation first suggested by von Kries in the work referred to. Dodt and Wadensten (1954), in a similar coneblind observer, only found the lower branch of the electroretinographic curve. The maximal values were around 20 flashes per sec.
Fig. 10. Perceived fusion frequencies recorded by Enroth for her own eye using wavelength 5.000 Å in Hilger-Tutton monochromator over its full range, plotted as log energy. Experiments carried out with the same apparatus as used in her experiments on cat single spikes, the purpose being to see how well the results could be fitted to the Ferry-Porter law, using separate constants for rod- and cone-range. (Enroth: Acta physiol. scand. 27: Suppl. 100 [1952].)

In favour of the classical interpretation of the two branches of the curve illustrating flicker fusion as a function of stimulus intensity are also the electroretinographic experiments carried out by Dodt, Enroth and Wirth in our laboratory, illustrated in Fig. 11. The pigeon, with cone dominance, has only the steep branch of the curve. Guinea pigs, with almost complete rod dominance, have a very small steep branch for which very high intensities are needed, the cat is intermediate, responding more or less like the human peripheral retina but requiring more light energy to reach the cone values.

In electroretinographic work flicker fusion provides a fast and convenient first test before one proceeds to a study of changes of form of individual flickering wavelets, discussed at some length above. In order to increase the sensitivity of the electroretinographic method we (Granit and Wirth, 1953) tried to utilize electrical resonance, a principle later applied independently to patients in this country by Henkes (see e.g. Hamburg Symposium ed. by Sautter and Straub, 1957). This method in many respects is an ideal one for ophthalmological purposes and I will try to explain how it works.

Essentially, the flickering electroretinogram, instead of being recorded by an ordinary amplifier, is recorded by an amplifier that can be tuned or set to respond only to a particular frequency of intermittence. The lower portion of Fig. 12 shows how very narrow bands of electrical resonance can be obtained by commercial resonance meters (in our case a Vibration Analyser made by
Fig. 11. Double logarithmic plot of fusion frequency of the electroretinogram against stimulus intensity in metre candles. Open circles: cat; half filled circles: guinea pig (2 animals); black dots: pigeon. Repotted from data of Dodt and Wirth (Acta physiol. scand. 30: 80 [1953]) and Dodt and Enroth (Acta physiol. scand. 30: 375 [1953]).

Fig. 12. Upper (A): two photographs of electroretinograms of cat's eye. Full dark-adaptation. Stimulation with light of wavelength 5,000 Å (top of visual purple curve) from Hilger-Tutton monochromator. Below, some flicker records. Time 50 c./sec. and light signal below records. Lower (B): some typical resonance bands of tuned amplifier (Vibration Analyser of General Radio Corp., U.S.A.) obtained with output from photo-cell signal to flicker at three constant velocities. (Granit and Wirth: J. Physiol. 122: 386 [1953].)
the General Radio Corp., U.S.A.). Hence, for any chosen flicker frequency, be it then from within the rod- or the cone-range, one obtains a deflexion of a galvanometer indicating magnitude of response. Now, since the amplifier only responds to the selected frequency, it is possible to obtain a very much higher signal/noise ratio than with an amplifier responding to all frequencies. In fact, one can by this instrument measure fusion frequencies with a precision unobtainable from photographic records for which ordinary amplifiers have to be used. Furthermore, it is possible to record very quickly the correct value of the fusion frequency at any desired intensity level and state of adaptation. This should be a great advantage in hospital work and the results of Henkes demonstrate the usefulness of the method very convincingly. This is therefore the method that I think is destined to prove singularly valuable in clinical electoretinography (see Hamburg Symposium for other work [Vanýsek, 1957] in clinical flicker electoretinography). I would like to end by recommending the resonance method as the best one at present available for ophthalmologists interested in this field. In particular I am looking forward to its application to the changes in flicker fusion with state of adaptation, feeling that new aspects of the adaptive process will come to the fore when purely static measurements of dark adaptation thresholds are supplemented with an analysis of the dynamic on-off-components responsible for differentiation velocity. The method is ideal for a rapid survey but samples of the flickering electoretinogram should at the same time be reproduced on the oscilloscope for inspection and photography.

References.