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The Pattern Electroretinogram

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Summary

Physiological experiments and the exploitation of clinical conditions have provided compelling evidence that retinal ganglion cells and other inner retinal structures generate the pattern ERG (PERG). As an increasing number of clinical reports have been published some contradictory findings have been reported. These may be ascribed to variation in recording and measuring techniques. The PERG consists of two major portions, the early positive and the following negative component which can be investigated separately if the stimulus conditions allow isolated (or "transient") responses to be recorded. Care has to be taken in positioning the reference electrode, maintaining accurate refraction, and the influence of pupil size must be considered. Furthermore the PERG is contaminated by a luminance component which may be generated in the outer retina. The size of this increases with low spatial frequency (large check-sizes) and high mean luminance. The PERG permits the examination of an additional level of the retina and helps the understanding of pathophysiology of various eye diseases, and is of clinical importance in routine diagnosis and assessment. In glaucoma the PERG amplitude is often reduced before it is possible to detect a scotoma and it is therefore an important prognostic indicator in patients with ocular hypertension. In diabetic retinopathy, retinal ischaemia sufficient to lead to the pre-proliferative state can be demonstrated. The PERG also has a major clinical role in examining localised retinal pathology. If combined with VECP recording, it greatly extends the interpretations possible, since not only can damage to the optic nerve be detected by both tests, but the normal PERG in the presence of an abnormal PVECP implies that the losses are confined to the central pathway.

The ERG evoked by flashes of light

Component analysis

For over 100 years it has been known that a flash of light will elicit an electrical response from the human eye, the electroretinogram (ERG).[1,2] An acceptable clinical recording technique was developed by Riggs[3] and Karpe[4] who devised corneal electrodes mounted in haptic contact lenses, and it became apparent that the ERG was useful in the diagnosis of retinal disease. Since then, great efforts have been made to identify the components of the ERG and the cellular origins of the signals.

The major waves of the ERG were named in order of appearance a-, b-, c-, and d- waves (the off response). Granit's[5-7] classical analysis showed how three processes that he termed PI, PII and PIII combined to produce the ERG. The a-wave corresponds to the onset of the cornea-negative PIII and is related to the photoreceptor potentials.[8-14] The b-wave is a large cornea-positive ERG component which is related to

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Granit's PII. Faber[15] first suggested that the b-wave reflects the extracellular current which follows local depolarisation of the radial orientated Müller cells. Miller and Dowling[16] and Miller et al[17] recorded intracellularly from every retinal neurone. None of the responses resembled the b-wave. However, the transmembrane voltage change of the Müller cell (at least in some circumstances) was similar to the b-wave of the ERG. Kline et al[18] and Oakley et al[19] showed that the Müller cell membrane voltage responded to small changes in extracellular potassium, and measured local light-induced increases and decreases in $[K^+]_{out}$ which could account for the Müller cell responses. Recently Newman and Odette[20] have shown that the vitreal end-feet of Müller cells contain active K^+ pumps, which may help to stabilise the extracellular ionic concentrations in the retina and to explain the local b-wave currents in the retina. In addition the Müller cell's membrane voltage is affected by glutamate, the photoreceptor transmitter, and this may account for other aspects of the b-wave. However, the sensitivity and light intensity/response characteristics of the b-wave strongly suggest that the Müller cells are driven by the activity of bipolar cells and in particular the rod-driven "on" bipolar cell. Further evidence for this point derives from toxicological experiments,[21] in which the loss of the b-wave is associated with substances specifically affecting on-bipolars. The c-wave represents Granit's PI. Microelectrode studies indicate the pigment epithelium as its site of origin.[22,23]

Minor components

Since Granit's[5] and Karpe's[6] analysis, other "minor components" of the ERG have been described, and some are of clinical importance. It would obviously be of interest if any component could be assigned directly to neuronal activity, and preferably to the activity of the inner retinal layers where the output to the optic nerve is shaped. The oscillatory potentials (OP) are a series of rapid wavelets superimposed on the b-wave.[24,25] Best seen in the inner retina[26] they have been said to be an index of diabetic retinal disease. The question where the oscillatory potentials originate still cannot be answered. Physiological experiments have demonstrated two further responses: the proximal negative response (PNR) is seen in the inner retina when the stimulus is a small spot of light centred on the exploring electrode. The generating current appears to flow tangentially, so with the corneal recording of diffuse flashes which illuminate the whole retina little can be seen. The m-wave or proximal threshold response,[27,28] a cornea negative response, can be seen with flashes that are subthreshold for the b-wave, but only with a narrow range of intensities.

Technical advances

Recently, new types of corneal electrode suitable for clinical recordings have been described,[29,30] which do not degrade the optics of the eye and which can be worn for prolonged periods without irritation. It has thus been possible to elicit ERGs by other means than by flashes, and in particular, with grating or chequerboard patterns in which the bright and dark regions reverse. The responses obtained, called pattern ERGs (PERGs) are small, and although they resemble b-waves have been found to possess properties which greatly extend the diagnostic value of the ERG. This has led to renewed interest and new microelectrode analyses of slow retinal responses. This is the topic of this review.

Stray light and the ERG

As early as 1935 Fry and Bartley[31] found that an intense flash focused to a very small spot on the retina produced a greater ERG voltage than expected and they suggested that the effective stimulus was stray light within the eye, which evoked a response from a large retinal area. In fact, if the image of the flash was confined to the optic nerve head, the ERG elicited was as large as one obtained when the image fell on a functional area of retina.[32] This observation highlights a clinical limitation of the flash-ERG: it is only altered in disease if large areas of the retina are affected. In localised disorders (such as disciform macular degeneration, branch vein occlusion etc) a normal ERG is often obtained. There have been many enthusiastic claims to the contrary, but where they are documented it is evident that the reduction in the b-wave voltage only occurs so late in the evolution of the disease, that the ERG findings have no significance for diagnosis or management.

The corneal responses obtainable in man from true localised retinal stimulation (see below) are

only a few uV in size, and thus too small to be characterised by early recording systems. To improve sensitivity, Armington et al[33] introduced analogue averaging systems to electroretinography. Nowadays, with the advent of microcomputers, such methods are widespread. They all depend on averaging the responses to many stimuli. The signal-to-noise ratio increases in proportion to the square root of the number of responses averaged. Thus, although very small ERGs can in theory be characterised, the time required to obtain a record increases very greatly. This is especially true for ERG recording, since for long periods blinks and eye movements prevent data collection, and in practice, it is clinically impossible to record more than 1,000 responses with a repetition rate of (for example) eight per second. The variability in the recorded voltage in the absence of a stimulus (the "noise level") is then about 0.2 microvolts. The small ERGs obtained are 2-5 microvolts in size, so it is now (just) possible to make objective quantitative assessments of the electrical activity of small retinal regions. Because prolonged recordings are needed, new composite electrodes were required.[29,30] It is also possible to record ERGs with electrodes placed on the skin,[34,35] and reliable responses have been reported. However, the responses are only one third of the already small responses when a gold foil electrode is used. Thus the recording period is increased about 10-fold and clinically this is unacceptable, except in special cases such as recording from infants.

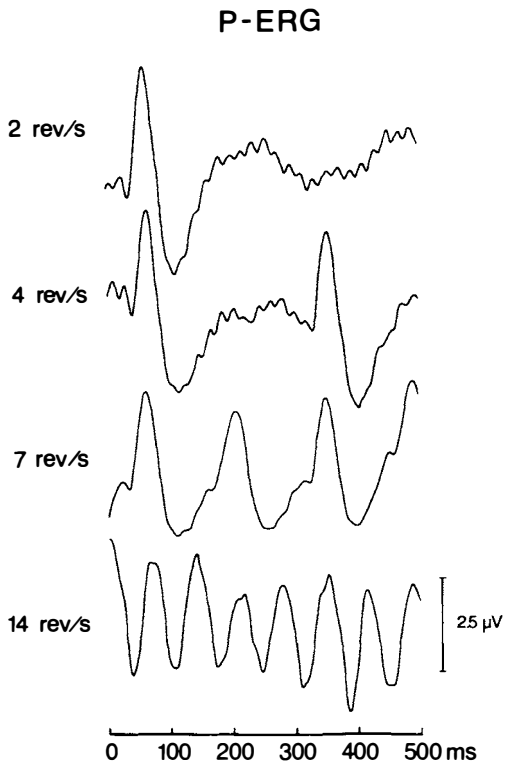

Fig. 1. *Normal pattern ERGs. The first three recordings are "transient" responses. The stimulus is a chequerboard pattern, with squares subtending 30' of arc, contrast 97%. From the upper row to the lower row the temporal frequency increases. Note the two components, an early positive (P-50) followed by a negative (N-95). The actual timing varies with the equipment: mirror systems reverse at the time of the command pulse, while with TV systems, the moment of reversal is delayed by the raster.*

The lowest row demonstrates a "steady state" response. The stimulus is the same as in A, except that the reversals rate is increased to 14 reversals per sec. Note that the response is approximately sinusoidal: most of the peak-to-trough amplitude is due to the N-95 component.

Berninger and Schuurmans.[60]

The pattern ERG

There are two main ways to reduce stray light. It can be suppressed by having the stimulus within a surround, the luminance of which is so high that the retina is light adapted and the stray light associated with the stimulus is below the ERG threshold. The focal ERG thus generated is much smaller and earlier than the conventional flash ERG seen in the dark-adapted eye. It is presumed to reflect exclusively the activity of the area directly illuminated.[36,37]

In 1964 Riggs et al[38] showed that when a pattern reversed in contrast, it generates a small electroretinogram, now called the pattern ERG or PERG. The significance of this finding is that if the pattern has equal areas of black and white, when it reverses in contrast the total flux entering the eye remains constant. The effective stimulus must lie under the image of the pattern on the retina and be the local increase (and the simultaneous decrease) of luminance which occur on each reversal. Outside the retinal image of the pattern, the stray light must remain constant and thus cannot contribute to the

response.[39-43] As described below, brighter areas of the retinal image scatter light onto the darker areas, and this poses a problem which has only been recently analysed (see below). Nevertheless, a stimulus which consists of numerous small spots of light evokes an ERG which is qualitatively different to one produced by a uniform stimulus which covers the same retinal region.[44]

The first attempts to characterise the PERG showed that it consisted of an initial cornea-positive wave P_1 or P-50 (from the time in msec from the pattern reversal to the peak of the response)], followed by a cornea negative wave (N_1 or N-95) (figure 1). At first, experiments concentrated upon the positive wave: later it was shown that the negative portion has a different retinal origin to the positive component.[45] The amplitude of the reponse elicited from the fovea and parafovea is larger than that of the more peripheral parts of the macula and paramacula. The amplitude of the reponse is largest when the pattern is accurately in focus on the retina and is larger for patterns of squares subtending about 30 minutes of arc than for larger checks. The responses in adult amblyopes were reduced below that in the fellow eye. Such claims suggested that the properties of the pattern-evoked responses differed from those of the flash-evoked responses and considerable interest was aroused in determining the site of origin of the responses which were suspected to arise in the inner retina, thus filling a most important gap in clinical electrophysiological investigations.

Origin of the PERG

Groneberg and Teping[46] were the first to provide clinical evidence for the suggestion that the PERG originated from the inner retina. They examined a 55 year old patient who had suffered an injury which included section of the optic nerve. PERGs were recorded some days after the accident and three months later. At the first examination the PERG and the flash ERG were normal. After three months no PERG was recordable while the flash ERG was unchanged. Dawson et al[47] reported similar results. Maffei and Fiorentini[48,49] recorded the PERG in cat, before and after unilateral transection of the optic nerve. The PERG remained unaltered in the affected eye for a few days after the section, then progressively decreased in amplitude and disappeared completely about four months later. The flash ERG remained unchanged and both flash and pattern ERGs remained constant in the unoperated fellow eye. Maffei et al[50] repeated the work in the primate, (fig 2) and took particular care to ensure that the flash responses originated in the same retinal region as the pattern responses. Because of these observations the authors concluded that the PERG originates from structures different from those responsible for the flash ERG. They assumed that the PERG is closely related to the activity of the third order retinal neurone, ie the retinal ganglion cells. Their proposal is supported by the investigation of Hollander et al,[51] who examined retinal morphology after intracranial optic nerve section. Light- and electron microscopic examination of cross sections through the retina showed pathological changes restricted to the innermost layers. However, there are other reports indicating that retrograde degeneration can also affect the physiology of the inner retinal layers.[52]

Although the evidence regarding the proximal origin of the PERG reviewed above (particularly the animal experimentation) is very persuasive, it may not be conclusive. In addition, not all the evidence seems to point in the same direction. Recently, Harrison et al[53] reported a seemingly contrary clinical observation. They examined a patient who had a surgical transection of the optic nerve in the course of an operation for removal of an optic nerve glioma. After 30

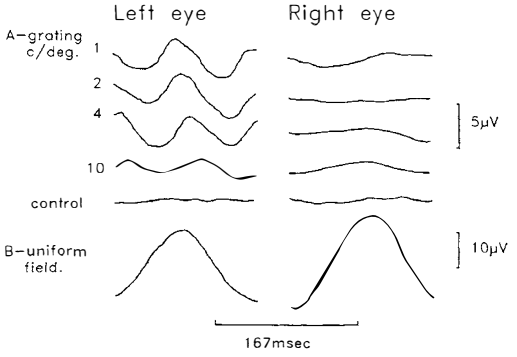

Fig. 2. *Loss of pattern ERG and preservation of flash ERG after experimental intracranial sections of the right optic nerve in monkey. Steady state pattern and flash ERGs are shown. Note the loss of the pattern ERG is only total for the higher statial frequencies. Maffei and Fiorentini.*[50]

months a PERG could still be recorded. However, it was significantly reduced when small checks were used and only slightly reduced when large checks were presented. Berninger (unpublished data, figs 3 & 4) also did not observe a complete extinction of the PERG three and a half months after transection of the optic nerve;. He examined a 22 year old girl after accidental transection of the optic nerve. While the negative component was extinguished, the positive component was still recordable but significantly reduced to approximately one third of the normal value. The authors conclude that not only the ganglion cells produce the PERG; part of it, maybe mainly the positive component, is elicited by other retinal structures. These experiments and direct clinical observations are supported by numbers of observations on patients with partial or presumed damage to the optic nerve — for example in glaucoma, or retrobulbar neuritis. For example, some weeks after an acute attack of retrobulbar neuritis, the pattern ERG amplitude may decline.

Are there alternative explanations for the observations which relate the PERG to ganglion cell activity? When the optic nerve is sectioned, more widespread damage may occur due possibly to temporary interference with the blood supply to the orbit. In the other clinical observations, for example on patients with multiple sclerosis, it is very difficult to be sure that damage to the outer layers of the retina has not occurred, as well as loss of optic nerve fibres and their associated ganglion cells. Therefore much work has been done to characterise the pattern ERG and demonstrate that it differs in its properties from the flash response: this would prove that in some aspects at least the two responses are different.

Stimulus parameters and the PERG

The earliest work on the PERG suggested that it was simply formed by the superimposition of the "on" and "off" components of the flash response. However, the former is the b-wave which is widely believed to be produced by Müller cells, and the latter, under most circumstances is caused by at least two processes. One is a cornea-negative wave caused by the termination of the positive on-response, and in addition there is a cornea-positive component due to the rapid termination of the cone receptor potential. The clinical evidence that the PERG corresponded in some way to

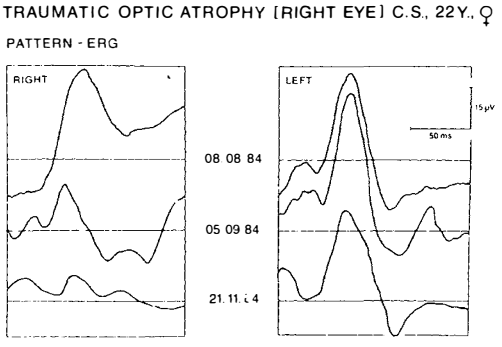

Fig. 3. *PERGs in a patient after accidental complete section of the right optic nerve. The first records were obtained one week after the accident, and responses are obtained from both eyes. In the later recordings, the loss of the right PERG is obvious, but not total.*

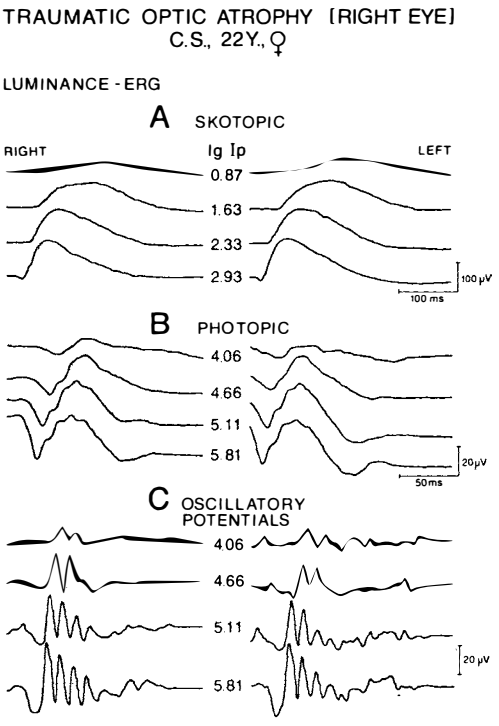

Fig. 4. *Flash ERGS in the same patient, 3 1/2 months after the accident. Note that there is no alteration in the scotopic, or photopic responses and that the oscillatory potentials are also well preserved in the blind eye.*

inner retinal activity therefore came as a surprise, and led to a flurry of investigations. One way of drawing an analogy between PERG and inner retinal activity was to examine the relationship between the size of the elements in the pattern and the response amplitude. Ganglion cells are known to respond optimally to a particular size of pattern, because the majority have concentric receptive fields in which centre and surround produce opposite and antagonistic effects.[54] Suppose that the receptive field centre is just covered by a dark portion of the pattern: the largest possible portion of the surround will lie in the bright area. If the cell has a on-centre field it will go from maximal inhibition to maximal excitation as the pattern reverses. If the pattern size increases or decreases, the change in excitation will not be so great because the centre and the surround will both be stimulated partly by bright regions, and partly by dark ones. Thus when the pattern reverses, the effective change in the stimulus will be less than optimal. Of course, there are ranges of size of receptive fields and the mean size varies with retinal eccentricity. Furthermore, bipolar cells have a centre-surround organisation, though in most animals tested, this property is most marked in the ganglion cells.

Another feature of the ganglion cell response is that it signals the *contrast* between centre and surround, and not merely luminance, as is the case for photoreceptors. Contrast is defined as:

$$C = \frac{L_{max} - L_{min}}{L_{max} + L_{min}}$$

and although in most retinal ganglion cells, a black-white border suitably placed evokes a prolonged discharge, it is the change (reversal) of the pattern which causes a temporal change in contrast which is the more powerful stimulus. If the PERG responded to contrast and not to luminance, it would be demonstrably different to the flash ERG which is luminance dependent.[37]

Experimental findings on the relationship between PERG amplitude and pattern size have been reported. Some of these studies have been done using chequerboards, and some with gratings. In the latter case, it is said that the responding structures shown "spatial tuning" and the size of the gratings or chequerboards is specified as a "spatial frequency", measured in cycles/degree of visual angle subtended by a single cycle of a pattern (e.g. a dark and a light bar). Various different accounts of the spatial tuning properties of the PERG have been given. Spekreijse et al[40] who made the first quantitative PERG measurements, were unable to detect any spatial tuning and used a very elegant technique to demonstrate that the amplitude of the PERG was not dependent upon contrast in the same way as the visual cortical evoked responses. Riemslag et al[55,56] and Arden and Vaegan[37,57] confirmed some of the findings of Spekreijse et al, but nevertheless showed that if the retina was stimulated by uniform patches of light, which increased and decreased in luminance, to mimic those which occur during the appearance and disappearance of the pattern, the resulting responses could not be summed to produce a PERG: the response to patterns is always larger than predicted. Under these conditions, an optimum check size could be found which produced the largest response. However, only for small fields surrounding the fovea did they find a clear maximum. They concluded that pattern reversal caused changes in luminance and produced small signals which contained all the usual ERG components, but to which the pattern response was added. Similar results were obtained by Baker and Hess[58] and Hess and Baker,[59] who showed that for smaller responses and rapid, sinusoidal changes in contrast, sharp PERG "tuning curves" could be obtained. Many other workers have made similar observations: Berninger and Schuurmans[60] evaluated the early positive and following negative component. No spatial tuning seemed to be present for the positive component, not only for one stimulus frequency but also for the whole range of temporal frequencies, while significant spatial tuning was observed for the negative component. Korth[61] also reported that the negative component demonstrated spatial tuning which is more pronounced when the stimulus is of low contrast. Korth,[62,63] Odom et al[64,65] and Schuurmans and Berninger[66] believed that the spatial tuning for the positive component might be obscured by a luminance component. The observation that only the negative component demonstrates a sharp spatial tuning helped to explain the different results in the literature. Armington et al,[67] Trick and Wintermeyer[68] and Kirkham and Coupland[69] and subsequently

numerous other investigators failed to find clear cut spatial tuning in the PERG. Almost all these authors measured the early positive component of the PERG. Sokol et al[70] measured the positive component and found no spatial tuning at lower temporal frequencies in contrast to higher temporal frequencies. On the other hand Odom et al,[64] Trick and Wintermeyer,[68] Odom and Norica[65] and Baker and Hess[57] found spatial tuning at most or all the temporal frequencies but they measured the size of the second harmonic component of the Fourier-analysed signals. Thus most experimenters who evaluated the positive component failed to record spatial tuning, while those authors who evaluated the negative component or evaluated a steady state response (either using Fourier analysis or measuring the whole amplitude) recorded a spatial tuning. (At high temporal frequency however the PERG is dominated by the negative component).[60]

In summary, most authors agree that the generators of the PERG are spatially tuned. The relationship between amplitude, pattern size and contrast has been determined and is difficult to explain on the basis that local regions of the retina respond independently of each other. There must be local lateral interactions, which modify the outer retinal responses to change in luminance.[71] Hess and Baker[59] and Korth and Rix[72,73] demonstrated that response amplitude increased linearly with contrast, up to the maximum available: this is quite unlike the ganglion cell or visual cortical response which is only contrast dependent for low contrasts.

The most extensive investigations have been done by Drasdo et al[74-77] and Thompson and Drasdo[78] (figures 5 & 6) who have calculated the retinal distribution of illumination caused by each pattern employed and have investigated the

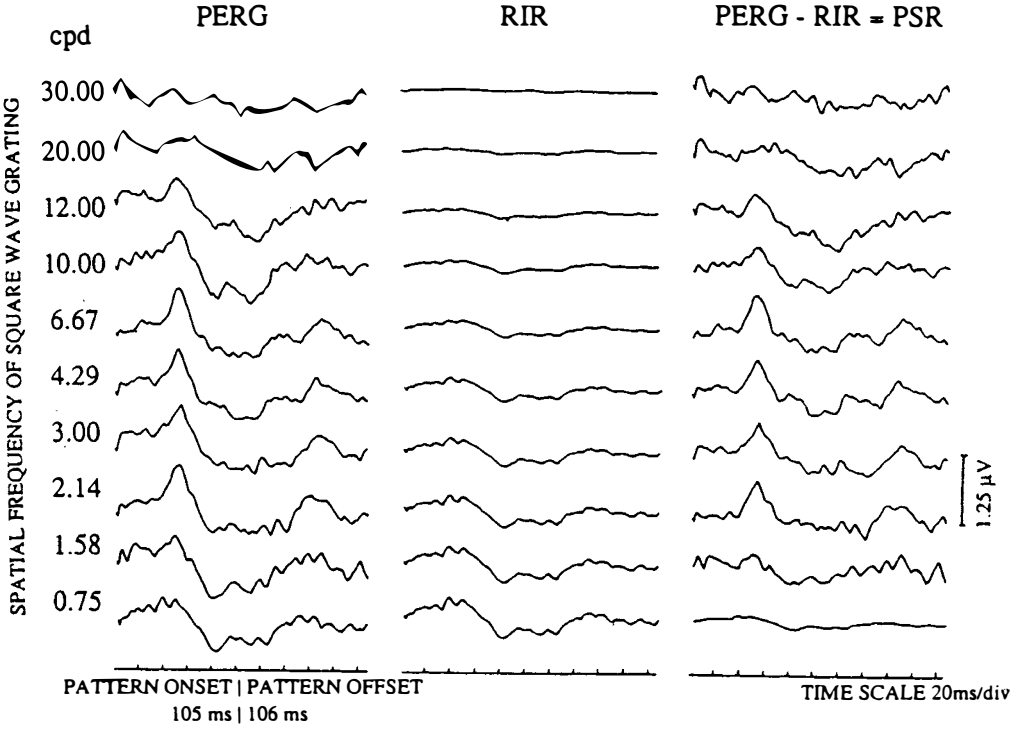

Fig. 5. *Method of separation of pattern ERG into illumination specific (RIR) and pattern specific (PSR) components. The spatial frequencies of the on-off gratings are given for each row. The lowest spatial frequency elicits (record in left column) a response which is due to local luminance changes. The luminance changes on the retina are reduced when the higher spatial frequencies are used, and the calculated luminance (RIR) responses are shown in the centre column. The right hand column shows PERG minus RIR=PSR. Note how the PSR increases for higher spatial frequency and the "spatial tuning" for positive and negative components. Drasdo et al.*[75]

amplitude/spatial frequency relationship for a small disc which includes the fovea, and for a series of concentric annuli. It is assumed that the largest pattern elements (each one of which completely covers the area investigated) must produce an ERG caused solely by luminance changes (the Retinal Illumination Response or RIR). When the pattern size is smaller, there will be additional contrasting borders on the retina. When these change an additional pattern specific response (PSR) may also be evoked. But, at each border, the bright square scatters light into the dark. This will have two effects: the dark squares will be made brighter, so the change of retinal luminance is not too great for small as for larger squares: this will reduce the RIR. Also the PSR will be reduced because effective contrast is reduced. However, it is also possible to make a direct calculation of these changes, from the known optical properties of the eye. If the experimental relationship between the PERG amplitude, square size, nominal contrast and nominal luminance is established, it is possible to correct for the imperfect optics of the eye, and to subtract the purely "luminance (RIR)" component from any experimentally obtained PERG. The resulting PSR amplitude can also be corrected for the reduced contrast. When this is done, it can be seen that the pattern response

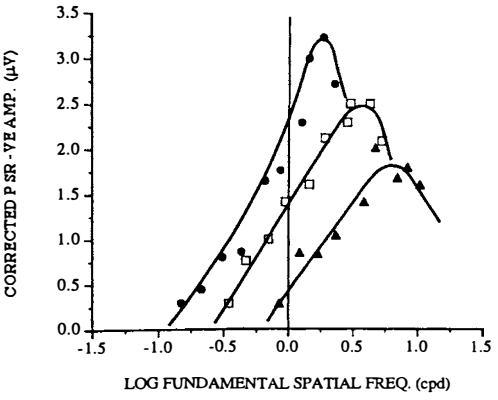

Fig. 6. *Relationship of the pattern specific response amplitude to the spatial frequency of the pattern. Results are shown for (triangles) a disc subtending 5.1 degrees and centred on the fovea (open squares), an annulus 5.6-12.6 degrees, and (closed circles) 12.3-25.6 degrees. Note the response is largest for the peripheral annulus but the amplitude/unit retinal area decreases in the periphery. The optimal spatial frequency increases for foveal stimulation. Thompson.*[221]

amplitude depends upon three factors: spatial frequency, the region of the retina from which response derives and also whether positive or negative components of the PERG are measured.

The maximum amplitude of the PSR is achieved at increasingly high spatial frequency as the region investigated moves toward the fovea. The luminance response is larger in relation to the pattern response when the average luminance is high. The relationship between stimulus eccentricity and response varies systematically for luminance and pattern response, and also for the positive and negative components. There is a surprisingly good relationship between the relative volume of the retinal layers and the amplitude of the various components of the PERG, such that in peripheral retina, the luminance responses (which are judged to come from outer retina) are the larger, while in the juxtafoveal region, where inner plexiform and ganglion cell layers are proportionally increased in thickness, the positive and negative pattern-selective elements are largest. The amplitude of the negative PSR (N-95) is correlated to the volume of the ganglion cell layer. This observation is the more interesting in the light of clinical observations by Holder[45] (see below).

This analysis thus provides results which are in agreement with experiments upon animal retinas with penetrating microelectrodes.

Analysis of the pattern ERG with penetrating microelectrodes

Steinberg et al[23] and Sieving et al,[79,80] Heynen and van Norren[81] and Baker et al[82] have all investigated the origin of the PERG using the technique of current source density analysis. The basis of the method is as follows: The ERG is produced by currents which flow radially through the eye (and also through parts of the retina), but at some point they must enter and leave the cells of origin. When current enters a cell, the local current density must decrease. Conversely, when current leaves a cell, the local current density increases. For any small lamina in the retina tangential to the electrical axis (which is essentially the same as the optic axis), current flows at right angles through the lamina down the extracellular resistance, giving rise to a voltage drop across the lamina. In an experiment on the origin of the ERG, responses are

recorded when the microelectrode is at the inner surface of the lamina and again after it has moved to the outer surface of the lamina. The difference in the two responses gives the voltage drop between the two positions. If the local resistance is known, the radial voltage drop gives the radial current (from Ohm's Law). Now the electrode is moved on and the same set of measurements made for another lamina, and so on through the retina. Consider two laminae which are in the vitreous: obviously the current in both must be essentially the same. But in the retina, the current may change for it can enter or leave the retinal cells: thus the difference in current between successive laminae gives the sites of the sources and sinks of the ERG.[83]

The results of the various groups who conducted these analyses differ in detail, but there is broad agreement that if the stimulus consists of a uniform patch of light, presented either as a short flash or a prolonged step, the ERG current largely originates and disappears in the outer layers of the retina. However if the stimulus is a chequerboard or grating, and the stimulus is pattern reversal, the sources and sinks are found in the inner retinal layers. The actual distribution of sources and sinks is complex and may be species dependent. Several different components may overlap in time. However it appears that the innermost current sink could be in the ganglion cell layer. Thus, these studies directly confirm the results of other investigations.

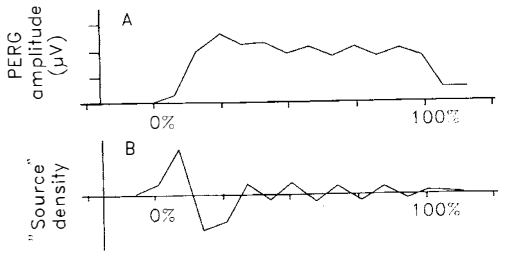

Fig. 7. *Current source density analysis of the pattern ERG in cat retina. "A" shows the voltage recorded by a microelectrode moving through the retina, 0% being the vitreal surface, and 100% the RPE. The reference electrode was in the vitreous. The stimulus was a squarewave grating reversing at 8 Hz. It can be seen that the voltage is greatest in the inner retinal layers.*

"B": the second differential of "A" shows the relative distributions of sinks and sources. These occur within the vitreal 20% of the retina. The sharp upward-going peak locates either a sink or a source (the method of analysis cannot distinguish between them) to the ganglion cell layer.
Sieving and Steinberg. [80]

Practical problems in recording reliable clinical results

Corneal electrode position

Variability in the size of the PERG can occur if the electrode position changes. The DTL thread electrode may be swept down into the lower fornix, and the gold foil electrode blinked into the lateral canthus: in both cases, the recorded response voltage decreases. Another source of variation which requires experience to exclude is the averaging of eye movement artefacts: these may be 100 times as large as the PERG, and if so, most artefact rejection routines will eliminate the spurious trace. There is a greater problem with the more frequent small blinks or eye movements. These may be only 5-10 times the size of the PERG, and in systems not designed for such discriminations, may be included in the averaging. Even one such eye movement record will decrease the signal to noise ratio to unacceptable levels. Unfortunately, such spurious voltages often resemble the PERG.

Reference electrode position

Another source of difficulty in interpreting clinical recordings can also be understood in terms of patterns of current flow, this time not through the retina, but through the tissues of the head. The PERG is a small response and can be easily contaminated by artefacts such as photoelectric effects and cortical potentials.[59,84-87] Seiple and Siegel[88] and Peachey et al[89] — using steady state conditions — demonstrated that the PERG can be contaminated by responses developed in the fellow eye. Hess and Baker[59] reported that the contamination of the PERG by cortical potentials is less than 10% when the reference electrode is positioned on the ipsilateral temple. Odom et al[90] report that the variability of responses elicited with a reference at the outer canthus was less and the signal-to-noise ratio greater than with other reference positions. Berninger[85] examined the influences on the PERG in detail using transient conditions. He reported only a slight reduction of the positive component (P-55) when the reference was fixed to the ipsilateral temple or the ear, respectively. A much larger difference was

observed for the negative component. Berninger,[85] Hess and Baker[59] and Yanashima et al[86] concluded that the ipsilateral temple should be used as a site for the reference electrode. This is important when both components of the PERG are evaluated or when steady state conditions are used, since the steady state response is a mixture of both PERG components the P-50 and N-95.

Pupil size

The PERG has frequently been used to investigate patients with glaucoma (for details see later). Since miosis is an appropriate treatment for many patients with glaucoma the question of the influence of pupil size on the PERG is important. In normal subjects Thompson and Drasdo[91] have shown that if the screen illumination is changed and the pupil size is reduced so that retinal illumination remains constant, the response to the appearance of a pattern *increases* when the pupil diameter constricts from 4.8 to 2.7 mm: this is the result of the improved optical characteristics of the eye. Under normal circumstances, therefore, alteration of the pupil diameter within the physiological range cause no significant change in the amplitude of the positive component of the PERG. However, this does not answer the question as to the effects of extreme miosis and so far as the visual cortical evoked potentials are concerned, there is no doubt that they are affected by miosis. Pupil diameter has been shown to affect the latency of the P-100 component of VECP.[70,92-94] Thus although Thompson and Drasdo,[91] Holder and Huber[94] and Berninger[85] observed no difference in the positive component of the PERG as the pupils were constructed, Berninger[85] by contrast observed significant reduction for the N-95 component and highly significant increase of the latency for both the P-50 and N-95 component. No difference was reported for the comparison

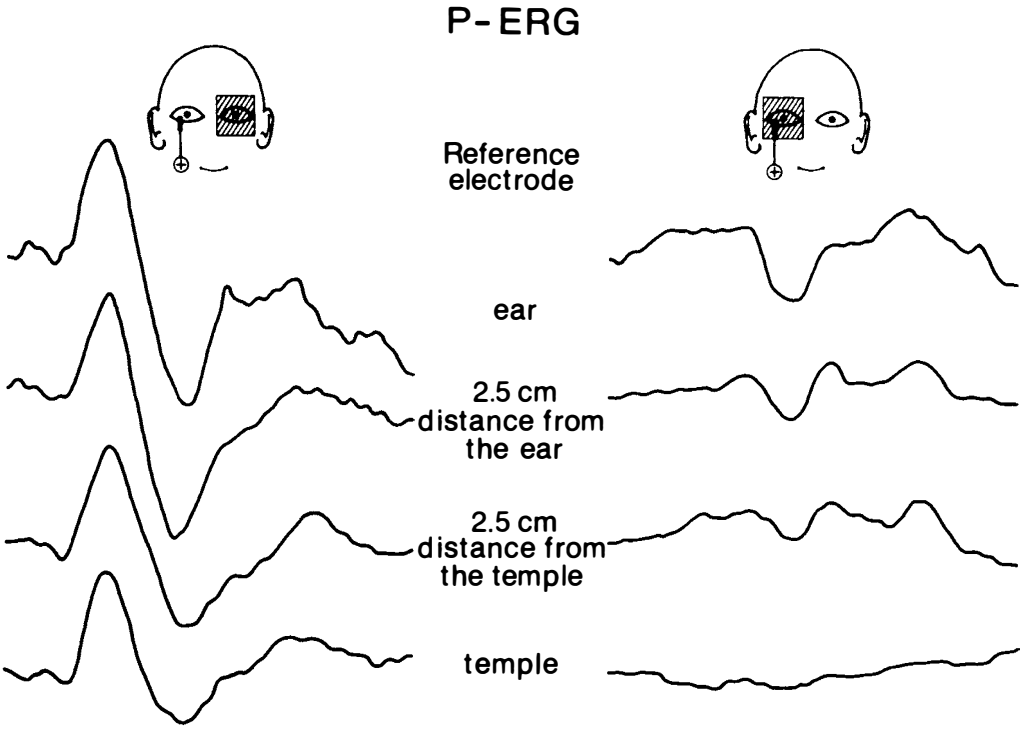

Fig. 8. *The effect of reference electrode placement on the PERG. In the left column are shown responses obtained by identical stimulation, when the reference electrode is placed as described and the eye is directly stimulated. In the right hand column, the electrodes were identically positioned, but the stimulus was only allowed to reach the fellow eye. Thus, the "responses" shown are due to current spread in the head. Note that when the indifferent electrode is on the temple, no contamination occurs.*
Berninger.[85]

of dilated and undilated pupils. However, Berninger pointed out that the normal pupil size in his standard condition is very large (5-7 mm) because of the low mean retinal luminance and this might be the reason why no difference was observed between normal and dilated pupils. Leipert and Gottlob[95] reported a significant reduction of both PERG components in miosis. However, they measured the PERG only 20 to 35 minutes after the application of the pilocarpine: at this time, the patients' accommodation was paralysed, and the reduction in PERG could be due to defocus.

Defocus

The PERG has been reported to be very sensitive to defocus.[37,59,70,95-97] With increasing spatial frequency an increased amplitude reduction can be observed. Thus Hess and Baker[59] noted a 50% reduction with 0.5 diopters blur when seven min of arc stripe size was used.

How to measure and assess the PERG

It is generally agreed that a decrease in amplitude is the first change in the PERG in eye disease. Depending on the method of stimulation, either one or two amplitude measurements can be made. If transient responses are recorded, the first positive peak at around 50 msec can be measured from the baseline or from a still earlier negative deflection which can sometimes be observed at around 35 msec. In addition the following negative wave (N-95) can be measured either from the baseline or from the P-50 peak, to the following trough. When stimulus repetition rate is more frequent, or if sinusoidal temporal modulation is employed, nearly sinusoidal "steady state responses" develop which are mainly dominated by the negative component.[85] This may be measured either from peak to trough or if an FFT (fast Fourier transform) is available, the amplitude of the second harmonic response (which is pattern specific[58,59,64,65]) can be obtained directly. The latency of the PERG has proven to be very stable and only rarely changed by disease. There are only a few reports about a delay of the P-50 PERG latency. Arden did not find any change of the P-50 latency in large groups of patients with diabetes,[98] amblyopia,[99] glaucoma[100] and macular degeneration.[101] Holder who also reviewed a large group of patients with various retinal and optic nerve diseases[45] did not see any P-50 delay in optic nerve disease, but did find significant P-50 delay in patients with retinal deatchment, inflammatory retinopathy, branch vein occlusion, refractive error and a patient with myxoedema[102,103] (and personal communication). By contrast Marx et al[104] reported a significant delay of the P-50 component in patients with ocular hypertension and glaucoma, while Howe and Mitchell[105] reported a significant delay of the N-95.

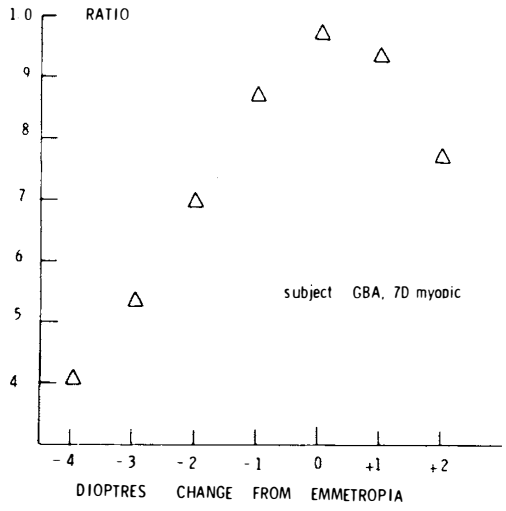

Fig. 9. *The effect of defocus on the amplitude of the pattern ERG.*
Vaegan et al. [87]

PERG and age

There have been many studies of the change in cortical evoked potentials with age.[106] To our knowledge there are only four such reports for the PERG.[101,107-109] All four agree that the amplitude is significantly smaller in older subjects. Two authors[107,108] also reported an increase of the latency while Trick[109] did not see any change of the latencies. An influence of the age related miosis can be ruled out since Korth[107] used Maxwelliam view and Trick[109] observed an even more pronounced reduction of the PERG for low spatial frequencies. Thus, the reduction in the number of the retinal ganglion cells[110] might be the reason for the age related reduction of the PERG.

Colour

In recent years the concept of parallel visual pathways has been developed, named after the lamination in the lateral geniculate nucleus (LGN).[111-125] Parvo and magnocellular pathways are separable from at least the ganglion cell layers. The latter starts from the alpha ganglion cells, which respond poorly to colour but are very sensitive to motion, flicker and achromatic spatial contrast. The beta ganglion cells originate the parvo-cellular system, are colour coded, have high spatial resolution and are less sensitive to motion and achromatic spatial contrast.

Thus the ideal stimuli for the magnocellular system are "black and white" patterns or gratings which are either presented in appearance or reversal mode, while the ideal stimulus condition for the parvocellular system is an isoluminant colour contrast grating, i.e. the grating and any background have identical luminance, and the average colour of the background and the grating is also identical. The stimulus is the changing chromaticity of the pattern and each recognisable colour in the grating has the same luminance. Of course, for single cell recording, for example from the surround of a ganglion cell which is exclusively connected to one type of cone, the alteration in pattern must cause a local change in luminance.

With these features of the processing of visual information in mind, it seems that a coloured PERG stimulus could be devised which would selectively activate the small (alpha) ganglion cells. The response to isoluminant red-green gratings of 40 cd/m^2 is nearly totally negative and small (about 1-2 uV after more than 1,000 sweeps). For blue-yellow patterns no colour PERG was recordable, a finding plausibly explained by the fact that only 5% of retinal ganglion cells respond to blue-yellow targets and there are correspondingly smaller numbers of blue cones in the retina. Such PERGs are due to colour contrast. Different results i.e. hardly any difference between colour and achromatic PERG have been reported from Korth et al[126] who projected bright (22,500 td) chequerboards onto the retina in Maxwellian view: under such circumstances, local luminance responses might be evoked which could be considerably larger than the colour contrast responses. Overall, we believe that the retinal responses, in contrast to the cortical responses, to isoluminant colour-gratings are too small to be used for routine clinical examinations.

PERGS in Specific Clinical Conditions

Recently Holder[45] has reported that P-50 and N-95 are separately affected in disease. While the P-50 is reduced in macular disorders the N-95 may be selectively affected in conditions where the optic nerve is damaged. This observation certainly increases the clinical value of the PERG and should encourage more clinicians to use this technique. Because the elucidation of the physiological basis of the PERG is so recent there is still much to be done before clinical PERG results can be used and interpreted with the degree of confidence possible with the Ganzfeld ERG.

Maculopathy

One advantage of the PERG is that a response can be evoked from a localised retinal area, which makes it ideal for the examination of the macula. Lawwill[42,43] was the first to use the PERG with this aim. Normal focal and flash-ERGs were obtained in patients whose PERGs

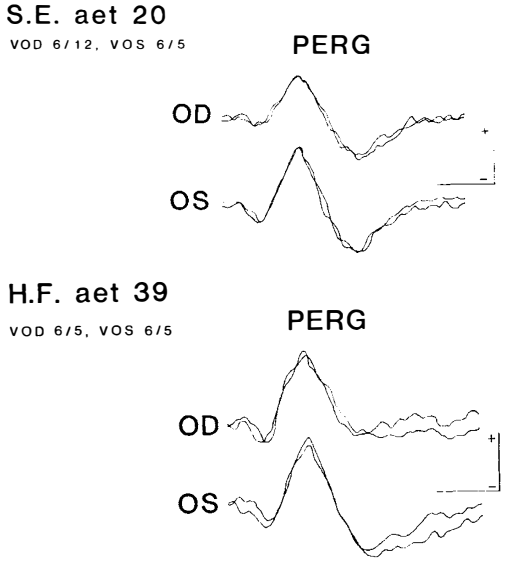

Fig. 10. *Abnormal PERGs in patients with macular and optic nerve disease. On the upper rows a record from a patient with right maculopathy can be seen. Note the reduction in the positive components of the response. The two lower rows show the responses in cases of right optic neuritis, and only N-95 is reduced. Holder.*[45]

were clearly pathologically reduced. A total loss of the PERG was observed in another patient with juvenile macular degeneration, while the flash-ERG was normal.[42] This observation could not be explained if the PERG was a response to change in retinal illumination originating in the receptor and Müller cells.[43] Many others have later confirmed this result[101,127,128]. There is a general consensus that in juvenile macular degeneration, the PERG is abnormal before ophthalmological changes are easily visible, and while acuity is generally only moderately reduced.

Kirkland and Coupland[129] found an abnormal PERG in a patient with Tay Sachs disease, at the stage where a cherry red spot is seen in the macula (and also myoclonus and mental deficiency occur.[130]) Despite the ocular changes, the flash ERG was normal. The histopathology of this condition is the deposition of abnormal white neurolipid metabolic products in retinal ganglion cells. Thus, the absence of the PERG is good evidence for its association with this layer.

Arden at al[101] showed that the PERG is a sensitive index of retinal abnormality. They reported abnormal PERGs in all but three of 40 cases with disciform maculopathy and were able to relate the degree of PERG reduction to the loss of visual acuity. Celesia and Kaufmann[131] described, in a patient with ophthalmoscopic unilateral disciform macula degeneration, a significant PERG reduction in the so called "unaffected" fellow eye. They suggested that the PERG could be used for early detection of macular lesions. Later Holder[45] also reported a patient with a reduced PERG but no ophthalmoscopic abnormalities and came to the same conclusion. Holder's[45] observation that the P-50 component is selectively reduced in maculopathies reinforces the conclusions of Celesia and Kaufman,[131] but they did not study the amplitude of the N-95.

These findings also illustrate another important reason for recording the PERG in macular disease. In these conditions, there is a loss of contrast sensitivity, which may be greater for low spatial frequencies. Consequently, the effective contrast of the stimulus decreases and this (and other aspects of retinal damage) can result in an abnormal pattern cortical evoked potential (PVECP). In such cases the peak time of the response increases. This is frequently (and erroneously) thought to be pathegnomonic of demyelinisation. Simultaneous PERG and PVECP recordings will help to eliminate such diagnostic errors.

Optic Nerve Dysfunction

If the PERG truly represents a ganglion cell response it must be affected in optic nerve disorders. Therefore much effort has been expended in examining such patients.

Primary optic atrophies

Vaegan and Billson[132] reported that the PERG can be reduced in patients with optic atrophy while the focal ERG is preserved. Berninger et al[133] examined six adult patients with dominant infantile optic atrophy (DIOA). A very large phenotypic variation within families is typical for DIOA. All patients tested had a typical family history. Four patients with severely reduced visual acuity (6/24 and lower) demonstrated the expected tritan axis in the 100 Hue, while two patients with preserved visual acuity (6/6) only had relative central scotomas in the visual field for blue test spots. Normal P-50 components were recorded in all patients. The N-95 component, however, was reduced in all four patients with significant reduced visual acuity and was normal in the two other patients.

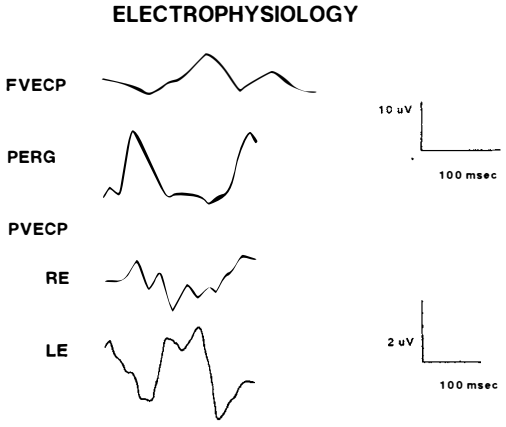

Fig. 11. *Electrophysiological results in a patient with Leber's Optic Atrophy.*
Note that there is a delayed response in the visual cortex to flashes (upper record, upper calibration). The PERG P-50 is present, but the N-95 is absent. The response to patterns in the visual cortex is absent for right eye stimulation and abnormal (a "W") configuration for left eye stimulation.
Berninger et al.[134]

Thus the characteristic features of isolated loss of optic nerve fibres is a selective reduction of the N-95 component. Similar results are reported by Berninger et al[134] for two patients with Leber's hereditary optic atrophy (fig 11). Again normal P-50 components were recorded while the N-95s were completely extinguished. These observations are in accordance with those of Holder[45] and Ryan and Arden[135] who found that the N-95 component is, in most cases, selectively affected in patients with optic nerve disorders.

Optic Neuritis and Multiple Sclerosis

In cases of retrobulbar neuritis (RBN) considerable recovery of function follows the acute onset. However, an electrophysiological test of visual function, the visual cortical response evoked by patterns (VECP) continues to be delayed, showing that at least one defect associated with demyelination persists.[136,137] Retinal abnormalities may also occur in optic neuritis. Lightman et al[138] observed retinal abnormalities and/or cells in the media in 25% of their patients with unilateral optic neuritis. Rucker[139] also reported sheathing of the vessels in up to 20% of patients with multiple sclerosis (MS). Thus it is of interest to determine the PERG changes in this condition.

Fiorentini et al[140,141] reported a reduced steady state PERG in a patient with acute optic neuritis. Seiple et al[142] could not record a transient PERG in three out of seven patients with acute optic neuritis. All three had severely reduced visual acuity in the affected eye. However the PERGs were recorded monocularly and therefore the patients could not fixate properly with the affected eye and this may have been the reason why no response could be recorded. Berdjis et al,[143] Bobak et al,[144] Plant and Hess[145] and Ryan and Arden[97] found a reduction of the PERG in a group of patients with the history of optic neuritis.

Arden at al[97] reported that the P-50 component was reduced after a delay of several weeks of the onset of acute optic neuritis. Porciatti and von Berger[146,147] studied and monitored the progress of the PERG for a year following the acute attack. The responses decreased during this period and those elicited by low and medium spatial frequencies were affected first. In addition the N-95 component was more reduced than P-50 component. Berninger and Heider[148] examined 20 patients with unilateral acute optic neuritis and reported a significant reduction of the P-50 and N-95 during the acute stage of disease while in chronic stage the P-50 was in the normal range (however slightly reduced in comparison to the unaffected fellow eye) while the N-95 became even more significantly reduced.

In multiple sclerosis the reports are contradictory. Kirkham and Coupland[148] (28 patients), Celesia and Kaufman[131] (two patients) did not find any difference between MS patients and a control group. Ota and Mikaye[150] reported that the PERG is extremely limited in its ability to detect unilateral optic nerve diseases. However, all such contradictory reports are from authors who measured the P-50 component, which Holder pointed out is hardly affected in optic nerve disorders. However, Holder[45] as well as Arden[95] reported that two patients with optic neuritis due to demyelination developed late reduction of the P-50 component which occurred during the period of clinical recovery. Persson and Wanger[151] studied the P-50 component in 15 patients with MS. None of their patients had suffered from acute attacks of optic neuritis in the six months prior to the examination but all had a delay in the VECP which indicated damage to the optic nerve. A reduction of the P-50 component was seen in 50% of their patients. Thus in optic neuritis both components may be affected. While the N-95 component remains affected in the chronic stage, the P-50 may or may not completely recover. Thus PERGs are generally abnormal in this condition but evidently the VECP is a better clinical test in this condition.

Glaucoma

In chronic glaucoma increased intraocular pressure finally leads to ischaemic damage of the optic nerve head followed by atrophy of the nerve fibres and retinal ganglion cells. Quigley et al[152,153] estimated that at least 40%-50% of optic nerve fibres are lost before a visual field defect can be found. If any objective test could distinguish a lesser degree of nerve fibre loss, it would be of great importance in glaucoma. Quigley et al[154] demonstrated that red free fundus photography of the disc can demonstrate nerve fibre bundle losses in many patients with ocular hypertension who have no field defects.

However, this method has its limitation and fails in up to 40% of patients with mild visual field losses. The VECP was found to be affected only in advanced cases of glaucoma with large scotomata[104,105,155-158] as expected from the close association between change in acuity with voltage. The flash-ERG, which is produced by outer retinal activity is of no use in detecting glaucoma. Our knowledge of the origin of the PERG suggests that it should be affected in glaucoma, and indeed many authors report such findings.[104,108,142,1443,146,158-166]

May et al[167] and Arden et al[97] were amongst the first who recorded the PERG in patients with unilateral glaucoma. They observed a significantly reduced response to pattern stimuli while the flash ERG was normal. Howe and Mitchell[105] examined 17 patients with unilateral chronic glaucoma and on non-miotic treatment. They evaulated both the P-50 and N-95 components of the PERG. Both were significantly reduced in comparison to the fellow eye. They further noted that the implicit times of the P-50 showed a tendency to increase although this was only statistically significant for the N-95. Wanger and Person[168] studied 11 patients with unilateral glaucoma and observed a reduction in amplitude below normal values in 10 out of 11 cases. There was a significant correlation between the decrease of the PERG amplitude and the loss of visual field. Later they reported a P-50 reduction in four out of seven patients with ocular hypertension.[169] Porciatti et al[170] reported that in 17 patients with ocular hypertension and early glaucoma the PERG was mainly reduced in the medium range of spatial frequencies. Trick et al[165] made the same observation and reported the highest statistical difference between normal subjects and patients occurred when the stimulus was one degree checks. By contrast Marx et al[171,172] induced experimental glaucoma in monkeys and found a more pronounced reduction at lower spatial frequencies. Recently Marx[104] reported on 15 patients (26 eyes) with ocular hypertension and early glaucoma. They divided their patients in to three groups

(1) ocular hypertension with no treatment,
(2) ocular hypertension with treatment,
(3) early glaucoma.

The mean PERG amplitude was reduced in all three groups. However, this was only statistically significant for the patients with early glaucoma. In contrast the P-50 latency was significantly decreased for all three patient groups.

A selective reduction of the N-95 was first reported by Ohta.[173] Weinstein et al[100] studied patients with ocular hypertension and 12 with glaucoma and reported a more pronounced reduction of the N-95 component than of the P-50 component (fig 12). This is in accordance with Holder's[45] view that if the N-95 component is affected it indicates an optic nerve disorder. However, Holder[45] himself has reported that glaucoma is the exception to the rule and observed a marked reduction of the P-50 component as have many other authors. It is remarkable that many authors report a more pronounced reduction of the PERG when they use steady-state stimuli,[165,174] and low or medium spatial frequencies.[104,165,170] It seems that both components are affected in glaucoma. This suggestion is also in accordance with the observation by Odom (personal communication) that in rabbits after acute increase of the IOP both components are reduced in amplitude.

Although many recent investigations suggest that glaucoma affects all the retina in the posterior pole, the first scotomata develop in an annular ring. The fovea is less affected, in that loss of visual acuity may occur later. Now the

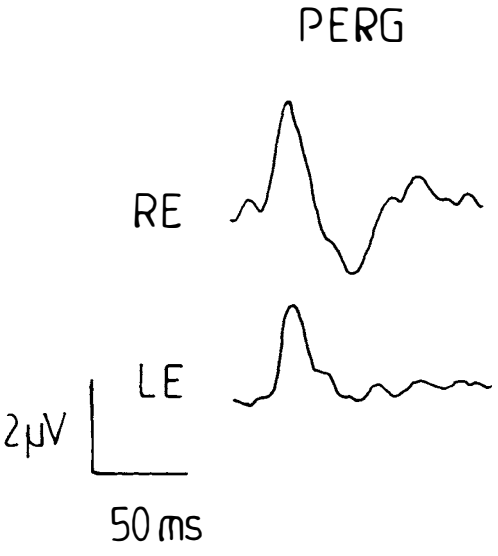

Fig. 12. *Abnormal PERGs in asymmetric ocular hypertension. The PERG from the R eye is normal, contrasting with the response obtained from the more severely affected L eye, in which the N95 is reduced.*

fovea is the only retinal region which can resolve higher spatial frequencies. Thus, Hess and Plant[175] demonstrated that a deficit maximal in the centre of the visual field will give rise to a contrast sensitivity deficit maximal at high spatial frequencies; that a parafoveal deficit predominantly affects medium spatial frequencies; and that a peripheral deficit sparing the fovea will cause a low frequency loss. The ring scotoma of glaucoma suggest that the PERG (which is evoked by quite coarse patterns, which covers a large area of the posterior pole) could be an intrinsically more sensitive test for glaucomatous damage. Another reason suggested by several authors is that the PERG is probably evoked by the larger retinal fibres, and these are known to be selectively damaged in glaucoma[152]: these fibres are connected to extrafoveal ganglion cells.

Alzheimer's disease

Histological examination in patients with Alzheimer's disease have revealed a significant loss of retinal ganglion cells, particularly the larger ones. Barris et al[176] presented PERG results on 16 patients. For transient responses they did not find any reduction of the P-50 component (they did not measure N-95). However, a significantly reduced PERG was found for steady-state conditions, which suggests that there is a selective reduction of the negative component; and indeed in their one illustration of a transient response in such a patient there is a significantly reduced N-95.

Amblyopia

The loss of visual acuity in amblyopia is thought to be cortical in origin.[177-180] However, Ikeda et al[181-183] recorded from retinal ganglion cells of amblyopic kittens and showed certain features of the responses were abnormal. They suggested that a retinal defect is responsible for the cortical anomaly. Jacobsen et al recorded normal focal ERGs in amblyopic patients and concluded that the pre-ganglionic cell function is normal in strabismic amblyopia.

Tuttle[185] examined four adult patients with a mild loss of visual acuity and did not observe any reduction of the P-50 amplitude. Sokol and Nadler however[186,187] reported the results of three adult amblyopic patients. The PERG was reduced in all of them. However the reduction was more pronounced for the N-95 component. In a preliminary report Arden et al[188] found in 13 patients a reduction of the P-50 amplitude of at least 50% when compared to the fellow eye. In order to remove inter-individual variation they measured the ratio

$$\frac{\text{PERG voltage in the amblyopic eye}}{\text{PERG voltage in the fellow eye}}$$

Arden and Wooding[99] examined 62 amblyopic children. In 12 children whose normal eyes were occluded until the morning of the test, abnormally small PERGs were obtained from the *occluded* eye and the ratio above was more than 1.0. In the others, the ratio was, as expected, less than 1.0 because of the reduction of the PERG in the amblyopic eyes. The ratio on the first visit was not related to visual acuity or to squint. A retrospective study was undertaken. In children whose acuity had been improved to normal (intraocular difference one line or less) by orthoptic treatment the ratio was not significantly different to normal. In those in whom visual acuity was improved, but regressed after the end of treatment, the ratio was <1, and in those in whom treatment was ineffective, the ratio was $<<1$. They reported that the relationship between loss of acuity, loss of grating contrast sensitivity, and the reduction in the PERG is complex and may differ according to the type of amblyopia. Wanger and Persson[189] reported a significantly reduced P-50 component in patients with strabismic amblyopia even after careful refraction. In 1984 they reported on eight adult amblyopic patients. Conventional flash-ERG and oscillatory potentials were normal while the PERG was reduced in all eight patients.[190] They concluded that there is no pre-ganglionic retinal dysfunction in this condition, but the ganglion cell function was affected.

Different results are reported by Hess et al[191,192] using steady state conditions, and from Gottlob and Welge-Lussen[193] who measured transient PERGs. Both groups investigated adult amblyopes. Hess et al[191,192] emphasised the importance of fixation control and accurate refraction. When these factors had been individually optimised they did not find PERG responses in amblyopes which were reduced below the lower limits of normal. (They used a 99% confidence limit, and the normal variation

was larger than reported in many other series). However, further analysis of their results suggests a different interpretation. They analysed the results of eight anisometropic patients[191] (Fig 13). In seven of them the PERG while within the normal range was reduced in comparison to the fellow eye and in one patient the amplitude was the same. The probability that seven out of eight patients gave smaller PERGs in the amblyopic eye is p=.03125. In a second paper seven anisometropic patients were investigated.[192] In each patient, the PERG was

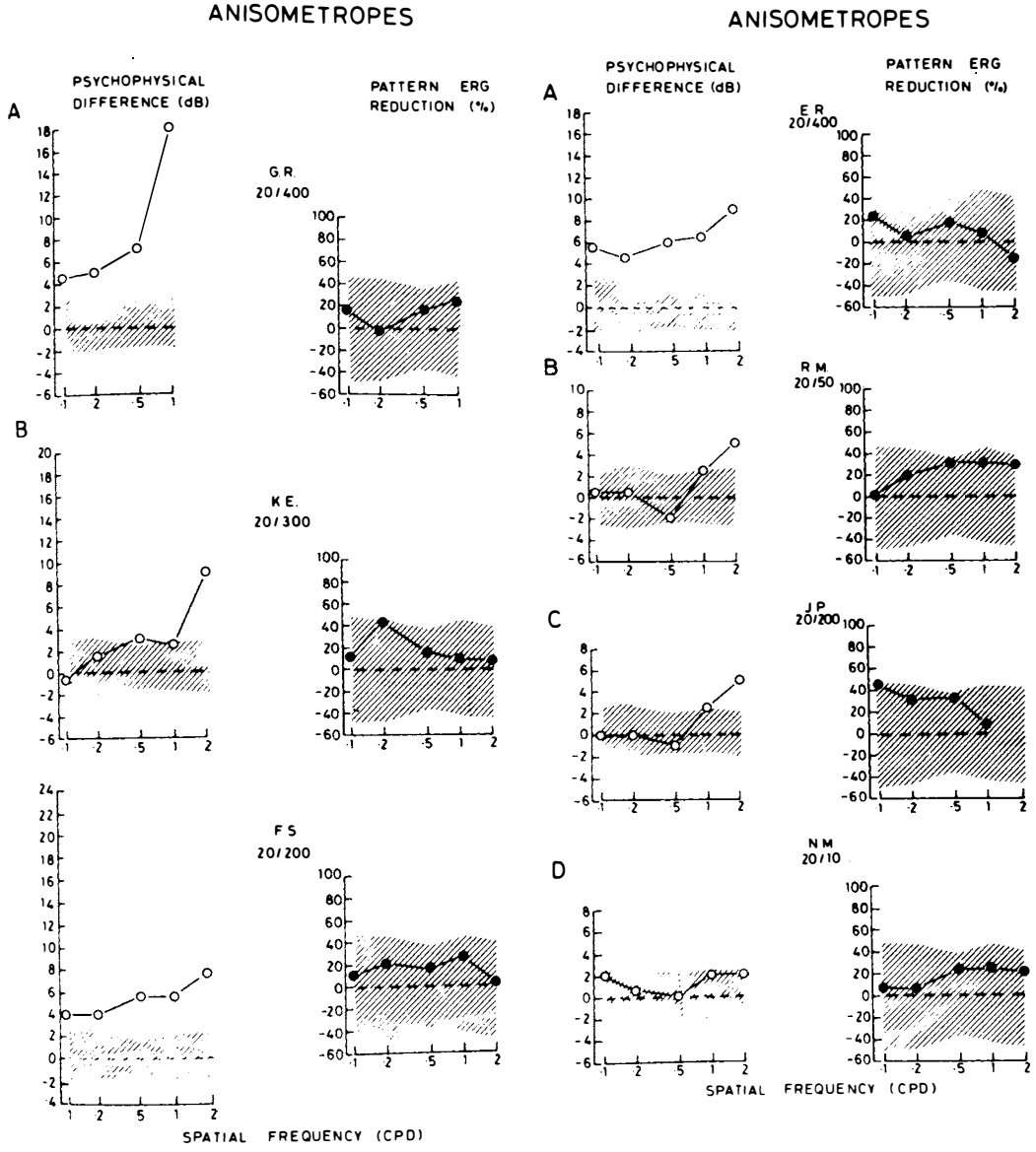

Fig. 13. *PERGs and contrast sensitivity in anisometropic amblyopia. Collected results from a series of patients. For each, the visual acuity and loss of contrast sensitivity is given (left) panel open circles. The horizontal line represents the mean intraocular difference in normals, and the shaded area, the limits of the mean. Note that the psychophysical threshold are considerably raised, especially at higher spatial fequencies. The PERGs are reduced in 29 out of 31 tests, though the differences are much smaller and do not exceed the total variability. Hess et al.*[192]

evoked with the series of different gratings, of five different spatial frequency varying from 0.1 to 2.0 cycles/degree. Thus, 31 separate sets of data were obtained on these patients. In 29 of these the response was smaller for the amblyopic than for the fellow eye. The probability that this result could be achieved by chance is very small ($p<<.01$). Thus, this result would appear to confirm the earlier reports, although, as Hess et al[191,192] pointed out, unless special care is taken to refract the amblyopic eyes, the PERG will be grossly underestimated and it is probable that such an artefact was not taken into account in other investigations. Hess et al[191,192] investigated a number of other sub-varieties of amblyopia, but the numbers in each group were not large enough to determine if any small reduction of the PERG occurred in these groups. Papst and Bopp[194] reported on six patients with refractive amblyopia. A reduced PERG was found in all six patients although the refractive deficit had been carefully corrected.

Although the PERG may be reduced in amblyopia, it is difficult to obtain good responses in young children, and particularly the age-group (2-3 years of age) where such records would be of assistance to the clinicians.

PERG in Systemic Diseases

Diabetic retinopathy

Diabetic retinopathy is common (and becoming more so) and is a very serious blinding condition. Panretinal laser coagulation is helpful in delaying the progress and preventing the complications of the proliferative phase. Fluorescein angiography is still the best method of assessing when background diabetic retinopathy starts to deteriorate. However, this method is invasive and in very few cases has severe side effects. Therefore there have been many attempts to devise an alternative noninvasive method. Flash-electroretinograms remain normal in cases of diabetic retinopathy unless gross retinal damage or vitreous haemorraghe has supervened.[195,196] Of particular interest has been the amplitude of the oscillatory potentials (OPs). These are fast wavelets on the ascending limb of the b-wave, and loss of the OPs is believed to be related to reduction in the blood supply via the retinal arterioles. However, it has been claimed that these wavelets are lost as long as 10 years before background retinopathy is evident.[197] Bresnick et al[198] give a more cautious account: the oscillatory potentials are progressively reduced in amplitude through stages of I-IV of diabetic retinopathy.

Arden et al[98] examined 53 diabetic patients ranging from those who had no retinopathy or funduscopic changes to those in the pre-proliferative state. None had visual symptoms. Bresnick's results[198] on OPs were confirmed. For patients in stages I and II (background retinopathy with microaneurysms etc only) the PERG was within normal limits. However, as soon as cotton-wool spots and angiographic evidence of areas of capillary non-perfusion were present, the PERG was reduced considerably below the normal value. The authors concluded that PERG abnormalities appear only when the capillary circulation is affected and not earlier. Thus the PERG has certain advantages as a screening test. Bopp et al[199] also report reduced P-50 components in 15 diabetic patients with non-proliferative retinopathy. Coupland[200] compared the PERG and the oscillatory potentials in 14 diabetic patients with no retinopathy and 21 patients with background retinopathy. Significantly reduced oscillatory potentials as well as P-50 and N-95 components were found in patients with background retinopathy. However, in patients with no sign of a background retinopathy both components of the PERG were within the normal range, while the OP2+3 amplitudes were significantly reduced. He claims that the oscillatory potentials are more sensitive than the PERG for the detection of incipient background retinopathy in patients who as yet have no ophthalmoscopic signs. Since for purposes of possible laser treatment it is important to distinguish when background retinopathy deteriorates to the pre-proliferative stage, the PERG results should be of clinical use.

Parkinson's disease

Other systems are affected beside the nigrostrial pathways in Parkinson's disease (PD). Abnormal metabolic processes are found throughout the brain:[201] there is reduced olfactory discrimination[202] and delayed pattern VECPs[203-209] have been reported. Bodis-Wollner and Yahr,[204] Gawel et al,[205] Onofrj et al[209] suggested that the visual changes in PD patients are linked to a lack of dopamine. Dopaminergic neurons have been

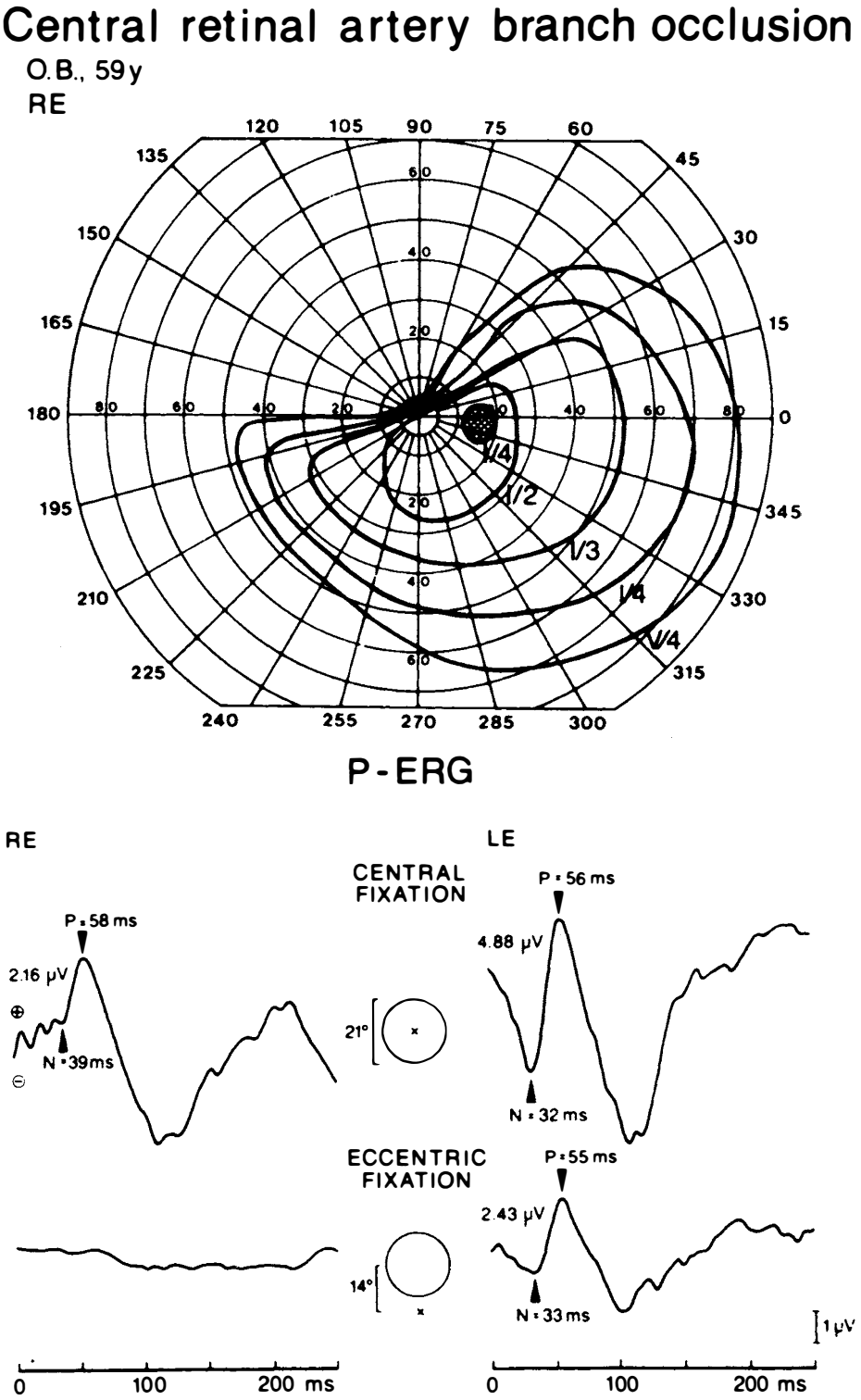

Fig. 14. *PERG in branch vein occlusion. The responses in the affected and non-affected eyes are compared. While the response evoked by central fixation is only slightly reduced, no response can be recorded in the affected eye when the stimulus is confined to the area of the branch occlusion.*
Dodt.[220]

found in the retinas of primates.[210,211]) Reduced flash ERGs[212,213,214] and pattern ERGs have been reported in PD patients.[208,213] Onofrj et al[209] and Ghilardi et al[215] reported a reduction of the PERG in a drug-induced Parkinson-like syndrome in monkeys. Ghilardi et al[215] observed that the reduction is especially pronounced when high spatial frequency stimuli are used. After administration of 100 mg L-DOPA and 10 mg carbidopa the retinal and the cortical responses improved. Thus they concluded that dopamine plays an important role in the generation of pattern stimuli in primates.

Chronic progressive external ophthalmoplegia (CPEO)

CPEO is a possible symptom of "ophthalmoplegia plus" and Kearns-Sayre syndrome, which it is suggested, are mitochondrial disorders. Berdjis et al[216] examined 12 patients with CPEO and found in some of them a reduced flash-electroretinogram while the PERG did not provide any further information.

Myxoedema

Holder[103] examined 11 patients with severe myxoedema for the presence of PVECP delays and changes in PERG responses. A delayed PVECP was only found in one patient. This was accompanied by PERGs of reduced amplitude and increased latency. Following treatment with thyroxin the patient became euthyroid and both PVECP and PERG became normal.

PERG in localised retinal areas

One unquestionable advantage of the PERG has to be seen in the fact that localised retinal pathologies can be investigated. Reduced or even absent PERG responses have been reported in central retinal artery and vein branch occlusion[217,218] and choroidal melanoma[219] when only the area with the pathological process was stimulated. (Fig 14).

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