COMMUNICATIONS

NEW CLINICAL TEST OF RETINAL FUNCTION BASED UPON THE STANDING POTENTIAL OF THE EYE*

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THE diagnosis of disturbances of retinal function is often accurate and simple. The affected structure can be inspected by the ophthalmologist, and the patient can give detailed accounts of the changes in his sensation. However, there are very few methods available for the objective investigation of retinal function. The only test which is not directly related to perception is the electroretinogram, ERG, which, in spite of its value in a few conditions, has not so far proved of very general use. The reason for this seems to be that the ERG is basically an index of the function of the retinal neurones, a less sensitive one than the patient's sensation.

This paper introduces another objective test of retinal function. It is based, as is the ERG, upon the measurement of potential changes. However, it differs fundamentally from the ERG in that, while the latter records rapid alteration in retinal nervous activity, this new test is concerned with the slower changes in potential which occur as a result of alterations in the metabolism of the pigment epithelium. The abnormalities detected by this test are therefore different in nature from those which may be demonstrated by any other diagnostic procedure, and the test is of value not only because it is an addition to the techniques available to the clinical worker but also because it sheds new light upon the nature of the disease processes. The technique of the test is to measure the corneo-fundal potential by placing electrodes on the skin medial and lateral to the globe. This method is well known, and is at present widely employed to register eye movements. It has been proved of value in aviation medicine, in studies of reading, in the analysis of amblyopia, and in the differential diagnosis of nystagmus, since it is accurate, rapid, and involves no discomfort to the patient. In previous work the presence of the eye movement potential is thus merely employed as a convenient way of recording mechanical displacement of the eye. By contrast, the present test depends upon an analysis of the nature and variation of the potential itself. The technique of measuring eye movements by monitoring potential changes is usually called electro-oculography, and accordingly we have termed this new functional test the electro-oculogram, abbreviated to EOG.

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The presence of a potential difference between the front and the back of the eye was first demonstrated by du Bois-Reymond (1849). In the normal eye the potential difference is about 6mV, the cornea being positive to the fundus. The eye is, in effect, a dipole with its axis orientated approximately along the visual and optic axes (Miles, 1938, 1939a,b; Leksell, 1939; Kris, 1958). As the eye rotates potential changes may be recorded between electrodes placed across the eye, and many workers have used this method to record eye movements. Thus the extent and frequency of nystagmic and reading movements can be analysed (Marg, 1951; Monnier, 1952; Shackel and Beaney, 1957; Mackensen and Wiegmann, 1959).

In brief investigations the size of the potential recorded varies accurately with the size of the eye movement but this is not true over long periods of time, because the size of the corneo-fundal potential itself is subject to fluctuations. Experimental alteration of the potential may be achieved in many different ways: by pressure (Miles, 1939c,d), acapnia and anoxia (Fenn, Galambos, Otis, and Rahn, 1949), ischaemia (Heck and Pabst, 1956; Stepanik, 1958), by the administration of adrenalin (Kolder and Scarpatetti, 1958) and (in laboratory animals) by the administration of retinotoxic drugs (Noell, 1953, 1958, 1959). These modifications have little to do with the spontaneous fluctuations the nature of which is bound up with the very large changes in the standing potential which are produced by the alteration of retinal illumination. The discovery of the effects of light on the standing potential has been made, apparently independently, by many workers (Miles, 1939a-d; Aserinsky, 1955; Kris, 1958; Kolder, 1959; François, Verriest, and de Rouck, 1955; Ten Doesschate and Ten Doesschate, 1956; Heck and Pabst, 1956; Arden and Kelsey, 1962a). All the clinicians who have made this observation (the last four groups listed immediately above) realised that the fact that the standing potential is altered by light might be of use in the objective diagnosis of eye disease. Unfortunately, the first attempts at the construction of a clinical test preceded an accurate description and analysis of the effects of varying the illumination in the normal eye. The type of test employed was necessarily arbitrary, and failed to exploit the full potentialities of the method. Recently, papers have appeared which firmly establish the basic nature of the phenomena which underly the variations in the standing potential, and it is now possible to describe a test which has already yielded very promising results, and is potentially an extremely powerful ancillary method in the diagnosis of many types of disease.

This paper gives a brief description of the experimental results upon which the clinical test is based (these will be published *in extenso* elsewhere), a detailed description of the test itself, and indicates some of the pathological conditions which give abnormal results. Future papers will be concerned with the detailed analysis of the results in normal subjects, and in specific diseases.

Description of Variations in the Standing Potential

(1) *Spontaneous Variations.*—Both short and long term cyclical variations have been described. The latter form part of the diurnal variation of potential (Kris, 1960) and need not concern us further since during short recording periods fluctuations from this cause are insignificant. However, whenever the standing potential is measured, cyclical variations in the amplitude of the potential occur with a period of about half an hour (Kolder, 1959). As the recording session continues the amplitude of the waves decreases and a baseline level is reached, usually after about two hours. These fluctuations are probably not truly spontaneous (see below) and are of importance only in that they obscure the baseline potential, the value of which is independent of the retinal illumination (Kolder, 1959).

(2) *Influence of Change of Illumination on the Magnitude of the Standing Potential.*—When the dark-adapted retina is reilluminated, a complex sequence of alterations in the standing potential occurs. These are demonstrated in Fig. 1. There first occurs an electroretinogram, but this rapid potential change is not apparent in the Figure, which shows very much slower events. The first change in the standing potential is a transient fall (*a*), but after about 90 sec. the potential begins to rise. This continues for about 8–9 min., when the potential reaches a peak (*b*). This maximum has been named the first light peak. It is relatively constant in amplitude and in
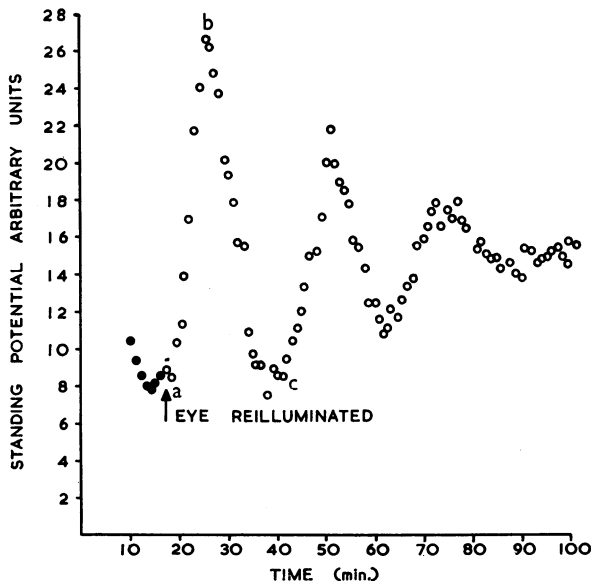

FIG. 1.—Oscillations of potential after reillumination of the dark-adapted eye. Full symbols imply reading taken in darkness. Note initial transient fall in potential (*a*), first light peak (*b*), and first light trough (*c*).

timing, and is of importance in the clinical test.   In the minutes which follow the first light peak, the potential falls to a very low level (c) which is called the first light trough.   After this, the potential continues to rise and fall in a series of cyclical oscillations which are similar to the spontaneous ones described above.   Though this complicated series of potential oscillations is initiated by reillumination, this does not mean that the entire sequence is dependent upon light.   It has been shown (Arden and Kelsey, 1962a) that only the first light rise is light-dependent, and the amplitude of the peak varies, within limits, with the duration of prior dark-adaptation and the intensity of the reilluminating light.   The first light rise may therefore be separated from the rest of the complex series of potential changes.

When retinal illumination is suddenly decreased, the standing potential undergoes another sequence of potential changes which are shown in Fig. 2. There is a transient increase in potential, followed by a decrease to what has been named the first dark trough (a).   This low level is also of importance in the clinical test.   It is followed by a series of potential changes which, again, are similar to the spontaneous ones.   At first sight it might appear that the potential changes which occur when retinal illumination is decreased are merely a reversal of the processes which follow reillumination of the retina. However, this is quite wrong.   The amplitude of the first dark trough does not vary with change in light intensity.   Any adequate reduction in light intensity produces dark troughs of equal size; the dark trough process is an all-or-nothing event, quite unlike the light peak, which is graduated in amplitude.   The dark trough differs from the light rise in other respects.
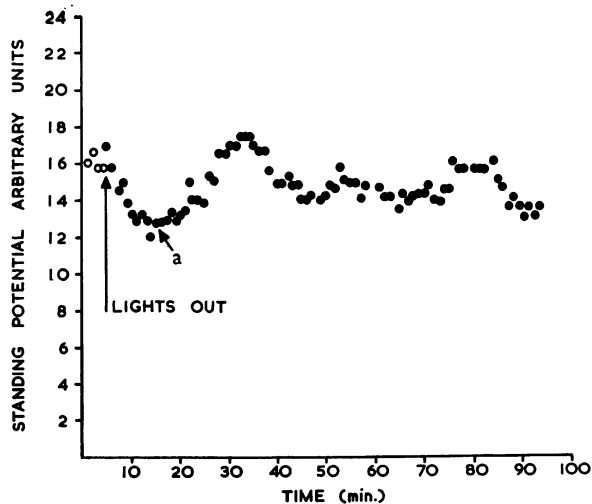

FIG. 2.—Oscillations of potential after decrease in retinal illumination. The first light trough (a) is succeeded by a super-normal phase and later by ill-defined oscillations. Note that potential changes are smaller than for reillumination.

There does not seem to be any relationship between the period of prior light-adaptation and the size of the dark trough, although (see above) the amplitude of the light rise is dependent upon the length of the previous dark-adaptation. Moreover, the decrease in the amplitude of potential which follows reduction of illumination is extremely variable. The reason for this is that a reduction in light intensity always causes the potential to assume a minimal value (that of the first dark trough) regardless of any former level. The fall from the baseline value is about 30 per cent., but if at the moment the lights are turned out the potential is greater or less than the baseline value, the dark trough will be more or less pronounced. One can produce enormous "dark troughs" by turning the lights out at the crest of the light peak (Fig. 3).
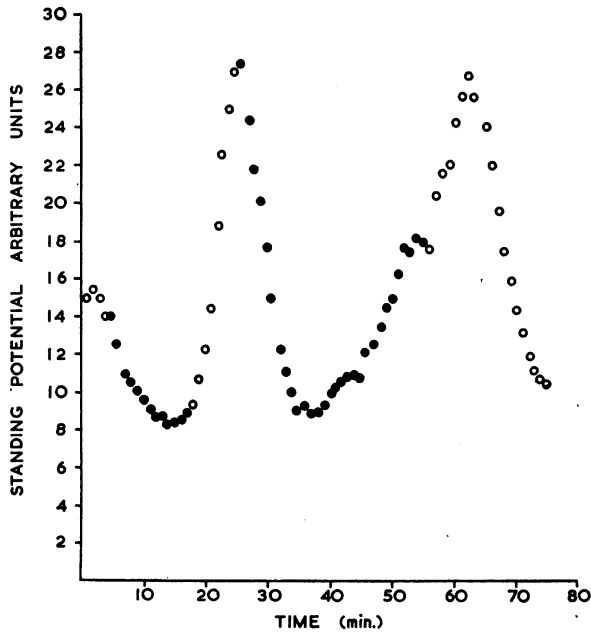

FIG. 3.—Effect of altering retinal illumination when potential level is changing. The potential rises or sinks to maximal or minimal values, which are (within limits) independent of the potential at the moment of alteration of illumination. When the lights are turned off at the first light peak, the subsequent fall in potential is not obviously affected by the change in illumination.

If the lights are turned out at the moment of the first light trough (Fig. 4, overleaf) there is no further fall of potential. It would seem therefore that reduction of illumination merely rephases a complicated series of cyclical potential changes. Increase of illumination may also achieve the same result (see Arden and Kelsey, 1962a) but in addition it produces a new potential change, the first light rise.

Although the alteration of illumination leads to the development of a new cycle of potential changes, all effects of previous illumination are not completely expunged immediately the lights are turned off (Arden and Kelsey,
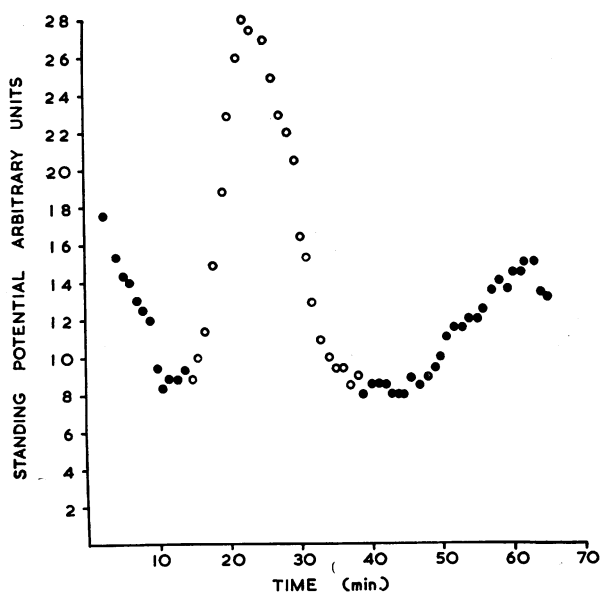
FIG. 4.—When the lights are turned out at the first light trough, no further fall in potential occurs, demonstrating that light trough and dark trough levels are identical.

unpublished).   However, providing the light intensity is not extremely high, this "memory" is negligible.   It is, however, on account of this phenomenon that in the clinical test the patient is prepared in a room lit only by normal artificial light.

All experiments must of course begin with a light-adapted eye, though for ease in understanding, the description above begins with the effect of reillumination.   It is convenient to summarise the sequence of potential changes which occur in the course of an experiment.   One begins with the subject light-adapted, and the standing potential fluctuating in a manner which is wholly unpredictable.   When the lights are turned off, the sequence of potential oscillations is stopped and rephased.   The potential decreases, and a dark trough develops.   This lower level of potential is a fixed value. Subsequently the potential oscillations begin once again.   If now the eye is reilluminated, the potential rises to the light peak.   This level is a maximal value determined by the light intensity and duration of the prior dark-adaptation: it does not depend upon the preceding potential level.   See Fig. 3—the two light peaks reach approximately the same amplitude, though at the moment of reillumination, the potentials are very different.

The sequence just described contains two fixed points, the dark trough and light peak, which are fixed in relationship to change of illumination, and not dependent upon the spontaneous fluctuations of potential.   This, as can be seen below, is the minimum necessary for the development of a clinical test.

(3) *Origin of the Potential.*—In animal experiments the standing potential has been found to consist of several fractions, but the bulk is generated in

the pigment epithelium (Noell, 1953; Heck and Pabst, 1956; Brown and Wiesel, 1958). In human eyes, it has been shown that the greater part of the potential is generated in the posterior segment, and remains after destruction of the retina (Arden and Kelsey, 1962b). On the other hand, the light rise occurs as a result of light absorptions in the retinal rods themselves, and therefore is due to some interaction between receptors and pigment epithelium.

(4) *Other Influences on the Standing Potential.*—Many modifications of the internal environment can alter the standing potential. Ischaemia reduces, but does not abolish it. On the other hand, no light rise whatsoever can occur during ischaemia (Arden and Kelsey, 1962b). This finding is extremely important, for it demonstrates that the light rise is dependent upon metabolism. In view of the preceding paragraph it becomes clear that the metabolic function in question must be related to the absorption of light by the receptors, and also a process which is carried on in the pigment epithelium. The processes involved in the breakdown of visual purple to vitamin A, and its subsequent re-synthesis admirably fit these requirements (Arden and Kelsey, 1962b).

Technique of the Test

Theoretical Basis.—The potential difference between the front and the back of the eye is measured by placing an electrode on either side of the eye and recording the change in potential which occurs when the eye is rotated. If the eye always rotates through the same angle, the change in potential difference between the two electrodes caused by the movement will be a constant but unknown fraction of the total standing potential and will vary as the total potential. It has been shown that except for very large excursions of the eyes, there is a linear relationship between the angle of deviation and the potential recorded (Miles, 1939a–d; Leksell, 1939; Kris, 1958a,b).

The voltage measured is an arbitrary fraction of the whole standing potential, and is not constant between patients, nor even from one eye to the other of the same person, due to variation in the positioning of the electrodes. Much of this is unavoidable, owing to differences in bone structure, especially in the case of the medial electrodes, and we have found such great variability between subjects that it has been considered of no value to calculate the actual potential recorded in an individual case. In a series of cases the calculated mean potential values may show a significant difference from the normal mean. The variability may be reduced if bi-temporal electrodes are used and fitted to the subject with a special jig (Shackel, 1960).

The Patient.—The patient should be seated as comfortably as possible, but the head should be fixed. It has been found that a dental chair is satisfactory. The head-rest locates the head quite adequately, and even in experimental sessions a dental bite effects no improvement. The chair faces a viewing box on which at eye level are placed two fixation lights, subtending an angle of about 34·5° at the eye.

Electrodes.—The potential changes are picked up separately from each eye by electrodes which are attached to the skin overlying the bony margins of the orbit opposite the lateral and medial canthi.   An indifferent electrode is conveniently placed on the forehead.   The electrodes are non-polarizable silver-chloride balls sunk in plastic flanges, which are about 0·5 cm. in diameter.   When the flange is pressed against the skin, the electrode is brought into approximation to the skin and contact is made through commercial electrode jelly.   Extensive preparation is not required.   The plastic flange is held against the skin with adhesive plaster. It has been found best to use colostomy plasters which are waterproof and remain tacky in the presence of moisture.   Discs of about 2 cm. in diameter are perforated, and the plastic flange pushed through the resulting "button hole".   The ensemble is stuck to the skin, and adhesion is adequate for the duration of the test.   It is important that the electrodes should be secure before the test begins: they cannot afterwards be replaced if they later become unsatisfactory.   Poor contact is revealed by mains pick-up, and also by bizarre-looking records.   These are caused by movement of the electrodes on the skin surface.   The exact type of electrode is important.   Bared silver wire secured by Collodion gauze is equally effective (Kris, 1958).   Normal EEG electrodes are not to be recommended.   They are so large that they cannot be placed close to the canthi, and the potential recorded is therefore much reduced.   Similarly, the suction electrode (Shackel, 1958, 1959) cannot be fastened to the side of the nose.   The more elaborate precautions described by Shackel and Beaney (1957) and Hallpike, Hood, and Trinder (1960) are unnecessary since A.C. amplification is employed.

Ocular Movements.—The patient makes voluntary horizontal eye movements between two fixation points.   The frequency of the movements is not predetermined, the patient being asked to move his eyes as frequently as is comfortable.   In almost all cases this produces about two excursions per second.   Movements tend to be irregular at first, but practice for a minute or so ensures regular movements from which good recordings can be obtained.   In the test itself, the patient is asked to make these eye movements once a minute, for a period of about 10 sec. so that he is active for only a small proportion of the duration of the test.   The angular deviation of the eyes should be as large as feasible so that large potentials may be recorded.   The limit (about 40°) is set by the ability to look from one point to the other in a single saccade.

Sequence of Change of Illumination.—The patient enters the test room and sits, with normal artificial room lighting, facing the unlit viewing box (see below). Preparations for the test take a few minutes, and during this period the influence of prior illumination wears off.   Recording begins, and after a couple of minutes, the room lights are switched off, so that the only light comes from the red fixation spots. Readings are taken every minute for 12 minutes.   The lights in the viewing box are then switched on and recording continues for about another 10 minutes.

Retinal Illumination.—In the first experiments the patients merely looked at a painted wall, which was evenly illuminated by the overhead lights.   Later a special viewing box was built, since it was appreciated that the greater the light intensity the bigger the light rise.   This box contained eleven fluorescent tubes, spaced 5 in. apart.   The box subtended about 60° at the patient's eyes, and since the patient

moves his gaze across the large illuminated area, the greater proportion of the retina is evenly illuminated. The advantage of this viewing box was that the light output was high, and could be altered electrically without changing the colour temperature of the source. A maximal retinal illumination of 80,000 scotopic trolands was available, but this is too great for most patients to bear.

The size of the light rise depends upon retinal illumination, and therefore upon the diameter of the pupil. In experimental sessions we were able to use mydriatics and ensure that the pupils remained maximally dilated when the viewing box was switched on. However, there are certain difficulties in following this procedure with patients. It is most uncomfortable to view a large and very bright area with dilated pupils; lacrimation and orbicularis spasm result. Furthermore, it is not sufficient to instil one or two drops of homatropine and cocaine into the conjunctiva. Unless the drug is applied several times, and reinforced by a sympathomimetic agent such as phenylephrine, the pupil will constrict when the viewing box is turned on. Again, in some patients the pupils cannot dilate (synechiae). Even if one is successful in dilating the pupil, after the test the instillation of eserine will not restore the patient's accommodation. In practice then it has been found that attempts to ensure a uniform and maximal dilatation of the pupils are unpleasant for the patient, and are often inefficient. We have therefore abandoned the whole idea, and worked with normal and variable-sized pupils. This has the disadvantage that the light rises recorded are smaller than would otherwise be the case. On the other hand, changes in pupillary diameter can largely compensate for changes in the intensity of the light source (see Arden and Barrada, 1962).

Amplification and Display.—Since the test is carried out with the patient sitting near a battery of arc-lamps, it might be thought that it would be difficult to eliminate mains pick-up from the records. This is not the case. The potentials recorded are relatively very large, and the electrode system symmetrical, so that a balanced differential input stage completely rejects pick-up. It is convenient to use a pre-amplifier with top cuts and time constants so that a final band width of 50–0·5 cycles per second is achieved. Any main amplifier and display unit can be used— every commercial ECG is potentially suitable though since measurements are to be made from the record it is desirable to have rectilinear recording with good linearity. The apparatus used in the present work was an ink-spraying machine (Mingograph).

Records and their Measurement.—The eye movements were recorded as a series of saw-tooths. The steep vertical deflections represent the eye movements, and the slower rising or falling phases, the decay due to the time constant of the amplifiers. The speed of the saccade is about 220°/sec. (Mackensen, 1958), and for eye movements of 40°, a 2 sec. time constant is ample. This would not be true if the patient was asked to make large (and longer lasting) eye movements (see for example, François, Verriest, and de Rouck, 1955, 1956a). The vertical excursions will be found to vary slightly in height, so that between six and ten may be measured and the mean amplitude found. Alternatively, the average excursion may be found by a line-drawing technique. A plastic ruler is laid along the trace, and moved till it lies on the visually estimated points where, on the average, the vertical deflections begin, and a line is drawn. A similar procedure is followed for those points where the vertical deflections end, and the distance between the two ruled lines gives a

very good average of the mean deflection. This method is subjective, but surprisingly accurate, and very rapid. Should the eye movements be much interrupted by saccades and blinks, it is the best way to measure the traces for otherwise a biased sample of "simple type" records will be selected for measurement. When the test is over, the record is calibrated against a known potential and the recorded excursion may then be expressed in terms of microvolts per degree of eye movement.

Difficulties in the Test, and Possible Modifications

Visual Acuity.—If the patient is able to see the fixation lights the test can be performed. The eye movements may not be precise, but the averaging of several records overcomes that difficulty. If vision is very poor, other methods may be employed to produce the movements. Nystagmus can be induced, or the patient may be asked to make the biggest horizontal eye movements that he can. This last method is inaccurate, however. In one totally-blind patient we obtained reproducible eye movements by asking him to look towards his index fingers which were supported a fixed distance apart.

Opacities in the Media.—If these are very dense, retinal illumination may be so much reduced that the test is unreliable. However, most opacities will merely cause better diffusion of light throughout the retina. The variability of illumination due to pupil size is a more serious complication, but in spite of this theoretical objection a valid clinical test is possible.

Irregular Records.—Some few patients seem incapable of moving their eyes regularly, or making clean movements, but no record has proved completely useless from this cause. It is more common to get large swings in the baseline due to poor fixation of the electrodes. These occur when the eye movements move the skin underneath the electrodes. It seems likely that electrodes which made contact merely by pressure on the skin would prove unsuitable for this reason.

Tears.—Care must be taken to ensure that tears do not reach the electrodes. If this happens, there is a low resistance pathway to the globe itself, and very large potentials will be recorded. Lacrimation tends to occur when the dark-adapted eye is reilluminated with intense light, and artefacts due to this cause can best be avoided by covering the electrodes with waterproof plaster, and by avoiding intense light.

Apparatus.—The apparatus used in this work is the simplest possible, and no more elaborate device is needed. However, the labour of analysis of the records can be much reduced by employing slow continuous recording, so that all the excursions due to eye movements fuse, and the resultant envelope is in fact the graph which otherwise has to be calculated. Apparatus which will produce such a record has been described by Tonnies (see Kolder and Scarpatetti, 1958). The test, as described above, involves the patient's cooperation, and is therefore imperfect. It is theoretically possible to measure the standing potential of the eye by direct D.C. measurement. This demands the use of special electrodes, which rotate as the eye rotates. These are now being developed.

Procedure in the Test.—Once the patient has been connected to the apparatus, it is a good idea to take several readings with the room lights on, to ensure that nothing will later go wrong with the electrodes, and that the patient can cooperate. The lights are then turned out for 12 minutes and readings taken every minute. With a little practice it is possible to work out the results in between each reading, and to see how the test is going. Rarely, the potential is still dropping after the 12th minute: one may then continue the test, until the minimal level has obviously been achieved. When the lights are turned on again, one can continue recording till the light peak has been passed. The test over, the results are graphed. It is not necessary to take so many readings as described, but the procedure is more accurate if one does so. Even with the time necessary for analysing the result, the test takes only about half an hour.

Results

Normal Eyes.—Typical graphs from normal eyes are shown in Figs 1, 2, 3, 4. In other figures the lower limit of the normal eye is shown. (For a detailed discussion of normal results, see Arden and Barrada, 1962). The results may be analysed as follows:

Dark Trough.—The test begins at the moment when the lights are turned out. It cannot therefore be appreciated that the subsequent decline of the potential is actually caused by the reduction of illumination. For figures which demonstrate this see Arden and Kelsey (1962a). The dark trough is reached after an average of 9·6 min. but this varies greatly. The potential is beginning to rise when 12 min. later the retina is reilluminated, and after an initial slight fall in potential, there is a rise to the first light peak, 8 to 9 min. after reillumination. A smooth curve is drawn through the points, and the trough and peak values are taken from this. The departures of the points from the smooth curve are larger than the apparent error of estimating each point, so that either the potential rises discontinuously (which seems unlikely) or there are small systematic sources of error. The causes of these have not been determined. The voltages are not the same in the two eyes, and, as shown elsewhere (see Arden and Barrada, 1962) vary so widely that in an individual case they are not of much significance. The ratio $\frac{\text{peak voltage}}{\text{trough voltage}} \times 100$ does not depend upon the position of the electrodes and gives an index of the functional capacity of the pigment epithelium; in normal eyes this ratio is greater than 185 per cent.

The other variable we can measure is the peak time; in normal eyes this is 7 to 9 minutes after reillumination and is often delayed in abnormal eyes. Since readings are taken only once a minute, only very gross changes in peak time are of any significance.

Abnormal Eyes.—Abnormal electro-oculograms have been obtained from a variety of pathological conditions affecting the retina and choroid.

Usually the departure from normality consists of a very small light rise. The dark trough seems relatively less affected, especially in cases of vascular disorders.   So far most of the work has been directed towards discovering how many different diseases give abnormal results, and as yet the number of examples within each type is small.   There has naturally been no opportunity (except in a very few cases) to relate the course of a disease to the change in the EOG.   The results described below are therefore preliminary.

Retinitis Pigmentosa.—The EOG of this condition is instantly recognizable, for there is usually no alteration of the standing potential, either with illumination, or spontaneously (Fig. 5).   The EOG is undoubtedly an easier test to apply in young children who can cooperate than is the ERG (not however in infants), and we prefer to use it in diagnosis.   In very early cases of retinitis pigmentosa, a scotopic ERG, perhaps of fair size, is sometimes found.   Such patients are by no means completely night blind and the degree of abnormality shown by the ERG is not great.
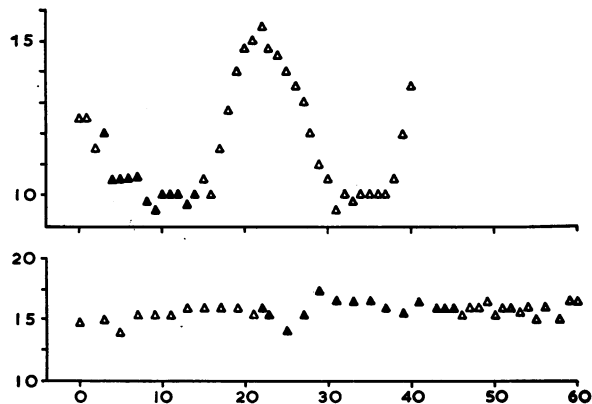

FIG. 5.—Abnormal EOG in retinitis pigmentosa.
     Upper: Very early case in a child of 14, with almost normal dark-adaptation and a large ERG.   The EOG is abnormal, since the light rise is small, increasing only about 50 per cent. above the dark trough level.
     Lower: Typical case with absent rod vision.   The potentials do not alter significantly throughout the test.

Nevertheless, in two such patients we have found grossly abnormal EOGs and it seems possible that the diminution of the light rise may be the earliest manifestation of the disease.   So far, we have not investigated the EOGs of unaffected carriers of this condition.   The actual potential recorded from retinitis pigmentosa eyes is low, as has been previously stated (Riggs, 1958) but it is not so very small compared with the normal baseline levels, and it seems likely that previous workers have measured potentials under

conditions which favoured the recording of large potentials from normals, *i.e.* during the light rise.

Retinal Detachment.—In cases of recent total or sub-total detachment there is no dark trough or light rise (Fig. 6). Instead, the potential falls when the eye is re-illuminated. In such cases there is evidence of residual, though disturbed, retinal function, for a small ERG can be recorded, and the patient reports the perception of light. The EOG shows a more complete disturbance than do other tests of retinal function which are based upon the neural activity of the retina. In long-standing cases of retinal detachment, where there is no retinal function remaining, the standing potential is very low, and invariant. We have not yet been able adequately to compare EOGs before and after surgical reposition, but there are indications that operation is not followed by the return of a normal EOG; this is scarcely surprising, since the EOG is derived from the retina as a whole and the surgical procedure is designed to cause damage. In cases of partial detachment, the EOG light rise is present but is abnormally small, and it seems possible that one might be able to correlate the fraction of retina detached with the degree abnormality of the EOG. We have seen one case of retinal cyst: this presents a picture identical with that of a detachment.
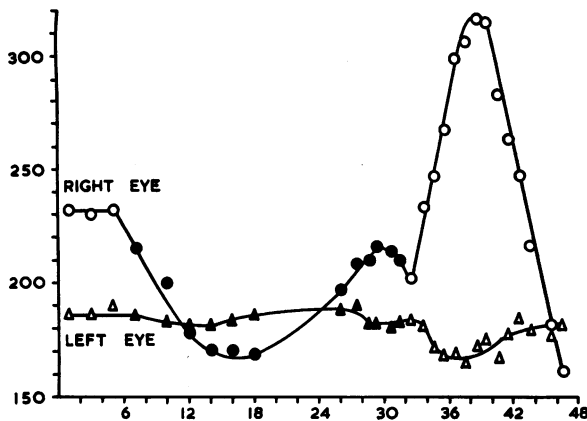

FIG. 6.—Abnormal EOG in retinal detachment. Total shallow detachment caused by boxing injury to left eye. Right eye is normal and serving as control. Note that period of dark-adaptation is non-standard. The left eye with the detachment produces no dark trough and the light rise is replaced by a fall in potential. Ordinate scale in μV—Note minimal potentials same for both eyes. The detached retina was partially functioning—an ERG could be recorded. In old detachments the standing potential is reduced.

As a routine, the "normal" eye of cases of detachment has been tested, and in these a high percentage of abnormal EOGs can be detected, but in the short period of our investigation no detachments have occurred in these eyes.

Myopia.—Many of the patients who had detachments were myopes, and their condition was related to the myopia. We therefore tested a series of high myopes. In scarcely any of these is the light rise as great as the normal mean, and in many it is about or below the normal lower limit. In those cases where myopic degeneration is obvious, very low light rises occur. It is quite certain that the EOG is a much more certain detector of myopic changes than the ERG. It seems possible that the EOG result indicates a lack of functional connexion between retina and pigment epithelium, and might reflect the increased likelihood of actual physical contact being lost as well—*i.e.* of a detachment occurring.

Choroidal Lesions.—In cases of well-marked choroidal sclerosis, the EOG light rise is very small (Fig. 7), and the potential itself is probably reduced.
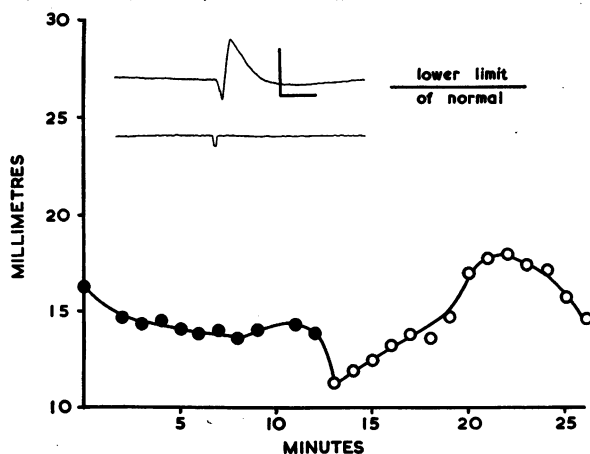

FIG. 7.—Abnormal EOG in choroiditis. Note that light rise is almost absent though ERG (inset) is normal—calibration bars 200 msec., 250 μV. Normal lower limit of light rise shown by bar.

This does not apply in cases of old choroiditis, where there is a small area of scarring and atrophy. In these cases, an insignificant area of retina and pigment epithelium has been destroyed. However, the picture is quite different in acute disseminated choroiditis. In the majority of such cases that we have seen the EOG light rise is very much reduced. This is not due to the vitreous haze preventing light from falling on the retina. The same patients have large, perhaps hypernormal ERGs (see Henkes, 1953; Henkes and van der Kam, 1954; Henkes, van der Kam, and Westhoff, 1954). Though the neural activity of the retina continues, there is therefore evidence of a rather widespread impairment of function in the pigment epithelium. The abnormal findings in the acute stage of the disease are most striking, and in contrast to those found in the quiescent phase. We cannot yet say whether the severity of the disease can be related to EOG findings, or if the EOG abnormality might herald a recrudescence, but follow-up studies are now in progress.

Vascular Lesions.—In experimental studies it was shown that the light rise cannot occur in the ischaemic eye, and that experimental procedures which might be expected to modify the circulation affect the standing potential. Hence one might hope that abnormal EOGs would be recorded in eyes with a vascular pathology, and this has in fact proved to be the case. In fact, very slight degrees of vascular insufficiency or abnormality affect the EOG in striking contrast to the ERG which is often not affected until large areas of retina are irreversibly damaged. We have furthermore been able to demonstrate that the EOG returns towards normal, and even recovers completely, as the clinical picture improves.
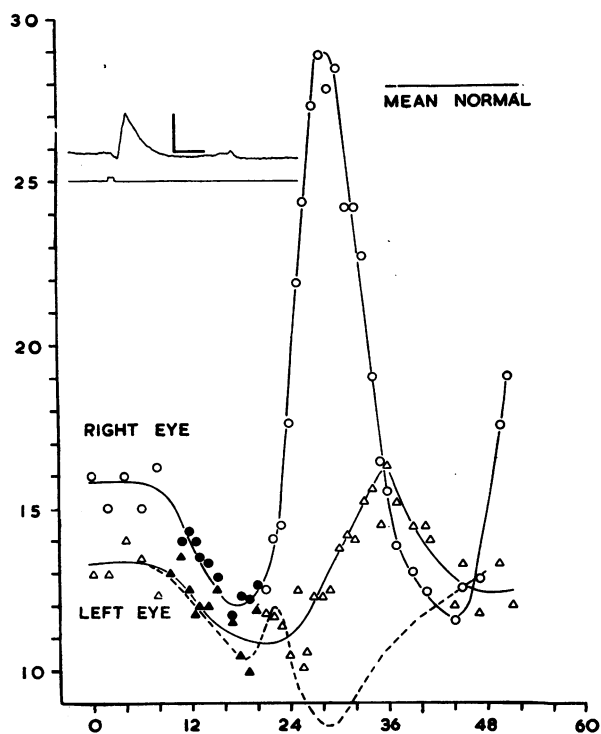

FIG. 8.—EOG in venous thrombosis. Right eye, normal control. Left eye, venous thrombosis, continuous line partial, dotted complete. The ERG (inset) normal during partial thrombosis. For further description see text.

In other patients, the results suggest that the EOG may have a prognostic significance. The following case history is illustrative.

A clerk aged 50 complained of sudden blurring of vision in the left eye. The right cornea was scarred and opaque, and the patient reported that he had suffered from absolute glaucoma in 1946, after which the eye had been useless.

Examination.—The left eye showed signs of central venous occlusion, with raised tension, haemorrhages, and a visual acuity of 6/24. In the right eye no observation of the fundus was possible, but light projection was good.

He was treated by rest in bed and anticoagulant therapy, and was seen at the electro-diagnostic clinic in May, 1960. At this time, the tension was normal in the left eye, and the field full, but the picture of a venous thrombosis was present. The EOG of the left

eye was grossly abnormal, the light peak being only 143 per cent. of the dark trough and the peak time 14 minutes. The right eye surprisingly enough gave a normal rise.

As a result of this test, it was questioned whether the right eye had suffered as much retinal damage as had previously been presumed and the patient returned to the clinic for further examination. At this time the venous thrombosis in the left eye appeared to be resolving very satisfactorily and the visual acuity was 6/18, though in view of the later occurrences, it is significant that the patient denied that his vision was improving. Bilateral ERGs and EOGs were performed, and in spite of the clinical findings, the EOG of the left eye was unchanged, grossly abnormal. This was in striking contrast to the ERG, which was normal in both eyes (Fig. 8). 3 days after the test, the patient was discharged, and anticoagulant therapy was stopped, as it was expected that full recovery would occur. The normal electrical findings in the right eye strongly suggested that the original diagnosis in 1946 had been mistaken (see above), but it was not considered worthwhile to graft the opaque cornea, since normal function could be expected from the left eye once the thrombosis had resolved. At this time it was noted that the EOG failed to correlate with the clinical findings; one week after discharge, the patient lost all vision in the left eye, through a total thrombosis, and, when he was seen again, vision was 6/60, and the left EOG was even more abnormal, the light rise being replaced by a fall in potential. Some recovery followed this second thrombotic episode, and the right cornea was finally grafted a year later. The left EOG at that time was still grossly abnormal, but the light rise was greater than when the patient was first seen, in spite of the poor vision.

Hypertensive changes in the retina are associated with abnormally small light rises, though the ERG may be normal (Fig. 9).
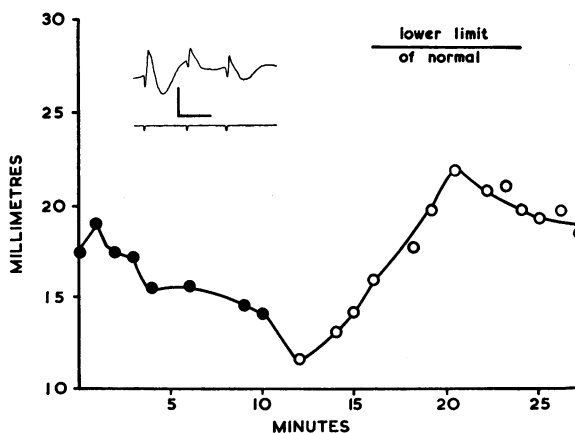

FIG. 9.—Abnormal EOG in hypertensive retinopathy. This patient had scanty haemorrhages and exudates. The ERG (inset) is normal, the EOG abnormal.

Elevated blood pressure *per se* (in benign essential hypertension) does not necessarily cause an abnormal EOG. We cannot yet say whether the abnormal results in cases of vascular lesions are all due to the same cause. For example, the oedema associated with Eales's disease may account for the abnormal electrical result, though arteriosclerosis must cause a low EOG merely through plain vascular insufficiency. In a case of carotid occlusion, it has been possible to demonstrate abnormalities in both eyes, which were neatly correlated with the degree of functional impairment discovered by ophthalmodynamometry (Lowe, 1961).

Other Conditions.—Chloroquine retinopathy produces a specific alteration in the EOG. Diabetic retinopathy causes a great decrease in the light rise, and the electrical abnormality seems to be closely related to the severity of the condition, judged by clinical findings. Sarcoid deposits in the retina also cause a decreased light rise. Cases of early glaucoma show abnormalities, but this may be consequent on retinal damage or concurrent arteriosclerosis. Finally, we have seen several cases of middle-aged people suffering from field defects for which there was no obvious cause. In these we have discovered abnormal EOGs and this serves to place the lesion in the retina, although its nature remains uncertain.

Discussion

Relationship of the Present Test to Other Work on the Standing Potential.—François, Verriest, and de Rouck (1955, 1956a,b) have previously elaborated a clinical test based on the standing potential, which is superficially similar to the one described above. They light-adapted the eye for 5 minutes, and then measured the potential as it declined during subsequent dark-adaptation. This procedure was followed because it was suspected that the potential change was related to dark-adaptation but a close correlation could not be found. After their work had appeared, experimental analysis of the normal potential changes revealed that their method was not ideal. Should the patient come from bright sunlight, the "light-adaptation" may cause a decrease in retinal illumination, and a dark trough will begin. During the subsequent dark-adaptation, there will only be a minimal fall in potential. However, should the same patient come direct from a dimly-lit waiting room, the adapting source will trigger off a large light rise, and this will continue for several minutes in the dark, after which there will be a large drop in potential. Examples of both conditions can be seen in François' papers, though, of course, most patients come somewhere in between. But in any event, the potential drop is measured from a point which is itself variable, and only what is here called the dark trough is measured. Our figures show that the dark trough usually represents a much smaller change in potential than the light rise, so that on this score alone the present method is preferable. It has, moreover, two other entirely overwhelming advantages: first that the test produces a fixed level of potential from which subsequent measurements may be made, and secondly that, in abnormal eyes, the light rise is affected to a greater extent than the dark trough. It is for these reasons that the present test yields dramatic and consistent results which confirm many of the previous authors' findings (François and others, 1955, 1956a,b; Ten Doesschate and Ten Doesschate, 1956, 1957).

Nature of the Process causing the Light Rise.—At the moment it is quite impossible to pin-point the exact process which causes the light rise, but there is a substantial amount of general information. The time course of the potential change is very slow, so that it can have no direct relationship with

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neural activity.   Furthermore, pathological changes in the light rise occur independently of abnormalities in sensation.   But when light falls on the retinal rods, it actually destroys the visual purple they contain, and this must be replaced by active metabolic processes.   The pigment epithelium has long been known to be concerned with the synthesis of visual purple (Kühne, 1878), and recently (Dowling and Gibbons, 1961) it has been demonstrated that the vitamin A fragment of the degraded visual purple molecule actually travels to the pigment epithelium, where the metabolism takes place.   It is here that the light-rise potential develops (Arden and Kelsey, 1962b).   The factors which one would expect to be necessary for a normal light rise are then:
  (1) Functioning rods;
  (2) Functioning pigment epithelium;
  (3) Contact between neural and pigment layers;
  (4) Adequate choroidal blood supply.
In practice, abnormal EOGs may be found in diseases where each one of these conditions is not fulfilled.

Relationship to the ERG.—The present test is not intended in any way as a rival to the ERG, for it investigates an entirely different function.   It rather supplements it, for there are conditions where both are affected and others where the EOG only is disturbed, so that we have the possibility of making differential diagnoses on electrical evidence.

Value of the Test.—No final pronouncement can of course be made, but our preliminary experiences strongly suggest that the EOG will be of great use in elucidating the mechanisms of certain disorders, in diagnosis, and also perhaps in prognosis.   The test enjoys the great advantage (which it shares with the ERG) that it can be used under conditions in which the fundus cannot be seen.   It suffers the disadvantage (also shared by the ERG) that it is a general test of retinal function, and cannot provide information relating to the fovea alone.   Another peculiarity, which is not shared by the ERG, is that abnormal results are given by an enormous range of diseases, and that trivial abnormalities may show up, as in the case of some myopes.   Re-illumination of the dark-adapted eye causes the rapid turnover of visual purple, and whatever mechanism causes the light rise is made to work at its maximal rate.   In the eye, as in all structures, there is plenty of reserve capacity, and light rises smaller than normal result from deficiencies which usually do not cause any obvious adverse effect on the organism.   The best analogy to the light rise is perhaps the pack-test of circulatory function employed in cardiology, which is an entirely non-specific but sensitive index of circulatory function.

Summary

  (1) A description is given of the changes which occur in the standing potential of the eye when retinal illumination is altered.

(2) Electrophysiological experiments which have permitted the identification of the site of origin of the potential, and have analysed the mechanisms which are related to the alteration in potential, are briefly reviewed.

(3) A clinical test elaborated from these experiments is described in detail.

(4) The test has been employed in the investigation of many retinal diseases, and abnormalities have been found.

(5) An attempt is made to assess the value of the new test and to relate it to other clinical electrophysiological findings.

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