THE PATTERN ELECTRORETINOGRAM AND THE PATTERN VISUALLY EVOKED POTENTIALS IN DISORDERS OF THE OPTIC NERVE

AN ELECTROPHYSIOLOGICAL
AND CLINICAL STUDY

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof. Dr. C.J. Rijnvos
en volgens besluit van het college van dekanen.
De openbare verdediging zal plaats vinden op
woensdag 24 maart 1993 om 17.00 uur

door

ANDREAS MELCHIOR WILHELMUS VAN HOUWELINGEN

geboren te Schiedam

1993

Promotiecommissie:

Promotor:	**Prof. Dr. G.H.M. van Lith**
Overige leden:	**Prof. Dr. H. Collewijn**
	Prof. Dr. H.F.M. Busch
	Prof. Dr. E.P. Krenning

Aan mijn ouders

De totstandkoming en verspreiding van dit proefschrift zijn mogelijk gemaakt mede dankzij:

Rotterdamse Vereniging Blindenbelangen
Flieringa Stichting
Haagsch Oogheelkundig Fonds

DANKWOORD

Door de inzet van velen is dit proefschrift tot stand gekomen. Ieder van hen ben ik heel veel dank verschuldigd. Het is helaas onmogelijk een ieder bij naam te noemen, echter een aantal personen en afdelingen mogen door hun bijzondere inzet niet onvermeld blijven.

Prof. Dr. G.H.M. van Lith. Beste Fried, zonder jouw begeleiding en mentale ondersteuning was dit proefschrift nooit tot stand gekomen. Met jouw hulp heb ik geleerd dat het in de wetenschap gaat om een zuivere en een beknopte weergave van gedachten en resultaten. Dank voor de vele uren besteed aan het corrigeren van de tekst. De kritische maar zeer leerzame besprekingen bij u thuis, afgerond met een goed glas wijn zal ik niet gauw vergeten.
Mw. van Lith. Dank voor de hartelijke ontvangsten en de overheerlijke vegetarische maaltijden tijdens mijn bezoeken. Het enthousiasme voor deze maaltijden was weliswaar wat minder bij de overige familieleden, maar ik heb ervan genoten.

Prof. Dr. H. Collewijn, Prof. Dr. H.F.M. Busch en Prof. Dr. E.P. Krenning. Bedankt voor het kritisch beoordelen van mijn proefschrift en uw bereidheid in de promotiecommissie plaats te nemen.

Mijn paranimfen Matty Sorel en Peter Don Griot. Jullie hebben met jullie enorme inspanning, niet alleen overdag maar ook s'avonds en in de weekenden, mij een heleboel werk uit handen genomen en er zo voor gezorgd dat ik mij helemaal kon toeleggen op de verdediging van het proefschrift.

De afdeling ERG. Dit hechte en vrolijke team bestaande uit Lies Adriaanse, Sylvia Groen, Matty Sorel, Carina Prins, Angelica Snoek en Caroline Bel wist steeds tijd en apparatuur voor mij te reserveren en de patientenstroom in optimale baan te leiden. Hun aanwezigheid en opgewektheid hebben mijn verblijf in de kelder tot een onvergetelijke tijd gemaakt.

De afdeling Perimetrie. Ook als er eigenlijk geen mogelijkheid bestond om van de apparatuur gebruik te maken wisten zij altijd nog wel een plaatsje te vinden. Bedankt Els van den Oever, Eleen Kranenburg, Geeske Nieuwdam, Marjo van der Horst en Wilma van der Linden.

De electronische werkplaats (Wilfried van Marle en Norbert Baars) en de instrumentmakerij (Gert-Jan Stolk en André Mooi). Er ging nogal eens wat stuk waarna jullie altijd direkt voor mij klaar stonden.

De proefpersonen en de patienten. Zij vormen immers de spil van het proefschrift.

De diverse MS-patientenvereningen via welke zich talloze patienten hebben aangemeld voor het onderzoek.

De stafartsen R. Wijngaarde, L.J. de Heer en J. de Vries die niet alleen trouw patienten stuurden maar mij ook van de benodigde aanvullende gegevens voorzagen.

Bob Schotel voor het maken van de schitterende tekeningen.

De heer P. Mulder van de afdeling Epidemiologie en Biostatistiek van de Erasmus Universiteit Rotterdam voor zijn enorme hulp bij de bewerking van de verkregen resultaten.

TABLE OF CONTENTS

CHAPTER I

INTRODUCTION

Light entering the eye passes through an optical system resulting in a sharp image of a visual object on the light-sensitive retina. The energy of a light quant reaching the retina is transformed into electric energy by the receptor cells in the retina. The resulting potentials are transported via the visual pathways to the visual cortex after which perception takes place. Disorders of the visual system can be found at each stage of the process: in the optical system, during the retinal processing, in the visual pathways, in the visual cortex and finally at the perceptual level.

There are various methods for studying the function of the visual system. On the one hand we have the subjective measures like visual acuity, contrast and colour vision, visual field and dark adaptation, on the other the objective examination of the optical system and the retina by means of optical instruments like the retinoscope, the slit lamp and the ophthalmoscope. Additional objective information can be obtained by electrodiagnostics, sonography, CT-scan and the recently developed Nuclear Magnetic Resonance (NMR).

Electrodiagnostic methods are the major focus of this thesis. Electrodiagnostics allow us to evaluate the retina layer by layer and have already proven to be of great clinical importance in arriving at a diagnosis. In visual electrodiagnostics three basic methods are at our disposal:
1) The Electro Oculogram (EOG), for the registration of the standing potential with its origin in the deep retinal layers. The ratio of this potential in dark- and light-adapted circumstances is clinically applied.
2) The Electroretinogram (ERG), subdivided into:
- The luminance Electroretinogram (ERG) evoked by light stimuli, a blank stimulus without any structures. This classical ERG consists of various waves originating in different structures of the retina. If only a part of the retina is examined, it is called a local electroretinogram.
- The Pattern Electroretinogram (PERG) evoked by a structured stimulus containing contours and contrasts. It is supposed to reflect the activity of the inner retinal layers and probably originates in the ganglion cell layer.

3) The Visually Evoked Potentials (VEPs), reflecting responses of the occipital cortex elicited by unpatterned (Flash VEPs) or patterned stimuli (Pattern VEPs). The last group can be subdivided into pattern reversal stimuli and pattern presentation stimuli.

Although in the last decade no new potentials have been added to the range of visual electrical potentials, a further refinement and standardisation of the existing examination methods plus a growing interest the less well-studied components of the methods mentioned disclose new points of view. One of the research areas in progress is that of the PERG.

The aim of this thesis is to study the PERG in relation to the PVEP in disorders of the optic nerve to find out whether in affections causing optic nerve atrophy not only the PVEPs, but by retrograde degeneration, also the PERGs could be disturbed. In the optic nerve disturbances examined in this study the classical luminance ERG, originating in receptor and bipolar cell layer, remains normal. If the PERG, as often supposed, is elicited in the ganglion cell layer, a ganglion cell disfunction could be reflected in the PERG.
For this purpose correlations between PERG peak amplitudes and latencies on the one hand and optic disc changes as well as visual field loss on the other were studied. Special attention was paid to the presence and degree of pallor (nerve fibre loss) of the optic disc.

Three major groups of optic nerve disturbances were investigated. Each of them may result in damage to the optic nerve fibres with a subsequent ganglion cell degeneration, though the mechanisms as well as the sites of the damage are slightly different. The following groups were studied:

- Glaucoma (subdivided in ocular hypertension, primary open angle glaucoma and normal pressure glaucoma). Mechanical compression by the intraocular pressure as well as ischaemia may be responsible for the damage to the nerve fibres at the optic nerve head within the eye.

- Ophthalmic Graves' disease (OGD) with a possible damage to the intraorbital part of the optic nerve due to direct compression by the ocular muscles.

- Optic neuritis /Multiple Sclerosis (MS). Inflammatory processes as well as demyelination may result in optic nerve atrophy.

All three patient groups underwent the same series of examinations including standardised ophthalmological examination, contrast sensitivity measurement, visual field examination and of course electrodiagnostic examination (PVEP and PERG).

In chapter II a survey is given of the electrodiagnostic methods using unpatterned stimuli. In Chapter III the use of patterned stimuli in electrodiagnostics is discussed. Special attention will be paid to the history, the origin, the anatomical and physiological aspects as well as the clinical applications of the PERG thus far. The influences of equipment and patient variables on the PERG and PVEP results will also be dealt with in this chapter.
An outline of the literature concerning ocular hypertension, primary open angle glaucoma and normal pressure glaucoma in relation to electrodiagnostic observations and ophthalmoscopic aspects is given in chapter IV.
The same is done for optic neuritis/ multiple sclerosis in chapter V, as well as for ophthalmic Graves disease in chapter VI. In chapter VII the methodology of the present study is described, after which the results are presented in chapter VIII. Conclusions and discussion are dealt with in chapter IX, followed by the summary.

CHAPTER II

ELECTRODIAGNOSTIC TOOLS

Introduction

In this chapter the following electrodiagnostic methods, all elicited by unstructured luminance stimuli, will be dealt with:

* The Electro Oculogram (EOG),
* The Electro Retinogram (ERG),
* The Visually Evoked Potentials (VEP).

In the next chapter the use of patterned stimuli will be discussed, resulting in a pattern-ERG (PERG) and a pattern-VEP (PVEP).

Figure 2.1 shows the various layers and cell types of the retina. The axons of the ganglion cells leave the eye through the lamina cribrosa and are gathered in the optic nerve. The sites where the EOG, ERG, VEP, PERG, and PVEP are thought to be generated, are marked.

The Electro Oculogram (EOG)

The Electro Oculogram (EOG) is the indirect measure of the standing potential. It represents an electric potential difference between the cornea and the posterior pole of the eye and can be registered by electrodes placed at the lateral and medial side of the eye. If the eye is rotated towards one of the electrodes an increasing potential will be measured at this side and a decreasing potential at the other. If the eye is rotated towards the other side the reverse will occur. The height of the potential is determined by the standing potential, the angle of rotation, the position of the electrodes and the skin/electrode resistance.

Initially the potential was thought to be related to muscle action potentials and therefore the electro-oculography was used to study eye movements (Meyers, 1929). Later its application for testing the retinal function itself was suggested by Francois et al. (1955) and Ten Doesschate and Ten Doesschate (1956). The standing potential is generated in the photoreceptor layer, Bruch's membrane and the retinal pigment epithelium (Noell, 1954 & 1963; Brown and Wiesel, 1961; Arden and Kelsey, 1962).

Level		Electric potential	
Occipital cortex		PVEP	
Optic nerve			
Retina:			
1)	Internal limiting membrane		
2)	Nerve fibre layer		
3)	Ganglion cell layer	PERG?	
4)	Inner plexiform layer		
5)	Inner nuclear layer	ERG (OPs + b-wave)	
	(bipolar/ Mueller cells)		EOG (light rise)
6)	Outer plexiform layer		
7)	Outer nuclear layer		
	Rods and cones inner segments	ERG (a-wave)	EOG
8)	External limiting membrane		
9)	Rods and cones outer segments	ERG (ERP)	EOG
10)	Retinal pigment epithelium	ERG (c-wave)	EOG (standing potential)

Fig 2.1: Schedule of the electric potentials and their origin.

The large interindividual variability meant that clinical application of the standing potential was disappointing. This variability can be circumvented by measuring changes of the standing potential per individual. One way in which it can be done is by changing retinal illumination. Arden and Barrada (1962) developed a feasible clinical procedure by using the ratio between the maximum value during light adaptation and the lowest value in a dark adapted phase before (see figure 2.2). This ratio, often labelled as the Arden index, is usually between 2.0 and 3.0 with a lower limit of 1.85.

For a normal light rise not only the deep retinal layers, but also the superficial layers have to be intact (Gouras and Carr, 1965). The Arden index is especially lowered in diseases of the deep retinal layers, but also in acute stages of diseases of the superficial retinal layers. The clinical application of the EOG, predominantly determined by the rod system (Elenius and Lehtonen, 1962), focuses on retinal diseases with rod involvement.

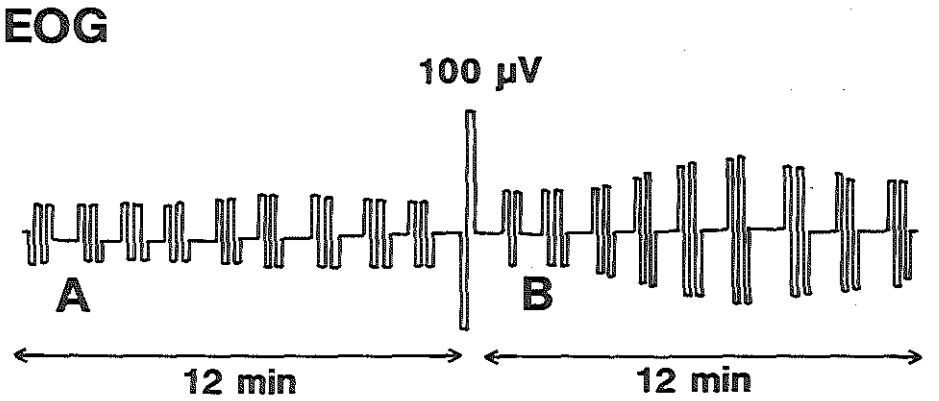

Fig 2.2: EOG recording with a penwriter. During the dark phase (A) and light phase (B) of 12 minutes each, the patient makes three to four standardised eye rotations per minute. The largest amplitudes can be found approximately 8 minutes after the light adaptation. The large streak at the onset of the light phase is a calibration of 100 microvolt. The Arden ratio can be calculated by dividing the highest amplitude during the light phase by the lowest amplitude during the dark phase.

The Electroretinogram (ERG)

The classical Electroretinogram (ERG) is the registration of the retinal potentials obtained by light stimuli. In diagnostics generally short stroboscopic light flashes are used. For recording these potentials contact lenses are usually applied.
The ERG contains various components deriving from different retinal layers. The presence of these components, their amplitudes and latencies, as well as the amplitude ratios depend on the stimulus conditions used. An example of the ERG is given in figure 2.3.

Major contributions to the basic research of the ERG component analysis have been carried out by Granit (1947, 1963), Noell (1954, 1963) and Brown (1961). Clinical pioneers were Karpe (1945), Francois (1952) and Henkes (1954).

The following components of the ERG can be recognized:

* The early receptor potential (ERP):

  Only after applying high intensity light flashes can this potential, originating in the outer segments of the photoreceptor, be detected (Brown and Murakami, 1964).

* The a-wave or late receptor potential (LRP):

  The negative a-wave is an on-response originating in the inner segments of the rods and cones (Brown and Wiesel, 1961).

* The b-wave:

  The positive b-wave is an on-response (Granit 1947, 1963; Noell 1954, 1963) originating in the bipolar cell layer, probably in the Mueller cells.

  Superimposed on the ascending limb of the b-wave three or four wavelets can be found after high stimulus intensities. They are called oscillatory potentials (OPs) by Cobb and Morton (1954) and have been located at the superficial retinal layers, probably the superficial part of the bipolar cell layer or in the ganglion cell layer (Heynen, Wachtmeister and van Norren, 1985).

* The c-wave:

  The c-wave probably originates in the pigment epithelium layer (Noell, 1954, 1963). It is a repolarisation wave with a limited clinical use up to now.

* The d-wave:

  The d-wave is a very small off response with no clinical significance.

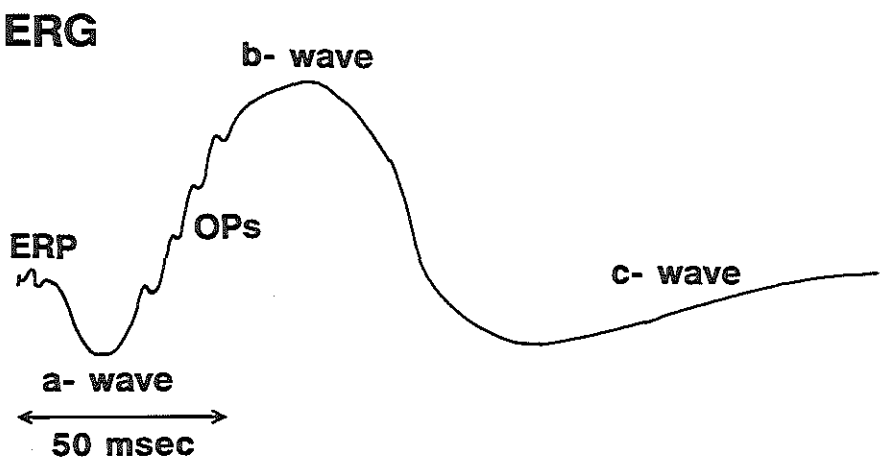

Fig 2.3: A penwriter recording of the classical ERG evoked by light flashes. Several components of the ERG can be recognized: The early receptor potential (ERP), the a-wave, the b-wave, four oscillatory potentials (OPs) superimposed on the ascending limb of the b-wave followed by the c-wave. A time scale is drawn at the bottom.

The ERG is a summation potential with contributions from both superficial and deep retinal layers. This allows some depth analysis of the retina, especially in combination with the EOG. Furthermore the rod and cone system can be measured separately by varying stimulus conditions like flicker frequency, luminance and colour as well as by varying the adaptive state of the eye. The scotopic (rod) ERG originates chiefly in the retinal periphery and midperiphery, the photopic (cone) ERG mainly in the posterior pole. Many attempts have been undertaken to develop a more local (foveal or macular) ERG by applying localized stimuli under photopic conditions in order to suppress rod activity and stray light influences. Its clinical application has remained limited thus far because of fixation and stray light problems (van Lith and Henkes, 1968).

The Visually Evoked Potentials (VEPs)

As early as the second half of the nineteenth century, Richard Caton (1875) had noticed the existence of spontaneous electric brain activity. This electric brain activity could be registered by means of a galvanometer. Caton explains: 'When any part of the grey matter is in a state of functional activity, its electric current usually exhibits negative variation'.
Nowadays the registration of this spontaneous brain activity with the aid of electrodes attached to the skin of the skull in a fixed topographic scheme (Electro-Encephalogram, EEG) is a basic test in neurological examination.
It was not until 1941, when studying the alpha rhythm of the brain, that Adrian (1941) discovered that spontaneous activity could be suppressed by offering a specific sensory input like visual, acoustic or somatosensory stimuli. These stimuli result in a competition between the spontaneous alpha activity and the specific response. From this moment on it became possible to register specific brain functions on restricted areas of the skull. Potentials obtained by offering visual stimuli are called visually evoked potentials (VEPs).
In the years following, major technical improvements and new stimulus-locked averaging-techniques were introduced by Dawson (1947 and 1951), providing a better detection rate of the specific signals by superimposition, summation and averaging techniques. The amplitudes obtained are low and masked by background activity, muscle activity and noise. Therefore a lot of responses have to be averaged before a reliable curve with an acceptable signal to noise ratio is obtained. Nowadays it would be unthinkable to work with electrodiagnostic tools without high-fidelity amplifiers and signal averagers.
Initially luminance VEPs elicited by unstructured light stimuli were applied. These cortical responses elicited by luminance stimulation represent mainly the 20° central retinal area and are predominantly cone driven (Armington, 1966 & 1968; van Lith and Henkes, 1968 & 1970). The clinical applicatibility of this method remained limited because of the substantial inter- and intra-individual variation of the responses. Nowadays flash VEPs in combination

with ERGs are only applied in patients with dense medial opacities in order to detect major abnormalities. Prediction of visual performances after removal of these opacities can only be roughly assessed (Vrijland & van Lith, 1983).

After major technical improvements in the years following, the introduction of patterned stimuli started a new epoch in electrodiagnostics leading to substantial clinical consequences.

CHAPTER III

PATTERN-VEP AND PATTERN-ERG

Pattern stimuli in electrodiagnostics

Pattern stimulation

In the last chapter we saw that the luminance ERG and VEP can contribute to the detection of and the differentiation between various visual disorders. They also help in a rough assessment of the functioning of the eye. Since vision is more than only the perception of light, additional information was obtained by the introduction of a spatial dimension by means of patterns built up of contours and contrasts. ERGs and VEPs obtained with the use of pattern stimulation are called pattern-ERGs (PERGs) and pattern-VEPs (PVEPs).
Pioneers in the evolution of pattern stimulation in electrodiagnostics are Schade (1956), Riggs (1964), Halliday (1972, 1973 and 1976) and Spekreijse (1973) for the occipital potentials, Lawwill (1974) and Maffei and Fiorentini (1981) for the retinal potentials.

Bars versus chessboard patterns

Structured stimuli in electrodiagnostics may consist of black and white stripes (sinusoidal or high contour gratings) or blocks (chessboards). Bars provide a more physiological stimulus and are more suitable in basic research (Campbell et al., 1966). In clinical situations chessboard patterns are preferred because of the higher response levels. Colour patterns have been carried out principally in basic research up to the present.

Reversal stimuli versus presentation stimuli

There are several methods available for pattern stimulation. Most frequently applied are a pattern reversal and an appearance-disappearance (presentation) method. An essential prerequisite of both procedures is that the overall luminance remains constant to minimize the luminance component. In the reversal method, the image of a pattern is phase-shifted in time; this means that all the bright pattern elements become dark and all the dark elements become bright at the same time without changing the overall luminance. In the appearance-disappearance method, the pattern is alternated with a blank field of which the luminance is the mean of the black and white pattern elements.

For generating these two types of pattern stimulation a projector system or a tv-system can be used. The first system is often applied for pattern reversal stimulation. A slide with a chessboard pattern is projected onto a mirror which can be rotated by means of an electromagnet (Cobb et al., 1967). The reflected image can be seen on to a translucent screen. The swing of the mirror can be controlled in such a way that the dark elements are completely replaced by the bright elements. Also the reversal frequency can be altered. This technique is a composite of pattern onset and pattern offset effects and probably of moving effects too. These effects can not be separated. A television system is more versatile and can be used for both the pattern reversal and the pattern presentation method. With the latter, a separation of pattern onset and pattern offset effects can be achieved.

Transient versus steady-state stimulation.
Low reversal frequencies (<8 rev/s) result in a transient response, i.e. no interference between succeeding responses occurs. The advantage of the transient stimulation technique is that the responses can be studied separately. Their various peaks can be analysed. For example in the PVEPs attention is usually focused on the amplitude and the implicit time of the main positive peak at approximately 100 msec, the so called P100. The PERGs have an initial positive peak at approximately 50 msec (P50) followed by a negative trough around 95 msec (N95).
If higher reversal frequencies (>8 rev/s) are used, a steady-state response is obtained with interference effects between successive responses resulting in less detailed curves, more and more resembling a sine wave as frequency increases.
In this study latency shifts were a subject of interest not only for the PVEPs but also for the PERGs therefore an accurate measurement of these latencies was essential. For this reason a low temporal frequency was preferred.

Television versus slide projector system
Both television and slide projector systems have their own advantages and disadvantages. TV-equipment is more versatile but has some major disadvantages like a low contrast range, a low contour sharpness and a 50 Hz frame frequency sometimes interfering with the specific responses. Watching television is watching rapidly changing frames every 20 msec composed of 600 lines written from the top to the bottom of the screen. This technique with an unstable reversal time induces a variability of the latencies which is unnecessarily high for clinical purposes (van Lith & van Marle, 1978) and may induce a 50 Hz response superimposed on the specific response.
Although the slide projector system is less versatile than the TV-equipment the disadvantages of a TV-monitor are absent. Less variable results with a slide projector system have been reported (Trau and Salu, 1984; Yoshii, 1988). Since in our clinic the best PERGs were obtained with a projector pattern reversal system (Ringens et al., 1984) this system was chosen for both the PERG and PVEP registration.

The pattern-VEP

After having used PVEPs in the basic sciences in the sixties, it was Halliday (1972, 1973 and 1976) who pointed out their enormous clinical possibilities especially in optic neuritis, multiple sclerosis and compressive lesions. From this moment on the PVEP became a fully grown electrodiagnostic method with a major clinical impact. It is one of the few available methods for studying visual processing in an alert and perceptually active human being. An example of a PVEP elicited with a pattern reversal slide-projector system is illustrated in figure 3.1.

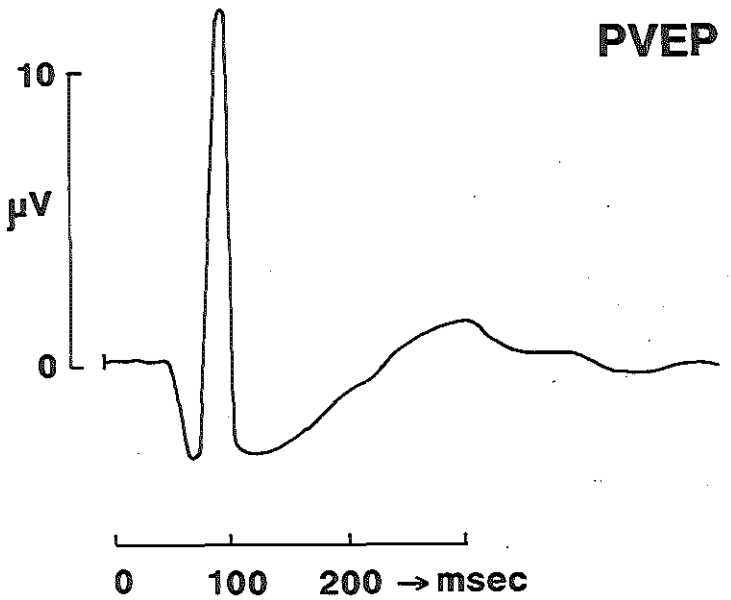

Fig 3.1: Transient reversal PVEP. Several peaks can be seen. For clinical purposes the amplitude and implicit time of the P100 peak are usually measured. Stimulus conditions: chessboard pattern stimulation with a check size of 80 minutes of arc, a contrast of 80% and a reversal frequency of 2 rev/s.

From the clinical work of Halliday et al. and many other authors it can be concluded that various disorders of the retina and of the visual pathways result in lowered amplitudes (atrophic diseases), prolonged latencies (compression or demyelination) or a combination of both (for example optic neuritis).

While the flash-VEP mainly represents the central 20°, the area represented by the pattern-VEP is determined by the size of the pattern elements used. The smaller the elements the more it will represent foveal function and the more the contour specific response will dominate the luminance specific response. For more details about the PVEP concerning theory, techniques and clinical aspects the review of Regan (1972) and Sokol (1976) can be recommended.
Equipment variables as well as patient variables which can influence amplitudes, latencies or shape of the curves will be dealt with after the section on PERGs as the same method and technique is used for the PVEP and the PERG.

The Pattern-ERG

Is the PERG a local foveal ERG?
As discussed in chapter II, attempts to develop a local or a local foveal ERG by applying localized stimuli under photopic conditions (Ganzfeld high luminance background) were not very successful due to the problems caused by fixation and stray light. These problems seemed to be solved, when Riggs et al. (1964) used pattern stimulation in the form of a sophisticated stripe-pattern optical system. The origin of the ERG is known to be in the receptor cells rising to the level of structures in the bipolar cell layer. Originally, this was thought to be true of ERGs elicited by pattern stimulation. It was supposed, however, that contrast-contour components rather than luminance would elicit the response. The finer the grating the more the PERG would originate in the central part of the fovea. This implied that the response was not determined by the size of the screen which circumvented the stray light and fixation problem. Observations that the PERG is indeed strongly cone-driven (Armington, 1966; Sokol, 1972 and Lawwill et al., 1977) supported the view of the PERG as a local foveal cone ERG. However the Rigg's technique disappeared from the scene due to the complicated technical aspects involved in its use and the disappointing clinical results provided (Lawwill et al., 1974 and 1977). It was not until 1981 that an animal experiment renewed interest in the PERG (Maffei and Fiorentini, 1981; Fiorentini et al., 1981). Immediately after the sectioning of the optic nerve of a cat, the luminance ERG and the PERG were both normal. Since the pattern reversal ERG responses were normal during the first week, this was taken as evidence that the operation did not cause circulatory disturbances or other secondary effects that could impair the ERG responses. During the weeks following, the PERG amplitudes decreased but only if large pattern elements were used. Eventually, the PERG elicited by small pattern elements disappeared too. After four months the PERG was totally lost while the luminance ERG was still present without any changes. Anatomical studies of the retina and optic nerve of the cat demonstrated a slow retrograde degeneration of ganglion cells starting several weeks after the sectioning of the

optic nerve. The authors concluded that the disappearance of the PERG is likely to be the result of ganglion cell degeneration. The initial decline of PERG amplitude using large pattern elements is explained by a selective loss of peripheral Y-type ganglion cells with large receptive fields. The X-type, slow-conducting type, ganglion cells with small receptive fields perish somewhat later.
In subsequent years a lot of basic studies (like that of Riemslag et al., 1983) and clinical studies were published. But until now no satisfying answer could be given to the following important fundamental questions: A) Is the PERG a luminance or contrast response or a mixture of both? B) If the origin of the PERG is proximal to the origin of the luminance ERG as indicated by the cat experiment of Maffei and Fiorentini, is the PERG exclusively generated in the ganglion cells or are other cell structures involved too?
A photograph of the slide-projector pattern-reversal system used in this study as well as an example of a registration of the transient reversal PERG can be found in figure 3.2.

Is the PERG a pattern or luminance response?
A major point of discussion remains the ratio between the pattern and luminance contribution to the PERG. The overall luminance of a checkerboard pattern remains constant during reversal stimulation. However, each dark-light transition not only evokes a spatial contrast response but also a local luminance response (i.e. an on- response of 50% of the field and an off- response of 50% of the field).
If the retinal system is linear, in other words if the dark and light elements evoke completely opposite responses, then these local luminance effects would be cancelled out. However, the retinal system is not linear because the on- responses are always larger than the off-responses. Therefore the net result of two counterphase modulated check elements is unequal to zero. Several authors have pointed to this non-linearity and concluded that the PERG is dominated by local luminance effects. (Spekreijse et al., 1973; Korth, 1981; Riemslag et al., 1983; van den Berg et al., 1988).
Of course, if the PERG is a mixture of pattern and luminance specific responses, then the ratio of these responses is important. Using pattern stimulation, Spekreijse et al. (1973) and Riemslag et al. (1983) observed no spatial contrast contribution whatsoever. In a later publication van den Berg, Boltjes and Spekreijse (1988) reviewed these results with a correction for modulation depth-loss due to imperfect optics of the eye (e.g. stray light). The authors concluded that for smaller check sizes the luminance modulation model accounts at best for about half of the response, the rest being a true pattern response.
Thompson and Drasdo (1987 & 1989) and Drasdo et al. (1987) developed mathematical models for the substraction of the luminance contribution to the PERG. After substraction the authors noticed a clear spatial tuning of the PERG amplitudes and concluded that the PERG contains a contribution from retinal generators with spatially receptive fields (ganglion cells). Based on these observations it can be concluded that although the ratio of the pattern component remains disputable at least some pattern component must be present in the PERG.

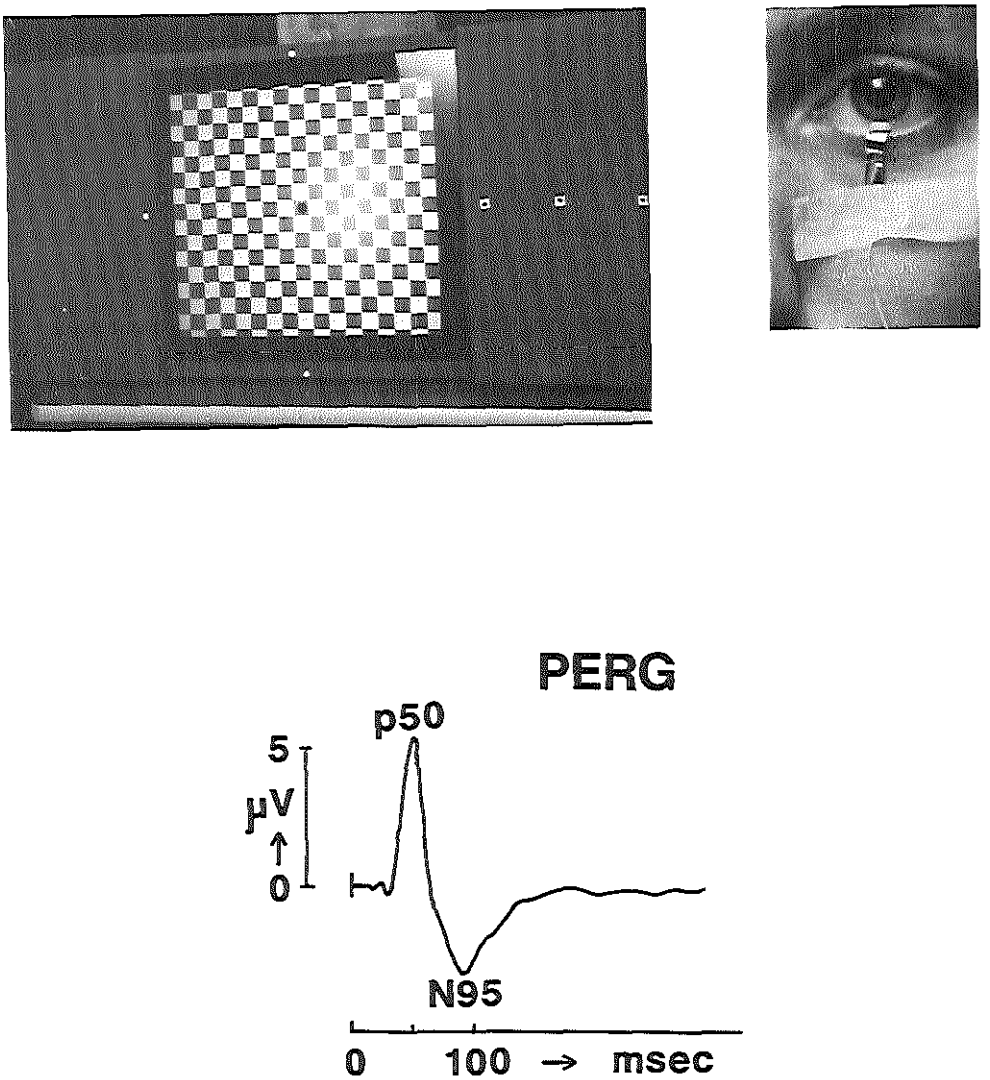

Fig 3.2: Top: Photograph of the pattern reversal equipment used in this study. An image of a checkerboard pattern is projected via a moving mirror system on a translucent screen. The extent of the swing of the mirror as well as the reversal frequency can be controlled. Registration is done with an Arden gold foil electrode inserted in the lower fornix. The ipsilateral earlobe is used as a reference while the contralateral earlobe is used as a ground.
Bottom: An example of a registration of a transient state reversal PERG (pattern element size 80', contrast 86 %, reversal frequency 2 rev/sec). A positive peak at about 50 msec (P50) is followed by a deflection resulting in a negative peak at 95 msec (N95). Amplitudes and latencies of both components are measured.

Is the PERG a ganglion cell response?

Anatomical and histological features of the retina and the ganglion cells

Before discussing whether the PERG is a ganglion cell response, some general features of the ganglion cells will be dealt with. The distribution of the ganglion cells is almost identical to the distribution of the cones (Dawson and Maida, 1984) except for the foveal pit in which no ganglion cells are to be found. The central foveal cones project to the ganglion cells immediately lateral to the foveal pit. Around the foveal pit, the ganglion cells are ten layers thick. This number decreases rapidly towards the periphery of the macula. Outside the macular area the ganglion cells are only one layer thick.

The retina consists of ten different layers. The photoreceptors (130×10^6) project to the bipolar cells which in sequence project to the ganglion cells (1×10^6). These ganglion cells send their action potentials through the optic nerve to the structures of the brain reserved for visual processing. The difference between the total number of photoreceptor and ganglion cells indicates that convergence of information takes place in the proximal direction. In the inner nuclear layer not only bipolar cells but also horizontal cells and amacrine cells are to be found. These cells are responsible for a horizontal spread of the receptor information along the retina. Thus not only convergence but also divergence pathways are present.

Physiology of the ganglion cells; receptive fields

Ganglion cells in the retina continuously generate action potentials which are transported to the parts of the brain associated with vision. Light stimuli can alter the rate of firing action potentials.

A complex interactive network is present within the retina. A ganglion cell not only has synapses with distal cell layers (vertical direction), but also with neuronal elements in its surrounding (horizontal direction). The surrounding neuronal cells of a particular ganglion cell can facilitate or inhibit its rate of firing action potentials. The complex interactive network within the retina causes a vertical as well as a horizontal spread of information. This enables one single photoreceptor to project to several ganglion cells, whereas various photoreceptors can project to one single ganglion cell.

Physiologically each ganglion cell has a receptive field with a central and peripheral part, resembling a target (Kuffler, 1953). The many ganglion cells in the retina give rise to an enormous overlap in these receptive fields. The central and peripheral part of a receptive field are antagonistic. If the centre of a receptive field reacts to switching a light on, the periphery reacts to switching a light off (type I: On-centre and off-surround). The opposite receptive field also exists (Type II: Off-centre and on-surround). Later new subclasses were discovered like X-cells (sustained ganglion cells) specifically suited to responding to the spatial pattern of a stimulus and Y-cells (transient ganglion cells) sensitive to the intention of a motion within the receptive field (Enroth-Cugell and Robson, 1966; Cleland et al.,

1971). An important finding is that across the retina the size of a receptive field is not constant, but increases towards the periphery (Wiesel and Hubel, 1966; Noback, 1967 and Jacobs, 1969). In 1974 two new subclasses were added, i.e. brisk (fast) and sluggish (slow) ganglion cells (Cleland and Levick, 1974). Thus within the centre surround units there are four subclasses resulting in eight classes of ganglion cells. For a broad discussion of the electrophysiology of these cells Davson (1980) can be recommended. If unpatterned light is projected to, or withdrawn from the total area of a receptive field, the rate of firing action potentials changes only slightly because of the antagonistic centre-surround organisation of the receptive field. In theory this can explain why temporal contrast is not such a strong stimulus for the ganglion cell. However, spatial contrast (pattern stimulation) is able to stimulate the centre and periphery of a receptive field with different luminance levels. As a result, both parts add to the response (Davson, 1980).

Support and criticism of the ganglion cell hypothesis

Support and criticism of the hypothesis that the PERG is generated in the ganglion cells can be obtained in three ways:

A) Anatomically by the sectioning of the optic nerve and correlating the PERGs with the histopathological findings. For these purposes animal experiments and a few human case studies are available.

B) Physiologically with experiments based on the physiologic functioning (receptive fields) of the ganglion cells as described above.

C) Clinically by comparing clinical PERG observations in diseases which affect various levels of the visual system with the histopathological aspects known for these diseases.

A) Correlations between histopathological findings and PERGs

Retinal ganglion cell degeneration in experimental optic atrophy in primates was demonstrated by Radius et al. (1978). The degeneration started within six weeks and was completed after ten weeks. A very interesting observation was that pallor of the optic disc could precede the ganglion cell degeneration by several weeks.

In cats and primates a strong correlation between ganglion cell loss and a decrease of the PERG was found by Maffei and Fiorentini (1981), Fiorentini et al. (1981) and Maffei et al. (1985), but such a correlation could not be observed for pigeons by Porciatti et al. (1985). After the sectioning of the optic nerve the attenuation of the PERG took place within four months in the cat and within five weeks in the monkey. Differences between the PERGs of the cat and primates were demonstrated by Hess et al. (1986). This means that the results of animal experiments can not be applied to the human situation.

As demonstrated in animal experiments, ischaemia selectively impairs the function of the proximal retinal layers, changing the firing rate of the ganglion cells resulting in a decrease of PERG amplitudes (Alder and Constable, 1981; Siliprandi et al., 1988).
None of the authors mentioned described histological evidence of circulatory disturbances induced by the sectioning of the optic nerve. In cases showing a normal ophthalmoscopic aspect, a normal flash ERG and a delay of several weeks to months before the PERG vanishes, Maffei and Fiorentini (1981) concluded that the sectioning of the optic nerve did not cause circulatory disturbances or other secondary effects that could have impaired the PERG responses.
In humans a selective ganglion cell loss associated with ophthalmoscopic alterations has been demonstrated by Kupfer (1963). Injury to the optic nerve fibres as far away from the eye as the chiasm resulted in pallor of the optic disc as well a retrograde degeneration of the ganglion cells.
As to circulatory disturbances in the human optic nerve, Harrison et al. (1987) describes a patient with a normal choroidal and retinal circulation after surgical resection of the optic nerve necessitated by a glioma. These findings are explained by large anastomoses between the central retinal artery and the laminar and prelaminar posterior ciliary artery circulation.

B) Support based on the physiologic functioning of the ganglion cells
Given the antagonistic centre-surround organisation of the receptive fields of ganglion cells, one might expect that certain pattern element sizes would elicit a maximal PERG response, a so-called spatial tuning effect.
It was not a spatial tuning effect but a P50 amplitude inversely related to the spatial frequency which was observed by Armington (1971), Groneberg (1980), Trick and Wintermeyer (1982), Dawson et al. (1982), Mitchell and Howe (1984) as well as by Berninger and Schuurmans (1985), whereas this type of spatial tuning effect could be demonstrated by others (Fiorentini et al., 1981; Vaegan and Arden, 1982; Odom and Norcia, 1984; Bodis Wollner et al., 1984; Korth and Rix, 1984; Hess and Baker, 1984; van den Berg and Boltjes, 1988; Porciatti et al., 1988 and Drasdo et al., 1987 & 1989). Spatial selectivity of the N95 component is reported by Berninger and Schuurmans (1985), Korth (1985) as well as by Yoshii (1988).
Those authors who were not able to find a spatial tuning effect in the P50 component offer several explanations. The pattern elements used are larger than the receptive fields of the ganglion cells and thus a maximal amplitude has already been reached (Groneberg, 1980), luminance responses dominate over the contrast responses especially if large pattern elements are used (Trick and Wintermeijer, 1982) or the P50 component is not sensitive to contrast at all (Berninger and Schuurmans, 1985).
Most authors who confirm a spatial tuning effect conclude that the PERG is a combination of luminance and pattern responses but they do not mention the ratio of these responses.

Apart from spatial tuning effects, further support to the ganglion cell hypothesis was provided by Strucl et al. (1984) who demonstrated that as check sizes used become larger the periphery of the retina will contribute more to the PERG. The use of a larger stimulus field causes a shift of the spatial tuning towards lower spatial frequencies (Hess and Baker, 1984; Thompson and Drasdo, 1987). These observations are compatible with the physiological increase of the receptive fields of the ganglion cells towards the periphery.

C) Clinical support and criticism of the ganglion cell hypothesis

Although diseases predominantly affecting the optic nerve will be dealt with in the next chapters, it is of interest to compare the changes of the PERG in diseases primarily affecting the retina with those primarily affecting the optic nerve because different effects are repeatedly observed.

In diseases of the retina the amplitudes of the P50, and to a lesser degree those of the N95, appear to be reduced (Holder, 1987; Ryan and Arden, 1988), while the P50 latencies are prolonged (Lorenz et al., 1989).

The P50 amplitude reductions in retinal diseases are often explained by ischaemia. Ischaemic influences on the PERG were found in patients with a temporary occlusion of the central retinal artery (Fiorentini et al., 1981; Porciatti et al., 1987). The latter authors noticed that ischaemia affects both the PERG and the luminance-ERG, in contrast to diseases involving the optic nerve, where only the PERG is abnormal. The authors conclude that perhaps the flash-ERG and the PERG generators may be similarly affected in retinal diseases, or that like a chain with successive steps the PERG can not be elicited if a distal generator has been destructed. In diabetes, known for its microvascular changes and ischaemia, changes of the PERG have been reported as well. Arden et al. (1986) found normal PERGs in patients with moderate diabetes, but decreased amplitudes in those with cotton wool spots and angiographic evidence of nonperfusion areas. Ryan and Arden (1988) observed changes of both the P50 and the N95 components of the PERG. Trick et al. (1988) noticed increased latencies of P50 even in the presence of minimal retinopathy but without changes of the PERG amplitudes. These results were confirmed by Boschi et al. (1989).

In glaucoma, which will be discussed in the next chapter, PERG amplitude reductions are often noticed; in this disease in particular ischaemia probably plays a major role.

In macular diseases, reductions in PERG P50 amplitudes are reported by Sokol (1972), Sherman (1982), Arden et al. (1984), Celesia and Kaufmann (1985) and Holder (1987). An increasing implicit time of P50 is described by Celesia and Kaufmann (1985) as well as Sherman (1982). No effects on N95 amplitudes or latencies are reported.

An explanation for the repeatedly noticed increase of the P50 latency is given by Lorenz et al. (1989): Latencies are increased because of an altered distal retinal input into the proximal retinal layers.

Although we have to know, what retinal abnormalities may do, more interesting are the changes of the PERG in affections of the optic nerve. In disorders of the optic nerve, amplitude reductions of both P50 and N95 are reported (Holder, 1987; Ryan and Arden, 1988), while P50 latencies appear to be reduced (Lorenz et al., 1989).
Significant P50 amplitude reductions or even absent PERGs are reported in optic neuritis, glaucoma and optic nerve trauma (Groneberg, 1980; Maffei and Fiorentini, 1981; Dawson et al., 1982; May et al., 1982; Fiorentini et al., 1982; Veagan and Billson, 1987). These authors all support the ganglion cell hypothesis. Mashima and Ogughi (1985), observed an amplitude reduction of only 50% in complete traumatic optic atrophy, concluding that the PERG probably is a ganglion cell response with both contour and luminance components.
Normal, or just slightly reduced, PERGs have also been reported in various diseases of the optic nerve like autosomal dominant optic atrophy, trauma and inflammatory processes accompanied by pallor of the optic disc (Sherman, 1982; Ota and Miyake, 1986; Harrison et al., 1987). These authors conclude that the origin of the PERG is not to be found in the ganglion cell layer but at a preganglionair level.
Not much attention has been paid to the P50 latencies thus far. These latencies appear normal or somewhat shortened in optic nerve disorders (Lorenz et al., 1989). They have attributed this to a loss of the slower contour response due to ganglion cell loss, leaving the faster luminance response.
As to the N95 component; Holder (1987) observed that demyelination as well as compression selectively affects the amplitudes of the N95 component, which is confirmed by Ryan and Arden (1988).
Not much has been written about vascular changes in diseases of the optic nerve. Frisén and Claesson (1984) observe a decrease in the central retinal artery calibre following nonvascular lesions of the anterior visual pathways with optic atrophy but are not able to tell which factor comes first; the narrowing of the vessels or the optic nerve atrophy. As already mentioned a normal choroidal and retinal circulation after section of the optic nerve was found by Harrison et al. (1987).

Although strong evidence to support the ganglion cell hypothesis is not available, and although experimental and clinical observations sometimes seem contradictary, the ganglion cell hypothesis remains an interesting theory. The differences found by the authors can probably be explained by stimulation and equipment variables as well as the number of patients studied. The PERG probably has pattern, as well as luminance, components, but the contribution of each appears to be dependent on the stimulation parameters used. In recent years a growing interest for the N95 component has been witnessed. If this component is taken into account two categories of PERG changes can be found, a retinal category, characterised by an amplitude decrease and a latency increase of the P50; and a optic nerve category, characterised by an amplitude reduction of both P50 and N95 as well as a decrease of the P50 latency. As to the clinical data thus far, the conclusion drawn by Dodt (1987) can

best be cited: " The PERG constitutes a new promising method of clinical electroretinography reflecting the activity of the hitherto omitted innermost retinal layers. It thereby contributes essentially to the location of disturbances within the visual system".

Variables which influence the PVEP and PERG response

As certain stimulus and registration parameters were chosen, a survey of the effects of these parameters on the PERG and PVEP amplitudes and latencies is necessary for the interpretation of our own results. The patient variables are essential information in drawing up the inclusion criteria.

Stimulus parameters

Stimulus parameters are the pattern element size, the testfield size, the luminance level, the pattern contrast, the pattern contour and the reversal frequency. Although each of these factors will be dealt with separately, it should be kept in mind that they are all closely connected.

Pattern element size, testfield size and sector contribution
In this study, element sizes of 40 and 80 minutes of arc are used with a testfield size of 22° x 20°. In publications concerning the PVEP, maximum amplitudes are reported using check sizes between 10'-40' (Harter and White, 1968; Armington and Corwin, 1971; Spekreijse, 1973). As to the PERG, an optimal element size between 6' (Hess and Baker, 1984) and 64' (Drasdo et al.,1987 & 1989) is mentioned. Differences in other stimulus parameters like luminance and testfield size are responsible for this spread. Those who report on the N95 mention optimal element sizes between 25-60' (Berninger and Schuurmans, 1985; Yoshii, 1988; Holopigian et al., 1988).

Testfield size
As to the testfield size, the PVEP mediates via the central 3-15 degrees of the retina depending on the pattern element size used (Harter, 1970; van Lith and Henkes, 1970; Spekreijse, 1973; Bartl et al., 1978). As to the PERG, several papers stating a spatial retinal summation with a macular overrepresentation (central 5°) also depending on the element size, are available (Lawwill et al., 1974 & 1977; Vaegan and Arden, 1982; Mitchell and Howe, 1984). From these publications it can be concluded that the PERG involves a larger retinal surface area than the PVEP and thus a larger testfield is needed for the PERG.

Sector contribution

The typical visual field defects reported in glaucoma and ON make it important to refer to publications on differences in the relative contribution of retinal sectors are important. As to the PVEP, the upper hemiretina contributes more than lower hemiretina (Bartl et al., 1978b).

In the PERG a similar observation is made by Yoshii and Päärman (1989), the amplitudes of the upper and nasal hemiretina being higher compared to those of the lower and temporal hemiretina. According to the authors, this is in accordance with the relative ganglion cell distribution as found by van Buren (1963a and 1963 b). Far more compiicated nasal and temporal hemiretinal differences were observed by Skrandies and Leipert (1988).

Luminance

Amplitudes and latencies of the PVEP and PERG are dependent on the mean luminance of the pattern. At lower luminance levels the PVEP amplitudes decrease, while the latencies increase (van Lith and van Marle, 1978). Similar observations were made for the PERG (Arden and Vaegan, 1982; Hess and Baker, 1984; Lorenz et al., 1989).

Not only amplitudes and latencies of the PERG are influenced by the luminance level, but also the spatial selectivity which shifts to lower spatial frequencies with decreasing luminance (Korth and Rix, 1984; Leipert and Gottlob, 1988).

Pattern contrast

Pattern contrast ((Lmax-Lmin)/(Lmax+Lmin)) influences amplitudes, while latencies are almost unaffected. At higher contrast the PERG P50 amplitudes increase linearly (Arden et al.,1982; Mitchell and Howe, 1984; Thompson and Drasdo, 1989) or logarithmically (Ambrosio et al.,1989). The PERG N95 appears not to be influenced by contrast, perhaps because of an early saturation effect (Berninger and Schuurmans, 1985). The spatial tuning frequency slightly shifts to lower frequencies when the contrast increases (Korth and Rix, 1984).

Contour

The more light-dark transitions present and the sharper the edges of the elements the larger the relative pattern contribution to the PVEP and PERG will be. Any circumstance which affects one of these two factors will result in an amplitude reduction. The smaller the pattern elements used the faster the decline in amplitude (Harter and White, 1968).

Pattern reversal frequency

In the literature no unanimous opinion concerning the best reversal frequency for the PERG exists. Some authors report higher PERG amplitudes under steady state stimulation with temporal tuning frequencies varying from 7.5 to 15 rev/sec (Trick and Wintermeijer, 1982; Seiple et al., 1983; Trick and Trick, 1984; Odom and Norcia, 1984). Maximum amplitudes

at 2 rev/sec (transient state) as well as at 16 rev/sec (steady state) are noticed by Hess and Baker (1984). Reversely others, like Ambrosio et al. (1989) report declining PERG amplitudes at higher reversal frequencies.
A remarkable observation concerning the N95 component has been carried out by Berninger and Schuurmans (1985). While the P50 fails to show a tuning effect at any temporal frequency, the N95 shows a spatial tuning around 25'-50' at all reversal frequencies used.
In a pilot study with the equipment available in our institute we found that the best PERGs were obtained with a pattern reversal projector at a transient reversal frequency (2 rev/sec). This frequency fits in well with our clinical experiences concerning the PVEP being best recorded under transient state conditions (1-4 rev/sec).

Registration parameters

Types of electrodes available and electrode placement
The PVEP is registered by silver cup skin electrodes placed over the cortex. The places of these electrodes are standardised.
For the PERG registration several electrodes are available like contact lens electrodes (Henkes contact lens), skin electrodes (Armington and Tepas, 1962), and conjunctival electrodes like the DTL electrode (Dawson, 1979), gold foil electrode (Arden, 1979) and Jet electrode (Grounauer, 1982). The signals obtained with skin electrodes are to low for clinical use. Compared to contact lenses, conjunctival electrodes have many advantages like user-comfort, no image interference and less intra individual variation (Dawson and Trick, 1979; Arden et al., 1979). Among the conjunctival electrodes, modified Arden gold foils are preferred (Ringens and van Lith, 1984). The electrode placement for the PERG registration is not standardised.
Several authors remark on a contamination of the PERG response by PVEP responses in relation to the electrode placement (Bodis-Wollner et al., 1984; Yanashima et al., 1984; Berninger and Schuurmans, 1985; Berninger, 1986; Tan et al., 1989). These contaminations are most likely to be found when the reference electrode is attached to one of the earlobes. However, these observations could not be confirmed by Odom et al. (1987) and Holopigian et al. (1988).
Warnings about a PERG cross-contamination from a non-occluded contralateral eye are given by Seiple and Siegel (1983b), but Tan et al. (1989) conclude that this is not of any clinically significance.
Since we see no substantial PVEP influences, our PERGs are recorded with a modified conjunctival Arden gold foil electrode and a reference electrode attached to the ipsilateral earlobe. The contralateral eye is occluded.

Patient inherent variables

Sex

A shorter latency and larger amplitude PVEP was observed in females compared to males (Celesia et al., 1987). As to the PERG, the same authors report no differences between the two sexes.

Age

As to the PVEP, somewhat decreasing amplitudes and increasing PVEP latencies, especially in the second half of life, are reported by Asselman and Chadwick (1975), Celesia and Daly (1977) as well as by Shaw and Cant (1980).

Reports on age-related PERG effects vary. A statistically insignificant gradual decline in amplitudes until ages over 70 is reported by Arden et al. (1984) and Wanger and Persson (1985 and 1987). Significant lower amplitudes among the elderly but under steady-state stimulation conditions are observed by Trick (1987) and Porciatti et al. (1988).

From an anatomical point of view PERG age-related effects can be expected. A continuous loss of nerve fibres and ganglion cells, especially after the seventh decade is repeatedly observed (Vrabec, 1965; Dolman et al., 1980; Quigley et al., 1982; Balaszi et al., 1984). In our study almost all patients were under the age of 75 and none of them were over 80 years of age.

Interocular difference

No significant difference is known, most authors even report a remarkable similarity between both eyes (Ringens and van Lith, 1984; Trau and Salu, 1984; Trick, 1987).

Pupil size

In analogue with the aperture size of cameras a smaller pupil diameter increases focusing depth but diminishes the luminance level with its effects on the PVEP and the PERG (Holder and Huber, 1984; Trick, 1984; Leipert and Gottlob, 1988).

In mydriasis, the luminance level increases but also a contrast degradation effect is present (Thompson and Drasdo, 1989). This balance between luminance and contrast effects has important clinical consequences.

Patients with a senile miosis or using miotics (like the use of Pilocarpine in glaucoma) and patients in mydriasis were not admitted to the patient groups studied.

Opacities

Any opacity of the optical system of the eye like vitreous opacities, cataract or corneal edema will increase light scatter and blurs the image, which results in diminished contour and contrast vision. Thus not only visual acuity but also the point spread function of the eye will determine the quality of pattern vision (van den Berg and Boltjes, 1988). In opacities the total

luminance will be somewhat lowered too, but this is of minor importance. Patients with evident opacities were not admitted to this study.

Defocusing
Refractive anomalies or inappropriate accommodation blurs the image. This selectively affects the pattern component while the luminance response remains unaltered. A refractive error of just a single dioptre can reduce both the PVEP amplitude (Millidot and Riggs, 1970) and the PERG amplitude by 25% (Persson and Wanger, 1982; Ringens and van Lith, 1984; Leipert & Gottlob, 1987; Lovasik and Konietzny, 1989). Patients with a visual acuity under 1.0 were optimally refracted.

Patient cooperation
Eye movements can influence the shape of PVEP curves resulting in flattened or double-peaked curves. Lovasik and Konietzny (1989) report on the influence of eye movements on PERGs and conclude that this factor plays a minor role compared to factors determining the image quality. The same conclusion is valid for eccentric fixation (Persson and Wanger, 1982) and excessive blinking (Holder, 1987; Holopigian, 1988). If during the measurements our subjects were hampered by a loss of concentration or excessive blinking then the resulting curves were rejected.

Variability of the PVEP and PERG

Variability of the PVEP and PERG is an important item for the interpretation of the results later on to allow a useful judgment about the clinical applicatibility of the PERG under discussion.
The PVEP latencies show a high reproducibility, especially if a slide-projector system is used (Van Lith and van Marle, 1978). The PVEP amplitudes are so variable that their clinical use is limited.
Variability of the PERG is a serious problem. In general, latencies have a better reproducibility than amplitudes (Trau and Salu, 1984; Trick and Trick, 1984). Amplitude variability is independent of age or spatial frequency (Porciatti et al., 1988) or temporal frequency (Holopigian et al., 1988).
Various authors attempted to diminish the variability by changing stimulus and recording conditions. No improvement of the variability could be obtained. The variability of the PERG remains high and is estimated between 26% and 43% (Holopigian et al.,1988).

CHAPTER IV

OCULAR HYPERTENSION, GLAUCOMA AND NORMAL PRESSURE GLAUCOMA

Introduction

Glaucoma is not a single disease, but is the name for a large group of disorders that are characterised by widely diverse clinical and histopathological manifestations (Shields, 1982). The glaucomas can be classified in open angle glaucoma, angle closure glaucoma and developmental glaucoma. They can be further separated into primary and secondary forms. In this study the word glaucoma refers to patients with primary open angle glaucoma (PAOG). For clinical evaluation of POAG three denominators are important: The intraocular pressure, the aspect of the optic nerve and the visual field.

The intraocular pressure

The pressure within the eye, necessary to maintain the shape of the eye, is determined by the quantity of aqueous humour produced in the ciliary epithelium and the amount of outflow via the trabecular meshwork and the uveoscleral flow. The normal intraocular pressure in humans is 10 to 22 mm Hg with some diurnal variation. Elevated pressures usually result from increased resistance to the normal outflow of aqueous humour from the eye. Hypersecretion is sometimes mentioned as another cause, but its existence is doubted and certainly does not play a major role in its pathogenesis.

Elevated pressures do not necessarily result in damage to the eye. Some people can withstand a supranormal pressure level for years without any evidence of damage to the eye. This condition is called ocular hypertension (OHT). The prevalence of OHT in the general population over 40 years of age is about 1-2% (Perkins, 1973). It is estimated that 3 - 35% of these persons will eventually develop glaucoma (Armaly, 1969, 1973; Perkins, 1973 and Shields, 1982). Especially those patients with pressures above 30 mm Hg appear to be at risk. No clinical tests are available yet to select the persons at risk.

If elevated pressures cause obvious damage to one or both eyes the situation is called primary open angle glaucoma (POAG). The damage can be demonstrated objectively (typical changes of the optic disc, nerve fibre layer defects) or subjectively (visual field testing). The changes of optic disc and visual field also occur without an elevated pressure. Apparently in these patients a normal IOP is too high for these eyes. This type is clinically labelled as normal

pressure glaucoma (NPG) An objection to this nomenclature is that in most cases previous periods of supranormal pressures can not be ruled out. Other causes mentioned are an abnormally vulnerable optic disc due to an abnormal disc configuration, low vascular perfusion pressure due to a hemodynamic crisis and a category of mimicking conditions. Glaucoma causes damage to almost every structure of the eye, but the clue to most visual problems is to be found in the damaging of the nerve fibres at the site where they enter the eye, the optic disc, reflected in a cupping. This aspect will be further expounded upon in the next paragraph.

Optic disc changes

In numerous ophthalmic textbooks a list of more or less typical glaucoma-induced visible changes to the optic disc can be found (Shields, 1982; Spencer, 1985; Becker-Schaffer, 1989). The most important changes, studied in the patient groups will be discussed now.

- Cup/Disc ratio (C/D ratio). The cup represents the volume of the optic disc not occupied by neural disc tissue. It is surrounded by a ring of pink neural disc tissue characterized by its evenness (neural retinal rim area). If neural tissue is lost, the cup enlarges. The ratio between cup and optic disc (which in most cases is below 0.4) as well as interocular differences are important parameters in glaucoma screening, whereas the progression of the C/D ratio is an important parameter in the evaluation of the glaucoma therapy. For anatomical reasons the superior and inferior quadrants of the optic disc are more vulnerable. Therefore vertical and horizontal ratios are separately assessed.
- Pallor of the optic disc is not caused by a loss of blood vessels or a proliferation of glia cells but must be attributed to a loss of nerve fibres and a change of optical transparency (Henkind et al., 1977; Quigley and Anderson, 1977; Radius and Anderson, 1979; Quigley et al., 1982). Cupping may progress ahead of the area of pallor. This differs from other causes of optic atrophy in which the area of pallor is typically larger than the cup (Schwartz, 1973). Also the pallor is not necessarily equally distributed but can be limited to one or more segments of the optic disc.
- Notches, a focal enlargement of the cup with small discrete defects in the neural rim area, usually in the inferior temporal quadrant. If the usefulness of studying the neural rim area is compared with the C/D ratio, several authors point to a stronger correlation of the neural rim area with morphology and psychophysical tests (Airaksinen, 1985, 1989; Guthauser et al., 1987; Kitazawa and Matsubara, 1989).
- Bayonetting of the retinal vessels. When the excavation enlarges and also deepens, a double and sharp bending of the blood vessels at the margin of the excavation, as well as onto the floor of the cup, can be noticed.
- Optic disc haemorrhages, flame shaped haemorrhages sometimes seen near the disc margin during progression, but not pathognomonic for glaucoma.
- Peripapillary changes, like a peripapillary halo which is a homogeneous light band lacking choroidal blood supply at the edge of the optic disc.

Visual field

Visual field defects appear to run parallel with cupping and notches of the optic disc. Early signs are baring of the blind spot, generalised constriction of the isopters, paracentral scotomas, arcuate (Bjerrum) scotomas, nasal steps and temporal wedges. If the glaucoma progresses, the scotomas become larger as well as deeper and break through towards the periphery. At a late stage, often a central island and a temporal island of vision are left. Finally the eye may turn blind.

Anatomical aspects of glaucoma

The diameter of the scleral ring, the strength of the lamina cribrosa and the vascular supply are the three characteristics which are responsible for the resistance of the optic nervehead to the IOP (Becker-Schaffer, 1989). The two important theories concerning the cause of glaucomatous damage (the direct pressure theory and the vasogenic theory) require special attention with regard to the site where the nerve fibres leave the eye (lamina cribrosa) and to the vascular blood supply of the optic nervehead.

In the perifoveal region the retinal ganglion cells are small in diameter and organized in several layers. Towards the periphery a broad diversity of ganglion cell diametres can be found, while the number of layers rapidly declines to one single layer. Each ganglion cell has a single axon which leaves the eye through the lamina cribrosa.
At the prelaminar region the unmyelinised fibres are surrounded by astrocytes, glia cells and capillaries. In the postlaminar region the nerve fibres are encompassed by a myelin sheath. All axons together form the optic nerve. It is estimated that the optic nerve contains 700.000 +/- 135.000 nerve fibres with a higher density in the superior and inferior quadrants. A non-significant decline in the total number of nerve fibres during life is reported (Quigley et al., 1988).

As to the blood supply, the central retinal artery and the short posterior ciliary arteries all contribute directly or indirectly to a capillary plexus that supplies the optic nervehead. The central retinal artery predominantly provides the central portions of the optic nerve, while the posterior ciliary arteries mainly supply the optic nervehead. The vascular supply to the retrolaminar portion of the optic nerve comes from branches of the meningeal arteries and centrifugal branches of the central retinal artery.

Histopathological evidence that axons and their ganglion cells are being lost in OHT, glaucoma and NPG has been provided in post mortem studies by Quigley and coworkers (1981, 1982, 1987, 1988 and 1989). Surprisingly in patients with OHT without any visual

field defects, nerve fibre losses up to 40% could be demonstrated. According to Quigley histologic study of the changes of the optic nervehead in OHT and glaucoma verified that these changes could hardly be attributed to the loss of glia cells, capillaries or connective tissue. Although all nerve fibres of the optic nerve are affected, a selectivity for the nerve fibres in the vertical direction of the optic nerve as well as for the large, but not the largest, nerve diametres has been demonstrated by Quigley et al. (1987,1988,1989). These fibres are derived from the midperiphery of the retina.

In the literature several characteristics of these large ganglion cells are mentioned. Large ganglion cells (also named Y ganglion cells or Pα ganglion cells) have large receptive fields and project, via a large diameter fast-conducting axon, to the magnocellular neuronal system (Quigley et al., 1987, 1988; Flanagan and Harding, 1988). The large ganglion cells are preferentially affected in glaucoma (Atkin et al., 1979; Towle et al., 1983; Quigley et al., 1987, 1988; Bach and Speidel-Fiaux, 1989) as well as in optic nerve compression (Flanagan and Harding, 1988). They are best stimulated by a low spatial frequency (Atkin et al., 1979) and a high temporal frequency (Atkin et al., 1979; Towle et al., 1983; Trick, 1985, 1987; Bach and Speidel-Fiaux, 1989).
An interesting aspect of the observations of Quigley et al. (1988 and 1989) is that the nerve fibres of the foveal area are involved too, but here no selectivity for any ganglion cell diameter appears to be present.
Not only histopathological evidence but also funduscopic evidence for axon loss in glaucoma is available. Several authors studied photographs of the nerve fibre layer (NFL) and observed a pattern of local or diffuse damage in glaucoma as well as in OHT (Quigley et al., 1980 & 1981; Anderson, 1983; Airaksinen et al.,1984 & 1989).

The direct pressure theory

The lamina cribrosa is frequently mentioned as the site of the initial damage in glaucoma (Vrabec et al., 1976; Quigley et al., 1979, 1981a, 1981b, 1983 and 1985; Minckler, 1989). Under the microscope the lamina cribrosa resembles a sieve, formed by approximately ten or more different layers (lamellae), containing 200-400 pores each, forming channels through which the axons traverse (Quigley et al., 1981). The number of pores increases in the posterior lamellae which correlates with the branching and division of axonal bundles in the laminar region (Minckler, 1989).
Those authors who adhere to the direct pressure theory, advocate that at this level the axons are destroyed by a continuous impairment of the axonal transport system due to a pressure gradient, or more rapidly, by kinking or a complete strangulation of the nerve fibres themselves.

In animal experiments a decrease or even a complete blockage of the orthograde as well as the retrograde axonal transport at the level of the posterior part of the lamina cribrosa has been demonstrated (Quigley and Anderson, 1976; Minckler et al., 1976 & 1978; Radius et al., 1981; Johansson, 1983).
Repair of the axonal transport after normalizing the IOP and a selective blockage for some nerve fibres was observed by Quigley and Anderson (1976). This selectivity was contradicted by Radius et al. (1981).
Histopathological studies in humans showed a collapse of the anterior lamellae of the lamina cribrosa. The collapse of the lamellae causes a misalignment of the holes followed by stagnation of the axoplasmic flow and strangulation effects (Quigley et al., 1981a, 1981b, 1983; Maumenee, 1983; Minckler, 1989).
Relatively large pores and narrow connective tissue bundles were observed in the superior as well as inferior poles of the optic nerve. As a consequence, these parts are more vulnerable to pressure damage and this can explain the selective damage as observed in glaucoma (Quigley et al., 1987 & 1988). At the level of the lamina cribrosa the same authors observe a normal amount of capillaries which only seem to disappear in the very late stages of glaucoma when all lamellae are collapsed and the entire lamina is bending backwards Although all the authors mentioned did not observe convincing evidence of circulatory impairment and although special attention has been paid in order to avoid circulatory influences in animal experiments as much as possible, a vascular component could not be ruled out by any of them.

The vasogenic theory

Those authors who adhere to the vasogenic theory have numerous reasons for assuming that ischaemia is at least partly responsible for the damage as seen in glaucoma.
Glaucoma predominantly affects the elderly, often in the presence of systemic vascular diseases. The existence of glaucoma without elevated pressures (NPG) also supports the vasogenic theory, as well as the observation that the incidence of visual field defects is much higher among persons with a low blood pressure (Drance, 1972). Furthermore, experimental hypoxia changes the maintained firing-rate of retinal ganglion cells, independent of cell type or location (Alder and Constable, 1981).
Henkind et al. (1967) as well as Kornzweig et al. (1968) thought anatomical support was also present for the vasogenic theory, as they observed long communicating peripapillary blood vessels around the optic disc sensitive to pressure damage. However, they could not establish a correlation between damage to these vessels and visual field defects (Henkind et al., 1968).
Anatomical support for the vasogenic theory could also be found in the paper of Hayreh et al. (1969), who assumed the existence of a highly pressure-vulnerable choroidal vascular

supply to the prelaminar part of the optic disc. The physiological role of this system was soon doubted by Francois et al. (1969). Later this theory was abandoned because such a vascular supply could not be proved convincingly.

As to the functional and experimental support, Kalvin et al., (1966) as well as Zimmerman et al., (1967) demonstrated ischaemical effects in the eye after a sudden increase in IOP level. However, the effects of a longstanding slightly increased IOP level remained unclear. Later, fluorescein angiography showed an impaired circulation at the level of the optic nervehead correlating with the level of the IOP, age and systolic blood pressure, while the choroidal circulation of the surrounding retina remained unaltered. Another important finding was that the ability of the capillary network of the optic disc to provide collateral support in the case of an arteriolar blockage is limited (Loebl and Schwartz, 1977; Schwartz et al., 1977; Hitchings and Spaeth, 1977).

Fluorescein angiography supports the view of an autoregulation system in the optic nervehead which becomes insufficient when the IOP rises or the systemic blood pressure lowers (Hayreh, 1980; Riva et al., 1981; Grunwald et al., 1982, 1984; Robert et al., 1989). This results in ischaemia due to an insufficient perfusion pressure (Hayreh, 1980). Normally the autoregulation mechanism appears to function perfectly between pressures of 7 mm Hg (Grunwald et al., 1982) and almost 30 mm Hg (Riva et al., 1981). In glaucoma, interocular differences in flow rate have been demonstrated as well as abnormal limits of the autoregulation system with an upper limit of 25 mm Hg (Grunwald et al., 1984). The disfunction of the autoregulation mechanism therefore remains a topic of interest (Grunwald et al., 1984 & 1984; Robert et al., 1989). Recently, a metabolic disfunction of the optic nerve was demonstrated even at low IOPs by Novack et al. (1990). This metabolic inhibition appeared to be related to optic nerve ischaemia. Optic disc haemorrhages can also be an indication of ischaemia caused by microinfarctions (Drance et al., 1977; Gloster, 1981). However, they appear only to be present at the retinal level and not at the level of the lamina cribrosa (Bengtsson, 1989).

In conclusion, although several arguments in favour of the vasogenic theory are present, none of the authors has been able to provide sufficient evidence for a vascular component being the only factor in glaucoma.

Electrodiagnostics in ocular hypertension and glaucoma

Of the diseases dealt with in this study, the PVEPs and PERGs have been most intensively studied in relation to glaucoma and OHT. No reports on NPG and electrodiagnostics could be traced. Any comparison of the PVEPs and PERGs is hampered by two major problems: the lack of standardization and problems inherent to the diseases themselves.

The lack of standardization predominantly concerns PERG registration. As discussed in chapter III many equipment variables and patient variables determine the shape, amplitude and latency of the PERG. Although all these variables influence the PERG to a greater or lesser degree, the most important one is the reversal frequency variable.
In the literature some authors advocate low frequencies resulting in transient state responses, others use high frequencies producing steady-state responses. Only a few authors have compared both frequencies. Therefore, if possible, a division will be made between transient and steady-state PERGs for all diseases. This division is also useful because of the different effects the two have on PERG latencies. In transient stimulation a real latency (in milliseconds) can be measured, while in steady-state stimulation only phase shifts (in degrees) are seen. However, many authors also use the term latency for phase shifts in steady-state responses. Realising that it is not correct, I will nevertheless also comply and use the term latency for these phase shifts.

Special attention must be paid to the level of the intraocular pressure (IOP) during the examination (Hawlina et al., 1989). If the PERG is generated in the ganglion cell layer, the glaucomatous damage can be reflected in changes of the PERG. Before one comes to this conclusion, one must be sure that the momentary IOP itself does not influence the PERG results. Indeed, in animal experiments (cats and monkeys) impairment of the electrical retinal activity induced by acute short term IOP elevation has been shown (Grehn and Stange, 1977; Siliprandi et al., 1988). Not only IOP elevation but also hypoxia without pressure elevation changes the maintained firing rate of the ganglion cells (Alder and Constable, 1981).

Indirect indications for a direct effect of the IOP on the PERG result were established in various clinical studies: Papst et al. (1984a, 1984b) observed normal PERG amplitudes in IOPs up to 26 mm Hg. Significant and only partly reversible PERG amplitude reductions with normal latencies occurred above 30 mm Hg. In their discussion Papst et al. suggested a non-fully functional autoregulation mechanism was the cause. Other authors also observed that the PERG results were influenced by the IOP (Van Lith et al., 1984; Wanger and Persson, 1987; Porciatti et al., 1987).
In studies on glaucoma patients, it is remarkable that most authors do not involve the IOP in their patient inclusion criteria except for Papst et al. (1984a, 1984b), Wanger and Persson (1987) and Korth et al. (1989).

The PERG and the PVEP in ocular hypertension

The PERG in ocular hypertension (OHT)

It would be of great clinical interest if the PERG could be used as a test to detect early changes caused by glaucoma. As generally known, not all patients with OHT eventually develop glaucoma. Therefore it is interesting to see whether PERG changes occur in OHT patients, and if so whether they occur in those patients who will later develop glaucoma.

No statistically significant differences in P50 amplitudes between groups of OHT patients and groups of normal respondents were reported by Papst et al. (1984a, 1984b), Wanger and Persson (1985 & 1987), Weinstein et al. (1988), Marx et al. (1988), Hawlina et al. (1989) and Korth et al. (1989). The number of patients studied ranged from 7 (Wanger and Persson, 1985) up to 21 (Wanger and Persson, 1987). The authors mentioned here used transient state stimulation conditions. Although no group differences were found, all authors report individual cases with lowered P50 amplitudes, e.g. Korth et al. (1989) observe a PERG P50 amplitude reduction of more than 2 standard deviations in 27% of their OHT patients.

Papst et al. (1984a, 1984b) observe normal P50 amplitudes only if the eye pressure is below 30 mm Hg, while marked amplitude reductions are found above 30 mm Hg. According to Wanger and Persson (1985) three of the four patients with lowered amplitudes developed signs of early glaucoma within 6-15 months, but in this study only seven patients were examined. Except for Wanger and Persson, none of the other authors mentioned above present a follow-up of their patients.

More promising seemed steady-state stimulation, since in 46-75% of the OHT patients statistically significant differences were found by Trick (1986 & 1987), Porciatti et al. (1987), Drance et al. (1987), Price et al. (1988), Ambrosio et al. (1988) as well as by Bach and Speidel-Fiaux (1989). The differences between both methods have to be carefully interpreted, since the groups studied in steady-state are much larger: from 12 patients (Porciatti et al., 1987) up to 52 patients (Drance et al., 1987; Price et al., 1988).

Those who compare transient with steady-state stimulation (Drance et al., 1987; Price et al., 1988) conclude that steady state stimulation reveals a much higher percentage of abnormal PERGs and thus has a higher sensitivity. The importance of the use of steady-state stimulation is also referred to by Ambrosio et al. (1988) as well as by Bach and Speidel-Fiaux (1989).

Various authors (Trick et al., 1986 & 1987; Drance et al., 1987; Price et al., 1988 as well as Ambrosio et al, 1988) wonder if those patients with the lowered PERG amplitudes are the ones at risk for developing glaucoma. None of these authors present a follow-up.

As to the P50 latencies, no unanimous opinion can be found. Under transient state stimulus conditions normal latencies were reported by Price et al. (1988), Drance et al. (1988) and Korth et al. (1989), while statistically significantly delayed responses were observed by Marx

et al. (1988) resembling the increased latencies of the glaucoma group in their findings. Under steady-state stimulus conditions a phase shift of responses was demonstrated by Price et al. (1988) and Drance et al. (1988).

Only two papers concerning the N95 component in OHT could be found. Under transient state stimulus conditions statistically lowered amplitudes with a bimodal amplitude distribution instead of a Gaussian curve distribution were observed by Weinstein et al. (1988). Based on these findings, the authors conclude that the PERG N95 component is a useful tool in the detection of early glaucoma. These findings are the opposite of those of Hawlina et al. (1989) who report normal N95 amplitudes. They come to the conclusion that the PERG N95 component does not play an important role in the detection of early glaucoma. The intraocular pressure in the patients of Hawlina et al. ranged from 16-23 mm Hg. In their discussion the authors explain that studying eyes exceeding 26 mm Hg did not purely reflect the real extent of ganglion cell loss, but might have revealed "vulnerability" of certain eyes to IOP rises.

The PVEP in ocular hypertension

Statistically normal PVEPs under both transient and steady-state conditions were reported by Sokol et al. (1981), Renard (1987), Abe et al. (1987), Marx et al. (1988) and by Price et al. (1988). Only in a small minority of patients are the latencies somewhat prolonged. Based on these findings, Sokol et al. (1981) conclude that the PVEP will probably not play an important role in the early detection of glaucoma, but Renard (1987) wonders if the patients with the increased latencies will eventually develop glaucoma.

Statistically abnormal PVEPs under both transient and steady-state conditions have also been reported with abnormal PVEPs percentages varying from 23%-77% (Towle et al., 1983; Howe and Mitchell, 1985 and Belizzi et al., 1988). The latencies are prolonged, which may reflect subclinical nerve lesions (Towle et al., 1983), while the amplitudes are lowered. The decline in amplitude appears to be reversible after adequate therapy, which makes the PVEP a very useful tool in preventing definite damage (Bellizzi et al., 1988).

The PERG and the PVEP in glaucoma

The PERG in glaucoma (GLAU)

As to the PERG P50 amplitude, both normal and abnormal amplitudes are reported by authors using transient stimulation, while those authors using steady-state stimulation observe significant amplitude reductions only.

For transient PERGs, normal amplitudes were reported by van den Berg et al. (1986), Weinstein et al. (1988) and Price et al. (1988). Based on these results van den Berg et al.

conclude that the PERG is not generated in the ganglion cells. Using more or less the same check sizes and reversal frequencies, statistically reduced transient PERGs but with a significant overlap with a group of normal respondents were found by Papst et al. (1984a, 1984b), van Lith et al. (1984), Ringens et al. (1986), Wanger and Persson (1983 & 1987), Marx et al. (1988), Korth et al. (1989) and by Hawlina et al. (1989). These authors support the ganglion cell hypothesis or at least see no reason to reject it.

Some of these authors have tried to correlate the transient PERG results with the level of the IOP, the aspect of the optic disc and psychophysical tests like PVEP and visual field testing. Significant correlations between the PERG and the IOP were observed by van Lith et al. (1984), but could not be confirmed by Marx et al. (1988). To exclude the direct influence of the IOP, Wanger and Persson (1987) selected glaucoma patients with normalised IOP. However, the PERG amplitudes remained abnormal. As to the C/D ratio small correlations were noticed by van Lith et al. (1984), Ringens et al. (1986) and Korth et al. (1989). In contrast, no correlation could be established Marx et al. (1988).
Correlations with visual field loss were found by Wanger and Persson (1983) as well as Korth et al. (1989). Compared to the PVEP and the visual field outcome, the transient PERG seems to be abnormal in an earlier stage of glaucoma and thus can provide a useful tool in early diagnosis of glaucoma (van Lith et al., 1984; Papst al., 1984a & 1984b; Wanger and Persson, 1985). The reverse was observed by Marx et al. (1988).

Several authors compared transient PERGs with steady-state PERGs. Equally reduced amplitudes in both types of PERGs are reported by May et al. (1982), Bobak et al. (1983) as well as Howe and Mitchell (1985). Other authors observe a stronger amplitude reduction and a higher sensitivity of the PERG using steady-state stimulation (Trick, 1985, 1986 & 1987; Drance et al., 1987; Price et al., 1988 as well as Bach and Speidel-Fiaux, 1989). The difference between the results of the two types of PERG stimulation is explained by a difference in vulnerability between X (parvocellular) and Y (magnocellular) ganglion cell systems. The magnocellular system, which has a high contrast sensitivity and is best tested with a large check size and high reversal frequency appears to be preferentially damaged in glaucoma (Towle et al., 1983; Trick, 1987; Quigley et al., 1987 & 1988; Bach et al., 1988 as well as Bach and Speidel Fiaux, 1989).

Those authors reporting on steady-state PERGs alone all find reduced amplitudes (Porciatti and von Berger, 1984; Bach et al., 1988 and Zrenner et al., 1988). They conclude that the steady-state PERG is a very sensitive indicator for the degree of damage caused by glaucoma. For steady-state PERGs, correlations with the C/D ratio were found by Trick (1986 & 1987), while Bach and Speidel-Fiaux (1989) observe a correlation with the extent of visual field loss.

Normal as well as abnormal PERG latencies have been reported. Using transient stimulation, normal latencies were observed by Papst et al. (1984a & 1984b), Howe and Mitchell (1985), Drance et al. (1987), Price et al. (1988) as well as Korth et al. (1989). A similar result for steady-state stimulation was found by Howe and Mitchell (1985).
Statistically increased latencies were reported for transient PERGs (van Lith et al., 1984; Trick, 1985; Marx et al., 1988) as well as for steady-state PERGs (Trick et al., 1985; Drance et al., 1987 and Price et al., 1988). Although the latter two groups of authors come to the conclusion that PERG latencies are only abnormal under steady-state stimulation their results are not in concordance with those of Howe and Mitchell (1985) or Trick (1985).

As to the N95 component, only two observations could be traced. Howe and Mitchell (1984) noticed lowered transient as well as steady-state PERG N95 amplitudes in glaucoma. Hawlina et al. (1989) observe a similar result for the transient PERG N95 but only in the presence of visual field defects. Significant prolonged N95 latencies were reported by Howe and Mitchell.

The PVEP in glaucoma
The PVEP in glaucoma appears to be abnormal under both transient and steady-state stimulation. In general the PVEP latencies and amplitudes differ significantly from both the normal as well as the ocular hypertensive groups (Sokol et al., 1981; Towle et al., 1983; Bobak et al., 1983; van Lith et al., 1984; Papst et al., 1984a & 1984b; Howe and Mitchell, 1985; Renard, 1987; Abe et al., 1987; Marx et al., 1988 and Price et al., 1988). Often the PVEP is unmeasurable (Marx et al., 1988).
The percentage of abnormalities reported ranges from 15-40% (Abe et al., 1987) to almost 90-95% (Renard, 1987; van Lith et al., 1984). This range can be explained by the extent of the glaucoma progression. Significant correlations with the C/D ratio, pallor of the optic disc and visual field defects but not with the IOP were found by Towle et al. (1983). Similar observations were done by van Lith et al. (1984). The fact that the PVEP shows almost no abnormalities in the early stages of glaucoma meant that Abe et al. (1987) could conclude that the PVEP is not useful in the detection of early glaucoma. If the PVEP is compared with the PERG, the PVEP is less often affected (Papst et al., 1984a, 1984b).

CHAPTER V

OPTIC NEURITIS / MULTIPLE SCLEROSIS

Introduction

Much has been written on optic neuritis (ON) and multiple sclerosis (MS), for example the impressive work of Walsh and Hoyt (1982).
Optic neuritis is a general term used to describe involvement of the optic nerve as the result of an aseptic inflammation, whether or not caused by infection, or as the result of demyelination. The optic nerve can be affected in the most distal part with swelling of the optic disc (called papillitis) or in more proximal parts behind the lamina cribrosa (called retrobulbar neuritis) at the intraorbital, intracanalicular or intracranial level. Numbers of the incidence of ON vary from 1.6/100.000 (Anmarkrud and Slettnes, 1989) to 3.5/100.000 (Percy et al., 1972). The incidence of MS is approximately 3.0/100.000 with a prevalence of 52-93/100.000 (reported in various areas in Finland by Kinnunen in 1983).
The diagnosis of ON is predominantly a clinical one, characterised by a (sub)acute remarkable or severe loss of vision within a few hours or days. The ON often affects only one eye, but sometimes both eyes are involved simultaneously or subsequently. The period of onset of ON is mainly between 20-40 years of age. Women are two to three times more involved compared to men (Hutchinson, 1976). Seasonal influences, with more ON attacks during spring and summertime, are reported by Taub and Rucker (1954), Bradley and Whitty (1968), Hutchinson (1976) and van der Poel (1985). Pain around the eye (swelling of optic nerve sheaths) or pain when moving the eye can precede the loss of vision. In many cases a pupillary defect (a so called Marcus Gunn positive reaction) can be noticed during the acute stage. Visual field tests show central or paracentral scotomas. Both colour vision as well as contrast vision are disturbed. Electrodiagnostics (flash-VEP or PVEP) can easily confirm the diagnosis in most cases.
The short term prognosis is rather good. Recovery of the visual acuity usually starts after two to three weeks and can be almost complete within one month. In some patients recovery is slow and can take more than a year. In only a very small percentage no recovery at all is noticed after a first attack.
Although visual acuity returns to normal in most cases, other parameters of the visual function like contrast sensitivity and colour perception often remain abnormal (Fleishman

et al., 1987). During effort and in environments with high temperatures (like a hot bath) blurring of vision (Uhthoff's symptom) is frequently noticed.
No specific treatment for ON is known. Corticosteroids can fasten the recovery of ON but have no effect on the final outcome. Recurrences of ON on the same or on the contralateral eye are not unusual. The percentage of recurrences of ON is estimated between 19% (Bradley and Whitty, 1968) and 42% (Cohen et al., 1979).

ON and its relation to MS
There are several indications that ON and MS are linked. Many authors have tried to assess the percentage of patients suffering an attack of ON who will subsequently develop MS. The result is rather disappointing as a wide range of percentages between 17% (Percy et al., 1972) and 78% (Hutchinson, 1978) have been reported.
Considering MS patients instead, ON is the presenting symptom of the disease in 15% - 36% (Percy et al., 1972 and McAlpine, 1964). Up to 37% of the patients with MS reports a history of ON (Percy et al., 1972). Several reasons for these differences can be mentioned like incorrect initial diagnosis and various diagnostic criteria for ON/MS, geographical and racial variations, methodological aspects like a retro- or prospective study, duration of the follow up, hospital based figures and the use of life table analysis.
Numerous papers have been devoted to the assessment of risk factors for the development of MS after an attack of ON. It is not in the scope of this study to deal with all these extensively. In summary, age (between 21-40 years old at the onset of ON), sex (female), recurrences of ON and certain genetic factors are established risk factors. No consensus exists on factors like seasonal influences, pain of the eye during the acute stage of ON and bilateral onset of ON. Edema of the optic disc as well as the severeness of vision loss during the acute stage appear not to be a risk factor at all.

Anatomical and histological changes in ON and MS

While ON is an acute aseptic inflammatory process of the optic nerve head or the optic nerve, the underlying pathology in MS is a combination of demyelination and axonal degeneration, both of which may be insidious (Feinsod and Hoyt, 1975).
At the retinal level axons are not myelinised and therefore demyelination can only take place proximal to the lamina cribrosa. The optic nerves and chiasma appear to be the most frequently affected sites (Lidegaard et al., 1983).
Initially damage to the optic nerve could only be visualised in vitro in autopsied eyes or in vivo by studying the pallor of the optic disc. Later, axonal degeneration at the retinal level could be demonstrated with red free light photographs which visualize the peripapillary nerve fibre layer (Frisén and Hoyt, 1974; Feinsod and Hoyt, 1975; Tagami, 1979; Boschi et al.,

1984; Wildberger and Bär, 1990). Nowadays, in addition to anatomical and histological studies, modern techniques like CT-scan and MRI allow us to study the demyelination process itself by visualising the optic nerve and brain vivo.

Anatomical and histological aspects

In the acute stage of optic neuritis, swelling of the optic disc (papillitis) or sometimes blurring in combination with hyperaemia of the optic disc (retrobulbar neuritis) can be noticed in 43% of the cases (Nikoskelainen, 1975). These signs gradually disappear in the subsequent months. In animal experiments with allergic optic neuritis a generalised impairment of axonal transport has been demonstrated (Rao et al., 1981). The obstructed axoplasm at the level of the lamina cribrosa causes swelling of the prelaminar portions of the optic nerve axons resulting in the clinical appearance of a swollen optic disc. Presumably, retrobulbar neuritis also causes impairment to the axonal transport and function of the optic nerve proximal to the lamina cribrosa; the posterior orbital, intracanalicular and intracranial portions of the optic nerve (Walsh and Hoyt, 1982).

As to nerve fibre changes in MS, irregular optic atrophy, predominantly of the papillomacular bundle as well as of the peripheral fibres, was found by Gartner (1953) in a postmortem study. Although Gartner observed these findings in all his patients, most of them were without a history of ON. The retina showed atrophy of the nerve fibres and ganglion cells, especially in the macula.

In demyelination the perivascular spaces of the optic nerve are infiltrated by lymphocytes, plasma cells and leucocytes. Subsequently the myelin sheaths break down into fat droplets removed by macrophages, followed by glia proliferation and scar formation. Demyelination may lead to slowing of conduction, an (in)complete conduction block and in a failure to transmit a rapid train of impulses (McDonald, 1974). As the degeneration proceeds the nerve fibres themselves are destroyed with an axonal degeneration towards both the proximal and distal segments (Walsh and Hoyt, 1982). At this stage transmission of action potentials is no longer possible.

Changes at the retinal level induced by ON/MS

One of the major questions is whether alterations of the PERG responses are caused by retinal ganglion cell loss. To answer this it is important to review the retinal changes as observed in ON and MS.

From a histopathological point of view, Gartner (1953) noticed a reduction of retinal ganglion cells in autopsied eyes of MS patients. With red light free photographs several authors have searched for evidence of retinal axonal degeneration and the localisation of these alterations within the visible part of the NFL. According to Frisén and Hoyt (1974) as well as Feinsod and Hoyt (1975) the examination of the NFL revealed two patterns of abnormalities in ON/MS patients. The first pattern consists of so called slit like defects (kinds of gaps) in the arcuate nerve fibre bundles combined with some diffuse thinning of the

NFL. The second pattern mainly shows a thinning of the temporal peripapillary nerve fibre bundles and a mild pallor of the temporal part of the optic disc. An important conclusion drawn by both groups of authors is that these alterations indicate nerve fibre atrophy from ganglion cell degeneration. It should be kept in mind that clinical detection of a localised NFL defect is not possible before 50% of the neuronal tissue is lost (Quigley and Addicks, 1982). A similar observation was done by Boschi et al. (1984) who confirmed damage to the NFL in MS patients even without a clear involvement of the visual function. Clinically, the damage became evident after one or more episodes of ON.

The maculopapillar bundle

The maculopapillar bundle (PMB) is of special interest, because ON and MS often affect central vision as can be demonstrated by visual acuity, perimetry, colour vision and contrast vision. Although the visual acuity normally recovers after an attack of ON, a permanent loss of some function can be demonstrated with the psychophysical methods mentioned before (Fleishman et al., 1987). Tagami (1979) reported on atrophy of the PMB in "recovered" optic neuropathies with a visual acuity better than 1.0 (as measured by the conventional methods). Reduction of sensitivity in perimetry and decline of temporal resolution of vision closely corresponded with thinning of the PMB.

Wildberger and Bär (1990) also focused attention on the PMB, but concluded that photographic representation and clinical interpretation of this part of the retina remains difficult because the PMB is thinner and the fibre diameter is smaller. The fibre density, however, is the highest in the retina. Nevertheless, a significant correlation between PMB damage and PVEP impairment was established by them. In their paper Wilberger and Bär also gave an example which demonstrates that even a long-lasting axonal disfunction does not necessarily result in a visible fibre atrophy. Several authors report that the pallor of the optic disc is not such a good measure for the degree of neuronal damage because it is only present in a fraction of the patients with proven damage to the NFL (Frisén and Hoyt, 1974; Feinsod and Hoyt, 1975; Wildberger and Bär, 1990). In contrast Fleishman et al. (1987) report pallor of the optic disc in 77% of the eyes affected by an attack of ON with a minimum recovery period of 6 months.

Vascular abnormalities

Not only NFL abnormalities but also vascular abnormalities in ON/MS on the retinal level are reported. In MS, perivenous cuffing around the cerebral venules is a prominent feature of the active lesion. Vascular abnormalities in the retina have also been detected funduscopically by several authors like Engell and Andersen (1982) and Lightman et al. (1987). The significance of these findings has remained uncertain because of disagreement about the frequency and even the validity of the findings and because little is known about the functional integrity of the apparently abnormal retinal vessels (Lightman et al., 1987). These latter authors find vascular abnormalities (perivenous sheathing and/or leakage of the

vessels) to be a risk factor for the subsequent development of MS after the first attack of ON. The authors suggest that sheathing of the retinal vessels is the visible clinical sign of the perivascular lymphocytic infiltration and accompanying edema which characterises the lesions in MS. Because no myelin is present in the retinal nerve fibres, it can not be secondary to myelin breakdown and focuses attention to the possibility that the primary events leading to demyelination occur at the vascular endothelium.

Electrodiagnostics in optic neuritis (ON) and multiple sclerosis (MS)

In ON it is important to make a distinction between changes in the acute stage, caused by the direct effects of the inflammation, and changes in the chronic stage caused by demyelination and a possible axonal degeneration. In patients with MS, special attention must be paid to the presence of previous attacks of ON. In the literature, obvious changes of the PVEP in ON and MS can be found, especially if it concerns the acute stage. However, changes in the PERG have remained disputable so far. Both the PVEP and PERG changes in ON and MS will be reviewed now with special attention to the stage of the disease.

The PVEP in ON and MS

The PVEP in ON (acute stage and during follow-up)
As to ON in the acute stage, unrecognisable PVEPs or decreased amplitudes in combination with strongly increased latencies are observed by almost every author, regardless of the check size or the reversal frequency. Lightman et al. (1987) observed normal PVEPs in one third of the patients with acute ON. Some authors also report PVEP alterations in the contralateral non-affected eye (Wildberger and van Lith, 1976; Berninger and Heider, 1985). No such observations were described by Halliday (1972).

Reviewing the PVEPs during the recovery of ON is difficult for several reasons. In the years following an attack of ON, some of the patients have ipsi- or contralateral recurrences, while a significant unknown part eventually develops MS. Other factors which contribute to the differences in the outcome of the follow-up are the duration of the follow-up and the sensitivity of the method used.
As to the amplitudes, remarkable differences concerning the degree of recovery of the PVEP after an ON attack can be found. Most authors agree that PVEPs becomes more recognisable during the weeks and months following an ON attack. Amplitudes recover first while shortening of latencies, if it takes place at all, occurs later.
Normal or almost normal amplitudes (>80% of the initial value) after recovery were reported by Halliday (1972), Sherman (1982), Berninger and Heider (1985, 1989), and Gottlob and Heider (1988). Amplitude reductions of 10-30% were reported by Bornstein (1975), which can be explained by the small testfield and the small check size used. Seiple et al. (1983a) reported an amplitude reduction of 50%, while Plant et al. (1986) noticed steady-state PVEP amplitude reductions over 50% several months after an attack of ON. Both groups of authors made no distinction between patients with ON only and those with ON as a part of MS. Wildberger and van Lith (1976) observed significant amplitude reductions in 50% of the patients. As to the PVEP latencies, a recovering latency, but not

one returning to normal limits during the follow-up is observed by Halliday (1972), Bornstein (1975), Wildberger and van Lith (1976), Engell et al. (1987), and Kaufman et al. (1988). Heinrichs and McLean (1988) were able to find normal PVEP latencies in one third of their patients after a follow-up of two years. The authors suppose that the large check size used (120') is responsible for the normalisation. Berninger and Heider (1985, 1989) observed an increase in latency during the first week followed by a decrease during the subsequent weeks until normality is reached. According to the authors this could be explained by the resolution of the edema of the optic nerve which had been present during the acute stage of ON.
As to the contralateral eye, Plant et al. (1986) reported several patients with delayed responses in eyes with no history of optic neuritis and no clinical evidence of MS.

The PVEP in MS
PVEP abnormalities are reported in a majority of the MS patients with a percentage range from 52% (van Dalen and Spekreijse, 1981) to almost 100% (Feinsod and Hoyt, 1975; van Lith et al., 1979; Bobak et al., 1983; Kirkham and Coupland, 1983 and Persson and Wanger, 1984). The presence or absence of a previous ON attack and the distinction between definite, probable or possible MS explains for the spread in percentages. Most authors mentioned none or only one of these two factors. An incidental problem in measuring PVEPs in MS patients is the repeatedly reported change in waveform (W-shaped responses), which makes it difficult to determine the latency of the P100-peak (Feinsod and Hoyt, 1975; Shibasaki and Kuroiwa, 1982 and Oishi et al., 1985).

If the question, whether a history of ON in MS patients could influence the PVEP, is considered, no significant effects are reported by Persson and Wanger (1984) and Heinrichs and McLean (1988). Reversely, van Dalen and Spekreijse (1981) observe a much higher rate of PVEP abnormalities among those eyes with a previous history of ON compared to those without (75% versus 52%), confirmed by Shibasaki and Kuroiwa (1982, 93% versus 40%), Engell et al. (1987, 95% versus 72%) and Sanders et al. (1987, 97% versus 82%). This implies that without a history of ON, PVEPs may still be abnormal, reflecting a subclinical demyelination (Feinsod and Hoyt, 1975). Not only the percentage of PVEP abnormalities is higher among those patients with a history of ON, but also longer latencies are reported (Boschi et al., 1984; Serra et al., 1984; Fujimoto and Adachi-Usami, 1987). These latencies did not improve during follow-up (Kaufman et al., 1988).

As to the distinction between possible, probable and definite MS, an increasing percentage of PVEP abnormalities is reported by van Lith et al. (1979) with percentages of 68% in possible and probable MS patients and 100% in definite MS patients. Shibasaki and Kuroiwa (1982) found percentages of 39% in cases of possible MS and 90% in probable/definite MS cases.
Similar findings were observed by Hutchinson et al. (1983) and Oishi et al. (1985). High

percentages of PVEP abnormalities in patients with definite MS were confirmed in several publications with percentages between 90-100% (Feinsod and Hoyt, 1975; Serra et al., 1984; Persson and Wanger, 1984 and Celesia and Kaufman, 1985).

An interesting aspect is whether correlations are present between PVEP results on the one hand and psychophysics or ophthalmoscopic findings on the other. High correlations between amplitudes and psychophysical methods like visual acuity, contrast sensitivity or visual field are frequently reported (Shibasaki and Kurowa, 1982; Plant et al., 1986 and Celesia et al., 1986). Less clear are the correlations between the PVEP latencies and psychophysics. No significant correlations were reported by Halliday (1972), Shibasaki and Kurowa (1982) nor by Pierelli et al. (1985). Reversely, high correlations between PVEP latency and visual field abnormalities, especially when there are combined central and peripheral defects, were reported by van Dalen and Spekreijse (1981). Fujimoto and Adachi-Usami (1987) observed such a correlation too, but only if there was a sensitivity loss in the most central part of the visual field.
Based on these findings, Sanders et al. (1987) concluded that the PVEP amplitudes represent spatial perception, while the PVEP latencies correlate with the degree of the demyelination.
As to retinal aspects, Boschi et al. (1984) as well as Wildberger and Bär (1990) report a correlation between PVEP impairment and damage to the NFL, especially in the papillomacular bundle.
Sartucci et al. (1989) compared VEPs with MRI imaging and concluded that VEPs have a higher sensitivity in detecting lesions involving the optic nerve or the pathways beyond than MRI imaging. Finally, Hamburger et al. (1984) as well as Sanders and van Lith (1989) observed that PVEPs can play a role in the assessment of the risk of developing MS after an attack of ON.

The PERG in ON and MS

The publications concerning the PERG in ON and MS focus on the amplitudes of the P50 peak. Only Porciatti and von Berger (1984) and Holder (1991) studied the PERG N95 component; using transient state stimulation the amplitude of the N95 appears to be more frequently and more severely affected than the P50 amplitude.
As to the PERG P50 latencies, somewhat decreased latencies during the acute onset of ON were reported by Gottlob and Heider (1988), the rest of the authors who reported upon PERG latencies always found normal latencies (Sherman, 1982; Kirkham and Coupland, 1983; Serra et al., 1984; Porciatti and von Berger, 1984; Ringens et al., 1986; Adachi-Usami, 1987; Vaegan and Billson, 1987).

The PERG in ON

As will be demonstrated, the time lapse between the onset of ON and the moment of examination is a very important factor in comparing the PERGs of the ON patients with the control group.

During the acute onset of ON, normal amplitudes were observed by Arden et al. (1982), Porciatti and von Berger (1984), Ringens et al. (1986) and Kaufman et al. (1988), while lowered amplitudes were observed by Fiorentini et al. (1981), Bobak et al. (1983), Berninger and Heider (1985, 1989), Gottlob and Heider (1988) as well as by Holder (1991). Those authors finding normal amplitudes conclude that PERG is not an indicator of optic nerve damage during the acute phase of ON. Four possible explanations for these seemingly controversial findings are available.

First, two of the five publications with reduced amplitudes deal with steady-state PERGs (Fiorentini et al., 1981 as well as Bobak et al., 1983), while the papers reporting normal amplitudes deal with transient PERGs (except for Porciatti and von Berger, 1984). Experiments with various reversal frequencies have demonstrated a recognisable P50 and N95 component up to 7 rev/s with a decreasing P50 amplitude and an increasing N95 amplitude (Berninger and Schuurmans, 1985; Berninger and Arden 1988; Holder 1991). These authors concluded that under a high (steady-state) reversal frequency mainly the negative PERG component contributes to the response. This interpretation can explain the abnormalities found by Fiorentini et al.(1981) and Bobak et al. (1983). Secondly, in three publications with lowered amplitudes the reduction is only found in the very acute phase of the ON and returns to almost normal within one or more weeks (Berninger and Heider 1985, 1989; Gottlob and Heider, 1988; Holder, 1991). This finding is explained by temporary edema of the optic nerve or by a temporary central retinal disfunction. Most other authors do not define their period of acute onset of ON. Thirdly, in the paper of Bobak et al. (1983) reporting on lower amplitudes, the affected eyes are not compared with normal ones but with the unaffected contralateral eye. Fourthly, those authors reporting normal PERGs studied larger patient groups.

Surprisingly in all the papers mentioned thus far not much attention has been paid to the aspect of the optic disc.

Some authors tried to correlate the PERGs with the PVEPs, but no correlations were found (Bobak et al., 1983; Berninger and Heider, 1985, 1989). Also no correlations with visual acuity or visual field defects could be established (Berninger and Heider, 1985, 1989).

Several authors re-examined their patients some time after the initial ON attack. PERG amplitudes within the normal range during the acute stage and also during a subsequent two years follow-up were reported in ON patients who did not develop MS (Sherman, 1982; Kaufman et al., 1988). Unfortunately, in both studies the results were not compared with the results of the contralateral eye.

Abnormal amplitudes after an initial normal amplitude were found by Arden et al. (1982), Seiple et al. (1983a), Porciatti and von Berger (1984), Plant et al. (1986) as well as by Vaegan and Billson (1987). Arden et al. (1982) observe a temporary rise in PERG P50 amplitude within a few weeks after the onset, explained by a neuronal hyperexcitability of the damaged ganglion cells. At ten weeks all the amplitudes were far below normal. A similar course in amplitude in cases of ON with confirmed MS is reported by Vaegan and Billson (1987). Porciatti and von Berger (1984) found a normal amplitude at the onset of ON gradually declining in time. Pallor of the optic disc was noticed. Both authors recommend low spatial frequencies and high contrast (84%) for steady-state stimulation and somewhat larger check sizes (48' or larger) for transient stimulation.
Seiple et al. (1983a) and Plant et al. (1986) using steady-state stimulation and different check sizes found statistically significant amplitude reductions four or more months after the onset of ON. Due to the considerable overlap with a control group Plant et al. (1986) concluded that the PERG is not a sensitive test in providing evidence of a previous attack of ON.

From these facts it can be concluded that for evaluating the PERG results in ON it is important to pay special attention to the moment of examination of the patient because different mechanisms like edema of the optic disc or temporary central retinal disfunction (during the acute onset of ON), hyperexcitability of the ganglion cells (after one or more weeks) and a retrograde degeneration of the ganglion cells (weeks to months later) can all affect the PERG amplitudes. In the acute phase of ON the PERG is probably normal. If an abnormal PERG is reported then this can be attributed to factors other than a loss of ganglion cells. During the follow-up, a reduction of the PERG amplitude is frequently found which can be explained by a retrograde ganglion cell degeneration.

The PERG in MS
Normal transient PERGs, regardless of a previous history of ON in one or both eyes, were observed by Kirkham and Coupland (1983) and Boschi et al. (1984). Although individual cases with abnormal PERGs (lowered amplitudes and prolonged latencies) were found, as a group, these patients did not differ from the control group. This observation brought Kirkham and Coupland to the conclusion that either the PERG is not generated in the ganglion cells or that only a few intact ganglion cells are needed for a normal PERG. Boschi et al. (1984) explained the normal PERGs and lack of correlation between PERGs and other investigations (like NFL loss and PVEP) as being the logical result of the method employed (low spatial and temporal frequencies with high contrast).

Abnormal PERG amplitudes were observed using steady-state stimulation (Celesia and Kaufman, 1985; Plant et al., 1986; Vaegan and Billson, 1987; Adachi-Usami, 1987 and Kaufman et al., 1988) as well as by using transient state stimulation (Persson and Wanger, 1984; Serra et al., 1984; Celesia and Kaufman, 1985, 1986). Special attention must be paid

to the recent paper of Holder (1991) because this is by far the largest study of patients with optic nerve demyelination (141 patients). The overall incidence of abnormal transient PERGs was 39%. Remarkably, 85% of these abnormalities was related to the N95 component. The PERG was abnormal in 53% of the patients with a history of ON and in 23% of the patients without such a history.

One of the possible explanations for the difference between transient and steady-state stimulation has already been mentioned i.e. under steady-state stimulus conditions the amplitude of the sinus wave is dominated by alterations of the negative component (Berninger and Schuurmans, 1985; Berninger and Arden 1988).
As to the normal and abnormal PERG results in transient stimulation the number of patients studied appears to be of some importance. All the authors using transient stimulation observe individual cases with lowered PERG amplitudes, but significance is only reached in those studies with large patient groups. However, even in the largest patient group (Holder with 141 patients) abnormal P50 amplitudes were only found in 6% of the patients. Another factor could be the number of recurrences of ON. Serra et al. (1984) observe amplitude reductions only in those patients with several attacks of ON, suggesting that axonal involvement only takes place after several attacks. The results of the other authors with PERG abnormalities after the first ON attack do not sustain this view.
In conclusion, in MS the transient PERG P50 amplitude is almost normal, but the steady-state amplitude is lowered which can be explained by influences of the negative component. The transient N95 component appears to be significantly reduced. Patients with a history of ON have more reduced PERGs than those without.

As to the correlation between PERGs and axonal degeneration three groups of authors advocate that PERG is a useful method in the differential diagnosis between axonal and demyelinating optic nerve impairment. (Serra et al.,1984: Kaufman et al.,1986 and Celesia and Kaufman, 1985 & 1986). These authors suggest a prognostic value for the PERG in optic neuropathy. Celesia and Kaufman (1985) find abnormal PERGs in a third of their MS patients and report a parallel of the PERG amplitudes with visual recovery, nerve fibre loss and optic atrophy. An interesting subdivision into four categories of MS patients is proposed by Celesia and Kaufman (1986). One category with normal PERGs and prolonged PVEPs indicating demyelination only, one with abnormal PERGs and prolonged PVEPs representing partial axon involvement and retrograde ganglion cell degeneration, one with total absence of PERGs and PVEPs which points to optic atrophy and one with normal PERGs with absent PVEPs indicating a total conduction block somewhere along the optic nerve.

Some authors tried to correlate the PERG results with psychophysic tests (visual acuity, contrast vision, visual field) or with ophthalmoscopic findings (optic disc pallor). However, these reports are sporadic. The following facts were mentioned: PERGs appear not to be

correlated with nerve fibre layer loss (Boschi et al., 1984), pallor of the optic discs (Persson and Wanger, 1984) or with visual acuity, visual field defects or any PVEP findings (Berninger and Heider, 1985; Adachi-Usami, 1987). These findings do not support the ganglion cell hypothesis.
In contrast, other authors do find correlations: PERG amplitudes correlate well with PVEP latencies (Wanger and Persson, 1984), visual field defects (Celesia and Kaufman, 1985) or with pallor of the optic disc (Serra et al., 1984, Celesia and Kaufman, 1985). These results do support the ganglion cell hypothesis. In conclusion, until now correlations between the PERG results and psychophysic examinations or ophthalmoscopic findings have not been studied systematically. The existing reports upon this item are rather contradictory.

CHAPTER VI

OPHTHALMIC GRAVES' DISEASE

Introduction

Metabolic activity is regulated by the thyroid hormones T3 and T4. In the plasma both hormones are bound to proteins for over 99.9% Biological activity is performed by the unbound fraction. Normally a feedback mechanism between hypothalamus, anterior pituitary and thyroid gland keeps the levels of these hormones between the required levels.
Several diseases can affect this autoregulation mechanism. One of them is the autoimmune Graves' disease, resulting in hyperthyroidism. Excessive levels of thyroid hormones result in general complaints like tremors, sweating, weight loss, tachycardia, nervousness, palpitations and heat intolerance.
The term ophthalmic Graves disease (OGD) might be somewhat confusing. Rundle and Wilson originally used the term 'ophthalmic form of Graves' disease' for ocular manifestations of Graves' disease unaccompanied by goitre and or hyperthyroidism (Rundle and Wilson, 1945). Later thyroid enlargement was included provided that the patient was euthyroid and had no history of hyperthyroidism (Hall et al., 1970). Since the ophthalmic signs of these entities are similar to those seen in Graves' hyperthyroidism it gradually came into use to apply the term OGD for the typical eye signs independent of the thyroid hormone levels at the moment of examination.
Hyperthyroidism and ophthalmopathy appear to be related. In an overview, Gorman and Bahn (1989) explain that a majority of patients with ophthalmopathy have a history of hyperthyroidism. Reversely, obvious infiltrative ophthalmopathy is seen in 3-5% of the hyperthyroid patients (Hamilton et al., 1960; Jacobson and Gorman, 1984), whereas after careful examination in 60-90% of the hyperthyroid patients some ophthalmic abnormalities can be demonstrated (Gorman and Bahn, 1989).
An autoimmune basis for OGD is probable. A thyroid antibody has been isolated. It is assumed that the ophthalmopathy is caused by a cross-reaction of this antibody with a common surface antigen on eye muscle cells and orbital fibroblasts (Hiromatsu et al., 1988; Salvi et al., 1990). A separate retro-ocular fibroblast antigen has also been considered as a possible cause (Gorman and Bahn, 1989).

In this chapter the clinical symptoms (classified by the NOSPECS system, see table 6.1) as well as the treatment of OGD will be dealt with in brief. Optic neuropathy, a rather rare complication of OGD will be discussed next. Finally, factors influencing the PERG and the PVEP in this disease, as well as clinical PERG and PVEP observations in OGD patients, will be reviewed.

Clinical signs and classification of OGD

Eyelid retraction due to muscle overaction or contraction has long been recognized as a cardinal sign of OGD. More important is the infiltrative ophthalmopathy because this may result in traction or compression of the optic nerve. Outside the orbit this can easily be noticed by a sometimes impressive injection of the conjunctiva, furthermore by chemosis, edema of the eyelids and kerato-conjunctivitis. Inside the orbit, total tissue volume increases due to an infiltration of the muscles and the connective tissue by chronic inflammatory cells. Proptosis of the eye(s) often takes place, which can be interpreted as a safety mechanism employed by the eye to relieve the compression. The amount of proptosis of the eye can be measured in millimetres with the Hertel mirror apparatus. In later stadia of OGD, the fluid accumulation and cellular infiltration of the orbit can be followed by a fibrotic stadium.
In a small percentage of the OGD patients (in less than 5%) the disease is complicated by optic neuropathy. Remarkably, this often occurs in the absence of a significant proptosis. Visual acuity, colour vision, pupillary reactions, visual field examinations and eye movements may be seriously affected. If this situation is not treated, it can end in blindness. Management of the thyroid ophthalmopathy may be topical (protecting glasses, prisms, lubricants), systemic (prednisone, or cyclosporin in combination with prednisone), irradiation (orbital or retrobulbar irradiation) or surgical (orbital decompression surgery or muscle corrections).

In order to classify the eye changes in ophthalmic Graves disease the NOSPECS classification was originally introduced by Werner in 1969 and modified by the same author in 1977. As can be seen in table 6.1 the mnemonics in the word NOSPECS stand for No physical signs, Only signs, Soft tissue involvement, Proptosis, Extra ocular muscle involvement, Corneal involvement and Sight loss. This classification allows an evaluation of the seriousness of the OGD. One of the disadvantages of the classification system and therefore criticised by authors like Wiersinga et al. (1989) and Mourits et al. (1989) is that it is based on momentary symptoms rather than the rate of progression of the disease. The process does not necessarily follow each of the classes and it is not unusual for one or more classes to be skipped. Although the introduction of the NOSPECS system provided a useful method for classification of OGD patients, a paucity of numerical data concerning the OGD remained.

Classification	Symptoms
Class 0	No physical signs or symptoms
Class 1	Only signs (upper lid retraction, stare and lid lag)
Class 2	Soft tissue involvement with symptoms and signs 2.0) Absent 2.a) Minimal 2.b) Moderate 2.c) Marked
Class 3	Proptosis 3 mm or more in excess of upper normal limits 3.0) Absent 3.a) 3-4 mm increase (23-24 mm measured by the Hertel apparatus) 3.b) 5-7 mm increase (25-27 mm) 3.c) 8 mm or more increase (≥28 mm)
Class 4	Extra ocular muscle involvement (usually with diplopia, other symptoms and signs) 4.0) Absent 4.a) Limitation of motion at extremes of gaze 4.b) Evident restriction of motion 4.c) Fixation of a globe or globes
Class 5	Corneal involvement (primarily due to lagophthalmus) 5.0) Absent 5.a) Stippling of the cornea 5.b) Ulceration 5.c) Clouding, necrosis, perforation
Class 6	Sight loss (due to optic nerve involvement) 6.0) Absent 6.a) Disc pallor or visual field defect, vision 20/20 to 20/60 6.b) Same, but vision 20/70 - 20/200 6.c) Blindness, i.e. failure to perceive light, vision less than 20/200

Table 6.1: The NOSPECS classification (according to Werner 1969/1977)

One of the few prospective studies concerning a large group of OGD patients (90 patients) has been published by Wiersinga et al. (1989). The mean patient age was 45 years, with a female-male ratio of almost 3:1. In most cases the disease was bilateral (86%). Clinically-obvious thyroid disease in the past or present was found in 78%. According to the NOSPECS classification, soft tissue involvement was observed in over 90%, proptosis in 42% and severe proptosis (> 3 mm) in 30%, eye muscle involvement in 60%, corneal involvement in 9% and sight loss in 34% (slightly in 29%, moderate to severe in 5%). No differences between right and left eyes were observed and no differences were found in age distribution between the OGD patients and patients with only thyroidal Graves disease. Neither does there seem to be no any difference in ophthalmological presentation between OGD patients with and OGD patients without clinically manifest thyroid disease. Only if the OGD is unilateral is the delay between onset of thyroidal disease and OGD shorter. In their conclusion the authors suggest that unilateral OGD is just an early stage of the disease which will end in bilateral involvement.

Optic nerve involvement (optic neuropathy in OGD)

The optic nerves can be involved in progressive stages of OGD. Trobe (1981) reviews symptoms and signs of optic nerve involvement in OGD. He estimates that the prevalence of optic nerve involvement in thyroidal disfunction is less than 5%. This percentage was later confirmed by Wiersinga et al. (1989) who observed some loss of vision in 34% of the 90 patients studied (Class 6a) and a severe loss of vision (Class 6b or 6c) in only 5% of their patients. Trobe (1981) observes that compression of the optic nerve often takes place without a marked proptosis. Loss of vision is often insidious and the elderly are more affected by the optic neuropathy than younger patients. Symptoms of OGD are always present but may not be florid. Surprisingly, eye movements are reduced in all directions in both eyes but without diplopia (indicating a panmyositis). In visual field examinations, central scotomas and inferior arcuate scotomas are frequently observed. In 25-33% the optic nervehead is hyperaemic, in 10 to 20% optic disc pallor can be observed, but in the remainder of the eyes the nervehead appears normal.
In a more recent review (Neigel et al., 1988) comparing 58 OGD patients with optic neuropathy with 60 OGD patients without neuropathy, these findings were largely confirmed. The diagnosis optic neuropathy was based on the presence of a visual deficit (any combination of decreased visual acuity, abnormal visual field and/or psychophysical tests) and/or an afferent pupillary defect. The authors observed that the optic neuropathy group presented at a later age and that the onset of OGD was at a later stage. The patients in this group were more likely to be male and/or diabetic, have more disturbances in colour vision and demonstrated a higher intraocular pressure especially after elevation of the eye.

Furthermore, a visual acuity less then 0.5 was found in almost 50% of the patients, optic disc pallor in 24%, elevation and hyperaemia of the optic disc in 28% and visual field defects in 66%. Their most sensitive indicator of imminent neuropathy turned out to be the PVEP (94% abnormalities), followed by colour vision. Ophthalmoscopy was not a consistent indicator, with slightly less than half of the patients having optic discs with a normal appearence.

Several explanations have been given for the optic neuropathy.
It is generally thought that the optic neuropathy in OGD is the result of direct compression of the optic nerve and/or of its blood supply. Since the introduction of the CT-scan, extraocular muscle encroachment has been implicated as the major cause of optic neuropathy in OGD patients. Trokel and Hilal (1980), Kennerdel et al. (1981) and Neigel et al. (1988) provide evidence that this optic neuropathy is secondary to compression of the optic nerves at the orbital apex by enlarged extraocular muscles (apical crowding: Figure 6.2). According to Kennerdel et al. (1981) it seems as if the optic nerve is more resistant to a stretch type of injury than to a perpendicular compressive type of injury. Feldon and Weiner (1982) found a correlation between the extraocular muscle volume and the total soft tissue volume with the severity of the ophthalmopathy. The best correlations were found for the medial and lateral muscles groups. In conclusion the authors think that horizontal eye movement disfunction may be an ominous clinical sign. In 1984 Feldon et al. suggest that it is not only the degree of extraocular muscle enlargement, but also alterations in the elasticity of these muscles which determine the risk for developing optic neuropathy.
The degree of proptosis therefore appears not to be such an important parameter neither in the evaluation of the extraocular muscle enlargement nor in the assessment of the risk of developing optic neuropathy. Optic nerve involvement was found to be a function of both total volume and limitation of motility (especially in horizontal direction) rather than either parameter singly. The authors conclude that apical optic nerve compression is more likely to occur with fibrotic muscle than with more flexible muscle of the same volume. Anderson et al. (1989) report three cases with optic neuropathy with normal sized or minimally enlarged extraocular muscles. According to the authors short optic nerves very sensitive to anteroposterior stretch appears to be the most logic explanation in these cases. On CT-scans the S-shape of the nerves disappeared and the optic nerves in these patients seemed to be stretched.
Vascular causes of optic neuropathy have also been postulated. The results of orbital venography and fluorescein angiography suggest that increased intraorbital pressure causes interference with the orbital and the ocular circulation (Cant and Wilson, 1974). An impaired venous drainage has also been mentioned by Gorman and Bahn (1989). Further indirect support to the vascular theory can be found in the observation that older patients with vascular diseases appear to be more vulnerable. Optic neuropathy in OGD is more frequently observed among older patients (Day and Carrol, 1962; Wijngaarde and van Lith, 1979; Trobe, 1981; Neigel et al., 1988).

Mourits et al. (1989) warn for the observation that not every decline in visual acuity must be attributed to optic neuropathy. Not only a raised intraorbital pressure level, but also corneal defects result in a decrease of visual acuity. This decrease is easily confused with that due to optic neuropathy.

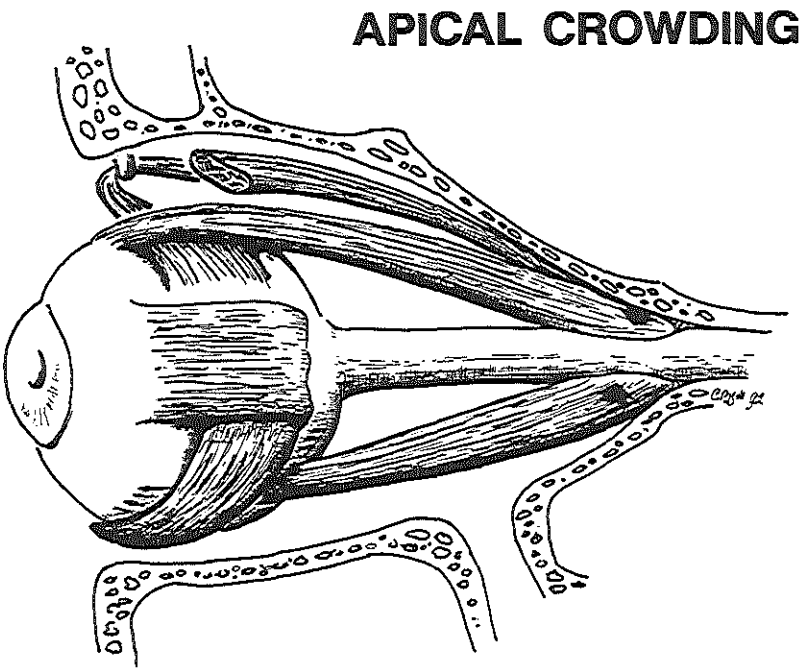

Fig 6.2: Apical crowding. The optic nerve lies embedded in the extraocular muscles. The orbita has a cone-shaped figure. At the top of this cone the optic nerve leaves the orbita towards the chiasm. In OGD patients, the extraocular muscles and soft tissue are infiltrated with inflammatory cells and therefore thickened. CT-scans (see text) point to the apex as the site, where the optic nerve is damaged because of the elevated pressure (apical crowding).

The PERG and the PVEP in endocrine orbitopathy

During the follow-up and treatment of an OGD patient it is not uncommon for the patient to go through a period of hypothyroidism. In this period ophthalmic complaints can still be present or even get worse. Therefore in a review concerning alterations of the PERG and the PVEP in endocrine orbitopathy the effects of compression (direct or ischaemic) as well as hypo- and hyperthyroidism must be taken into consideration.

Effects of optic nerve compression on the PERGs and PVEPs

As to the PERG only a few papers are known, which are rather contradictive, because most of them are case reports with only a few patients. Normal PERGs are reported in a patient with a pituitary tumour and evident optic atrophy by Ota and Miyake (1986), and in two patients with orbital tumours by Mizota et al. (1988). Lowered amplitudes but normal latencies are found by Lorenz et al. (1989) in six patients with a tumour compression and finally a total absent PERG in a patient with a meningioma impinging on the optic nerve is observed by Seiple and Siegel (1983a).

As to the PVEP, increased latencies and lowered amplitudes in compressive diseases along the optical tract were already described by Halliday et al. (1976) and confirmed by Holder (1978), van Lith et al. (1982), Mizota et al. (1988) and Flanagan and Harding (1988). Marked disturbances of the PVEP P100 latency however are only noticed in those tumours exerting real pressure on the optic nerve fibres (van Lith et al., 1982).

Flanagan and Harding (1988) report changes of the PVEP even in the absence of any visual field changes if large pattern sizes are used. The authors think that their results reflect the sensitivity of the magnocellular projecting cell system to compressive damage (stimulated with large check sizes). The parvocellular system (triggered by smaller check sizes) seems less vulnerable to optic nerve compression. Histopathologic evidence for optic nerve degeneration secondary to optic nerve compression is provided by De Vita et al. (1987).

Influences of hypothyroidism and hyperthyroidism

Only one publication concerning the effect of hypothyroidism upon PERGs could be traced (Holder and Condon, 1989). Delayed and reduced PERGs were observed, especially if a PVEP change was present. PERGs as well as the PVEP normalised following thyroxine therapy. The authors conclude that the findings of a delayed and reduced PERG P50 are not those of an optic nerve disfunction, but suggest disfunction distal to the retinal ganglion cell layer.

As to the VEPs, in hypothyroidism lowered amplitudes and slightly increased latencies in some, but definitely not all, patients were reported by Nishitani et al. (1968) using flash-VEPs, and by Mastaglia et al. (1978) and Ladenson et al. (1984) using pattern reversal VEPs. These alterations appeared to be completely reversible after adequate thyroid hormone suppletion.

In hyperthyroidism, Takahashi and Fujitani (1970) observed remarkably increased flash-VEP amplitudes, but no statistical differences in implicit time compared to a group of normals. Mitchell et al. (1988), using pattern reversal stimulation, confirmed the observation of somewhat higher amplitudes but without statistical significance, while again normal latencies were observed. No differences in amplitudes or latencies before and after treatment of the hyperthyroidism were observed. The authors concluded that hyperthyroidism had little effect on the PVEP.

Clinical observations in patients with endocrine orbitopathy

Several authors have reported on PVEP changes in endocrine orbitopathy, however without paying special attention to the hormone status.

Wijngaarde and van Lith (1979) reported normal low frequency reversal PVEP amplitudes in combination with slightly delayed responses in 33 patients with endocrine orbitopathy. Compared to demyelinating or compressive diseases the latencies were much less prolonged. In their discussion the authors suggested that various factors play a role simultaneously. The most important factors were thought to be a pure mechanical pressure effect on the nerve fibres combined with an ischaemic component arising from compression on the blood vessels, already narrowed by changes in the vascular walls.

Ouwerkerk et al. (1985a, 1985b) observed delayed PVEP responses in patients with severe OGD. Prednisone therapy resulted in a statistically significant decrease of the latencies, whereas irradiation resulted in a mean increase of 11 msec in the first year after the irradiation.

Bobak et al. (1988) reported normal latencies in transient PVEPs but abnormal phase shifts in steady-state PVEPs. The authors suggested that neuropathy selectively affects the high temporal frequency Y-axons which are more numerous in the periphery of the optic nerve (Burke et al., 1986) and thus more vulnerable to compression.

As to optic neuropathy Leone and Bajandas (1981) observed lowered flash-VEP amplitudes, which showed slight to moderate improvement after decompression. Neigel et al. (1988) reported abnormal PVEPs in 94% of the OGD patients with optic neuropathy and only in 9% of those without optic neuropathy. The authors considered abnormalities in the PVEP to be the most sensitive indicator of incipient neuropathy.

CHAPTER VII

METHODOLOGY

The electrodiagnostic tests (the PERG and the PVEP)

Both the PERG and the PVEP were obtained by means of a slide projector pattern reversal system (see figure 3.2). The equipment was placed in a room protected against electrical influences from the environment (in a so-called Faraday cage). For pattern stimulation, two chessboard patterns with element sizes of 80' and 40' minutes visual angle (at the viewing distance of 80 cm) were used. Both patterns had a contrast between the dark and light elements of 85%.
The screen luminance of 135 cd/m2 could be reduced to 15 cd/m2 by an approximately 1 log grey neutral density filter. The screen dimensions were 22' x 20' at the viewing distance of 80 cm. The screen was surrounded by a dark background. The pattern reversal frequency was constant at two reversals/sec and a reversal time of approximately five msec.
The signal amplification factor was 5000 with cut off frequencies at 0.16 Hz (TC 1 sec) and 70 Hz (impedance of 300 Mohm//2.2 pF). The amplifiers, the averager (time base 500 msec) and XY penwriter (2 μv/cm) were located outside the examination room.
The subject tested was seated in a comfortable chair and was asked to fixate on a small dark spot located at the centre of the screen. During the examination the patient could be monitored on a tv screen by means of a closed tv circuit. The total time necessary for the registration of the PVEP and PERG was approximately 45 minutes.

The PERG
For the registration of the PERG the tip of a gold foil electrode was inserted into the fornix of the lower eyelid (figure 7.1). The proximal part of the electrode was attached to the skin of the lower eyelid with some tape. Although the gold foil electrode is hardly felt at all, each patient first received a drop of anaesthesia (Oxybuprocainehydrochlorid) for optimal wearing comfort. The reference electrode was attached to the ipsilateral earlobe, while the contralateral earlobe served as an electrical ground. The contralateral eye was always patched except for the few cases in which the patient was not able to fixate the central spot on the screen monocularly (like in cases of very severe ON/MS). For the PERG registration both

pattern sizes of 40' and 80'.(Abbrev. D0 40 and D0 80) were used, but without the neutral density filter because the responses obtained with this filter were to low. Each measurement was repeated twice with a minimum of 64 responses averaged. Not only the mean amplitudes and the mean latencies of the P50 as well as the N95 component of all three measurements were calculated and loaded in a dBase IV software (TM) program, but also the amplitudes and latencies of the best PERG curve (the curve with the highest P50 amplitude) were noticed. A picture of the equipment used and an example of a PERG curve can be found in chapter III (figure 3.2).
If the PERG component was not recognisable because of an amplitude below the background activity, which was mostly approximately two microvolt, a value of one microvolt was read in for the amplitude, while the value for the latency was left open. The total time needed for the PERG registration was approximately ten minutes.

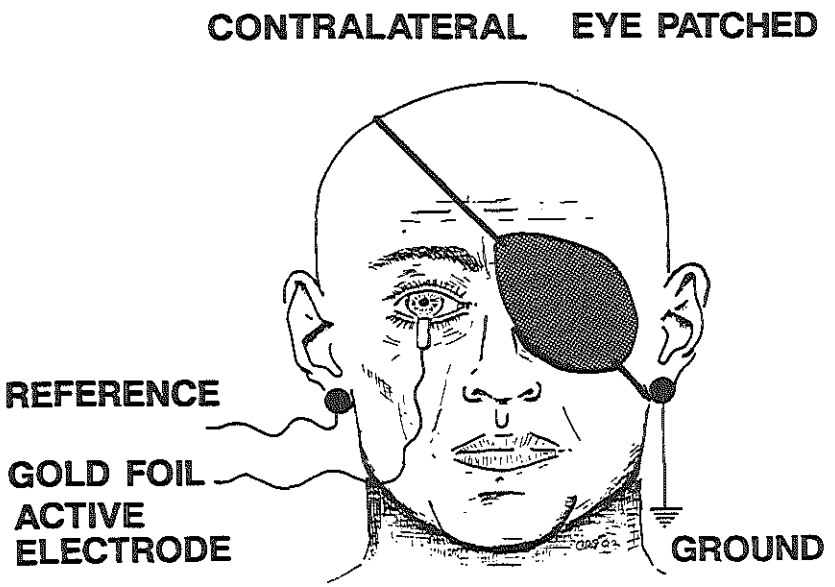

Fig 7.1: The PERG electrode placement.
For the PERG registration the tip of a gold foil electrode was inserted into the fornix of the lower eyelid. The reference electrode was attached to the ipsilateral earlobe while the contralateral earlobe served as a ground.

The PVEP

For the registration of the PVEP skin electrodes were used at 2.5 and 5 cm above the inion in the midline. A reference electrode was also placed in the midline at 12 cm above the nasion. Both earlobes were used as a ground (figure 7.2). The PVEPs were registered for each eye separately with the other eye patched. Only in the few cases in which the patient was not able to fixate the central spot on the screen was the patch in front of the other eye removed.

The PVEP was registered without a density filter at a pattern size of 80' (D0 80) and with a density filter reducing light intensity with one logarithm at 80' and 40' (D1 80 and D1 40). Each measurement was repeated twice with a minimum of 64 counts. Mean amplitudes and latencies of the three measurements were calculated. If the PVEP was not recognisable because of an amplitude below the background activity of approximately three microvolt then a value of one and a half microvolt was noticed while the value for the latency remained unfilled.

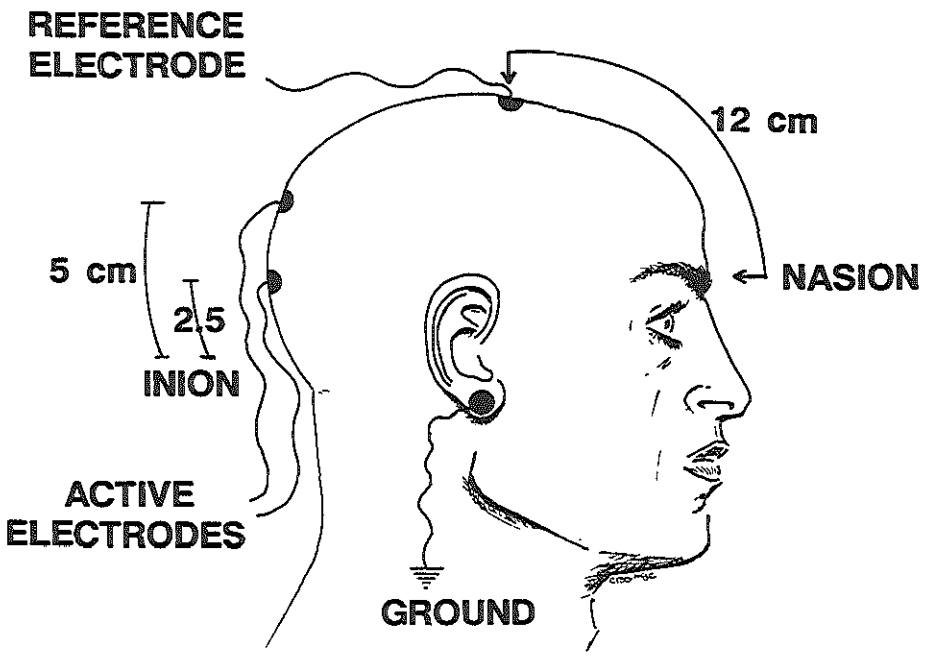

Fig 7.2: The PVEP electrode placement.
For the PVEP registration skin electrodes placed at 2.5 and 5 cm above the inion in the midline were used. A reference electrode was placed also in the midline at 12 cm above the nasion. Both earlobes were used as a ground.

The psychophysical tests

Visual acuity

The visual acuity was tested with a Snellen standard visual acuity test chart at a testing distance of six metres. The following lines were available: 0.1, 0.15, 0.25, 0.4, 0.5, 0.7, 0.8, 1.0, 1.25, 1.6 and 2.0.

Contrast vision

The contrast sensitivity was tested with the commercial available Vistech 6000 contrast sensitivity chart, which tests the contrast sensitivity at five different spatial frequencies. This chart has five horizontal rows containing nine circles. Each of the five rows (A - E) represents a spatial frequency (1.5, 3.0, 6.0, 12 and 18 cycles/degree, see figure 7.3).

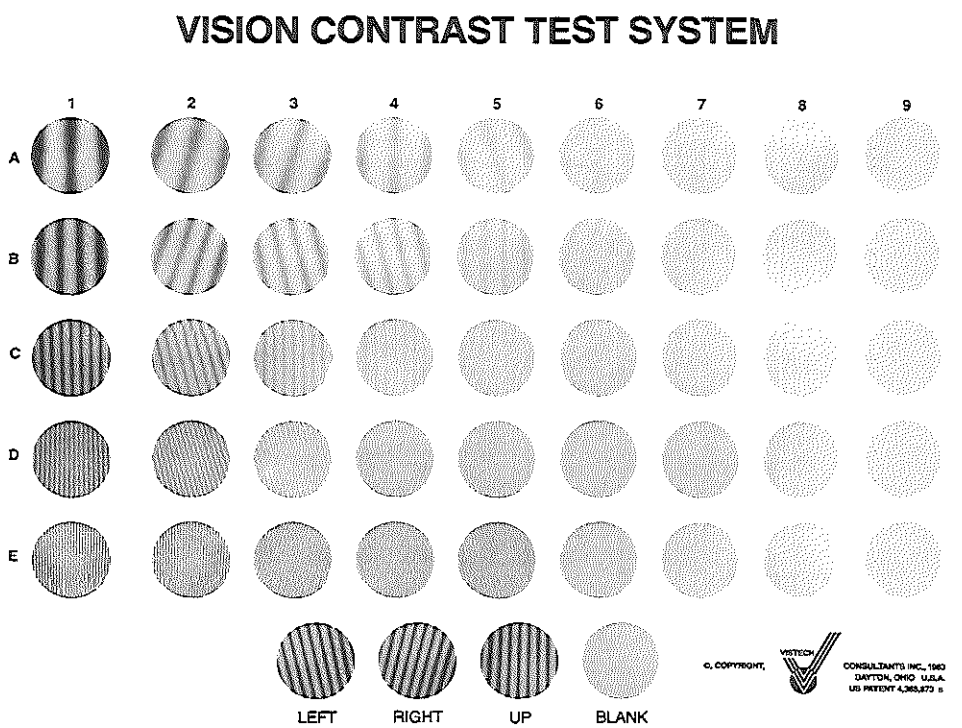

Fig 7.3: The Vistech 6000 contrast sensitivity chart. At a distance of three metres the contrast sensitivity is tested at five different spatial frequencies (rows A - E: 1.5, 3.0, 6.0, 12 and 18 cycles/degree). Each row has nine circles filled with a stripe pattern with a stepwise decreasing contrast. The number of the circle with the least amount of contrast per spatial frequency is noted and plotted in a special form (see text).

The circles in a row (1 - 9) are filled with a sine wave stripe pattern. From the left to the right the contrast of the stripe pattern decreases stepwise. By means of a forced choice technique the patient must name the direction of the stripe pattern within a circle (left, right, up or blank). The number of the circle with the least amount of contrast seen was noted per spatial frequency. These data can be plotted in a special form available for this sensitivity chart (figure 7.4). By connecting the plotted data a so-called contrast sensitivity curve is obtained.

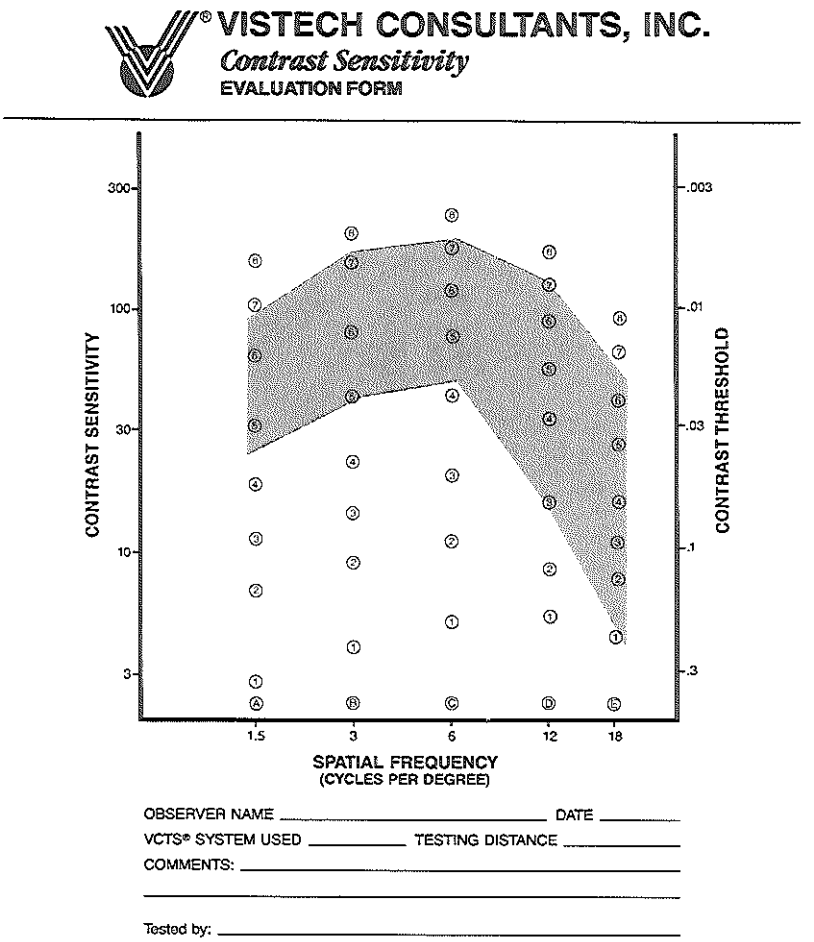

Fig 7.4: Form for the Vistech 6000 chart.
At the X-axis the five spatial frequencies are printed. At the left Y-axis the the contrast sensitivity and at the right Y-axis the corresponding contrast threshold can be found. The shaded area is the area of normal contrast vision. Per spatial frequency 9 steps of decreasing contrast were available, each corresponding with a contrast sensitivity/contrast threshold. For each spatial frequency the these nine steps (1 - 9) are plotted with encircled numbers.

Visual field

The visual field was tested with an Humphrey Allergan computerised static perimeter (full threshold central 30-2 program). This program tests 76 points within a radius of 30 degrees from the fovea as well as the foveal threshold (in db). Each point in the visual field is presented several times with different light intensities. The automatic perimeter calculates the sensitivity (in dB) for each of the 76 points. A statistic program (statpac) was available which calculates the loss of vision (in dB) for each point by comparing the results with those of a control group.

The 76 points visual field was divided in three different zones (figure 7.5). With help of the statpac calculations the loss of sensitivity for each of the three zones was estimated in steps of 10% in a parametric scale (1 = loss of less than 10%, 2 = loss between 10 and 20%, 3 = loss between 20 and 30% .... 9 = loss of ≥80%). Later these results were correlated with the PERG data.

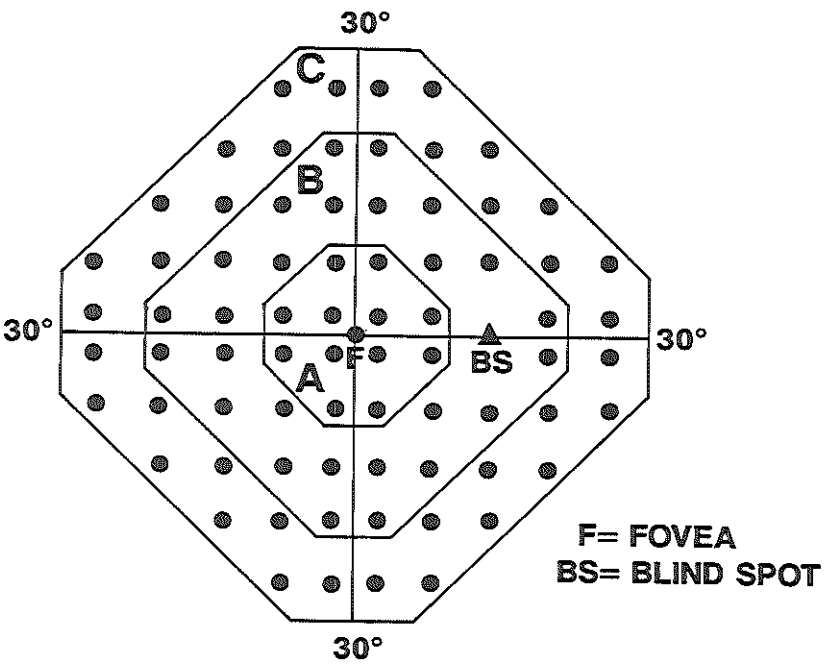

Fig 7.5: Humphrey Allergan 76 points full threshold central 30-2.
For each point the automatic perimeter calculates the sensitivity (in dB). A statistic program pack was available which calculates the loss of vision (in dB) for each point. The 30' visual field was divided into three zones: A central zone with a radius of 10' (containing 12 points), a middle zone with a radius between 10'-20' (containing 26 points) and an outer zone with a radius between 20'-30' (containing 36 points). For each of these three zones the total loss of vision was calculated in steps of 10% (see text).

General inclusion criteria / the control group

General inclusion criteria

The patients and controls were all examined during the period January 1989 - June 1990 at the ERG department of the Eye Hospital Rotterdam. For all patient groups, as well as for the control group, the general inclusion criteria of table 7.1 were formulated. A visual acuity of < 1.0 was tried to improve with optimal refraction. If new glasses had recently been prescribed ($\leq$ 6 months) these glasses were used without further refraction.

- Volunteer after informed consent
- Good cooperation during the examination
- Age if possible below 75 with an upper limit of 80 years of age
- Absence of ocular diseases (like lens or corneal opacities) except the disease studied
- Absence of nystagmus
- No coloured glasses or coloured contact lenses
- No use of miotics or mydriatics, natural pupil diameter $\geq$ 3mm.
- No allergic reaction to Oxybuprocainehydrochlorid

Table 7.1. General inclusion criteria. All the patients and the subjects included in the control group had to meet all the criteria mentioned above before they were admitted to this study.

The control group

Reference values for visual acuity, contrast sensitivity and visual field were available, but normal values for the PERG and PVEP had to be determined. Therefore the PERG and the PVEP were registered in 66 normals, aged 19-77 (41.6 $\pm$ 17.2) with normal visual acuity and normal contrast sensitivity. The fundus had to be normal as judged by a senior staffmember. All subjects met the general inclusion criteria at least for one eye. In each person the right eye was tested, unless the eye did not met the inclusion criteria. Special attention was paid to age-induced effects on the electrodiagnostical data. The reference group was divided into two groups, one group with 30 subjects younger than 40 years old and one group with 36 subjects older than 40, with a view providing age-matched control groups for the patient groups if necessary.

The patient groups

Ocular hypertension (OHT)
The group of 30 OHT patients consisted of 14 females and 16 males aged between 26 and 77 years of age (58.3 ± 14.4). Inclusion criteria were: 1) An eye pressure over 21 mm Hg observed repeatedly. At the moment of examination the eye pressure was below 30 mm Hg to avoid a direct pressure effect on the optic nerve as much as possible. 2) No visual field defects suggesting the beginnings of glaucoma like Bjerrum scotomas, arc scotomas or a nasal step, and 3) No damage to the optic nervehead indicating glaucoma. The aspects of the optic discs in ocular hypertension, glaucoma and normal pressure glaucoma were judged by two of our staff members specialised in glaucoma. Their observations were noted according to the criteria listed in table 7.2. The most important items which the optic disc was examined for were the cup/disc ratio, the presence of notches in the neural rim area of the optic disc, optic disc haemorrhages, the degree of pallor of the optic disc, the visibility of the lamina cribrosa and the degree of absence of neural rim area of the optic disc.

Glaucoma (GLAU)
In the glaucoma group 30 patients were studied (14 females and 16 males aged between 36 and 73; 66.1 ± 8.6 years of age). Inclusion criteria were: 1) An eye pressure over 21 mm Hg observed repeatedly, 2) visual field defects indicating glaucoma and/or 3) aspect of the optic disc as seen in glaucoma. Again these aspects were noticed according to the criteria as can be seen in table 7.2. Patients with very severe glaucoma were excluded because of loss of visual acuity or fixation problems. Also patients using miotics were excluded.

Normal pressure glaucoma (NPG)
The NPG group consisted of 30 patients (21 females and 9 males with ages between 31 and 79; 64.4 ± 11.7 years). In these cases the inclusion criteria were the same as for the glaucoma patients except for the eye pressure: 1) An eye frequently measured and never reported over 21 mm Hg, 2) visual field defects indicating glaucoma and/or 3) aspect of the optic disc suspect for glaucoma.

In the following groups the pallor of the optic disc was always evaluated by the same staffmember without prior knowledge concerning the disease and the eye involved. The aspect of the optic disc of each eye was written down and the degree of pallor of the optic disc was estimated.

Optic neuritis (ON)
In this group 30 patients with an acute attack of ON but without a history of a previous attack and/or MS were studied. The group consisted of 25 females and 5 males between 20 and 45 years old (31.0 ± 8.2 years). The clinical complaints were: a sudden loss of visual

acuity (n=30), pain when moving the eyes (n=21) and colour weakness especially for red colours (n=30). All patients were examined within four weeks of the onset, almost half of them within the first week (n=14). An afferent pupil defect was noticed in all patients (Marcus Gunn positive reaction), while the aspect of the fundus was normal and certainly not suspected of being subject to a vascular accident.

The patients were not only examined during the acute phase but again one month later (26 patients) and 6 months later (20 patients). The ten patients lost at the third examination can be accounted for: two patients who refused another examination, two patients who could not be traced and six patients who were not examined because their 6-month examination fell after the closure date of the data collection period of this study. In both the neuritis and MS patient groups the extent of the optic disc pallor was noticed according to the classification as can be seen in table 7.3.

Eye pressure at the examination	(mm Hg)
Highest eye pressure thus far	(mm Hg)
Cup disc ratio in vertical direction	(0.1-1.0)
Cup disc ratio in horizontal direction	(0.1-1.0)
Presence of notches in the neural rim area	(yes/no)
Presence of optic disc haemorraghes	(yes/no)
Degree of pallor of the optic disc	a= none b= one quarter c= half sided (i.e temporal) d= total
Visibility of the lamina cribrosa	a= not visible, b= just visible, c= visible
Degree of absence of neural rim area of the optic disc (estimated in clock hours)	a= none b= 0-2 hours c= 2-6 hours d= > 6 hours

Table 7.2: parameters OHT/GLAU/NPG

Multiple sclerosis (MS+/ MS-)

Two groups of MS patients were formed, one group of 21 patients who had previously suffered an acute attack of ON (MS+) and one group of 21 patients without a history of acute ON (MS-). The MS patients were referred from two sources. Several neurologists from neighbouring hospitals were aske | to submit patients definitely suffering from MS. Another batch were recruited through the MS patients' associations.

Each patient was thoroughly examined for signs of a previous attack of optic neuritis. Some had been in our eye hospital with a confirmed attack of optic neuritis, others with complaints indicating a previous attack of optic neuritis had been seen by their local ophthalmologist or only by their neurologist. All these patients were classified as MS+ patients. This group consisted of 16 females and 5 males aged between 27 and 63 (mean $\pm$ sd: 42.9 $\pm$ 12.4). Here 20 patients were known to have had a definite diagnosis of MS and 1 patient was a probable MS case. The duration of the MS was 9 years (1 - 29 years). A non-recurring attack of acute ON had been experienced by 15 patients, while 6 patients had suffered several attacks.

If signs of a previous attack of acute neuritis were absent, the MS patients were classified as MS- patients. This group consisted of 12 females and 9 males aged 29 - 69 (mean $\pm$ sd: 47.9 $\pm$ 13.7). As to the diagnosis, 17 patients were known to be definite MS cases and 4 patients probable MS cases. At the moment of the examination the mean duration of the disease was 8 years (1 - 25 years). For all MS patients the same classification for the degree of pallor of the optic disc was used as for the ON group (table 7.3).

Ophthalmic Graves disease (OGD)

This group consisted of 30 patients with OGD (age 44.9 $\pm$ 15 years). Each of them had a mild or moderately ocular involvement according to the NOSPECS classification. All patients were known to have had abnormal thyroid hormone levels at the moment studied or had returned to normal hormone levels with aid of medication or radioactive I131 treatment.

The electrophysiologic parameters were correlated not only with the presence of pallor of the optic disc but also with the presence or absence of some general aspects of this patient group like the momentary use of prednisone (20 - 60 mg, 10 cases), a history of irradiation of the eyes (8 cases), a history of treatment with I131* (10 cases) and the presence of hypothyroidism (2 cases).

Also the correlations between the PERG/PVEP parameters and the NOSPECS classification (Table 6.1.) were calculated.

This classification involves the degree of soft tissue involvement (class 2), the amount of proptosis (class 3), the degree of extra ocular muscle involvement (class 4), the degree of corneal involvement (class 5) and the amount of sight loss (class 6).

The extent of the pallor of the optic disc was noticed according to the classification as presented in table 7.3.

A) Presence of pathological optic disc pallor: Yes or No.

B) Classification of the degree of optic disc pallor
- a = Completely normal aspect of the optic disc.
- b = Non-pathologic (but suspected) half-sided (i.e. temporal) pallor of the optic disc.
- c = Non-pathologic (but suspected) diffuse pallor of the optic disc.
- d = Pathologic half-sided (i.e. temporal) pallor of the optic disc.
- e = Pathologic complete pallor of the optic disc.

Table 7.3: Classifications (A and B) for the presence and degree of optic disc pallor.

Statistical support

This thesis was statistically supported by the department of epidemiology and biostatistics of the Erasmus University Rotterdam. All statistical analyses were done with the SPSS/PC+(TM) program. A p-value smaller than or equal to 5% was considered statistically significant. Age-induced effects on the PERG and PVEP in the control group were studied with the Spearman rank correlation test.
For differences between continuous variables (like the PERG and PVEP parameters) between two groups, the Mann Whitney U test was chosen; if an adjustment for age was necessary, a multiple regression analysis was done with the age as a covariable. Differences of a continuous variable between two or more categories of another variable were tested with the Mann-Whitney U test (two categories) or the Kruskal Wallis test (three or more categories). A student Neuman-Keuls procedure was done to reveal group differences between the groups of normals, glaucomas, OHTs and NPGs in order to compare the groups in a pairwise way. In the patients within the neuritis group all variables were repeatedly measured (three times). For revealing time-induced effects on their variables a Friedman two way-ANOVA analysis was selected.

CHAPTER VIII

RESULTS

The PVEP and the PERG in the reference group

The PVEP

In table 8.1 the PVEP data are listed. All these data are based on the mean of three measurements. A change in luminance by placing a one logarithm density filter (D1) in front of the chessboard resulted in a mean amplitude decrease of approximately 21% as well as a latency increase of almost 15% (D0 80 vs. D1 80). With a similar luminance level the larger check size (D1 80) produced a somewhat higher amplitude (10%) but an equal latency compared to the smaller check size (D1 40).

The distribution of the P100 amplitudes did not completely resemble a bimodal curve, because several subjects had very high amplitudes. Therefore these results had to be transformed logarithmically for the assessment of useful clinical limits. The PVEP data did not show age-induced effects, except for the latency of the PVEP P100 component which steadily increased with age for the D1 80 as well as for the D1 40 stimulus. This effect appeared to be statistically significant (Spearman rank correlation test, $P \leq 0.05$).

That a statistical correction for age became inevitable is demonstrated in table 8.1 where the results of two subgroups are presented. The first group included the subjects under 40 years old (n=30), the second group included the results of the subjects above 40 years old (n=36). As can be noticed from the results, a difference in latency between the two groups is found as well as a larger standard deviation in the older subgroup.

After consulting the department of epidemiology and biostatistics of the Erasmus University Rotterdam the following decision was made: The PVEP results of all 66 subjects of the control group could be directly used for comparison with the ON, OGD, MS+ and MS- groups, but a statistical correction was necessary for the PVEP latencies in the OHT, GLAU and NPG groups. With aid of a statistical correction program ('age-adjusted means') the PVEP latencies of the group of 66 normals could be compared with the glaucoma groups.

The PERG

In table 8.2 the PERG results can be found. As mentioned before, per patient both the best and the mean of three measurements were used for statistical analysis. Only the means are listed here, because the data of the best PERG of three measurements did not reveal more statistical differences or better correlations with any of the parameters of the various patient groups.

There is not much difference in PERG amplitudes for the two check sizes applied, whereas a longer latency was found for the smaller check size (49.2 $\pm$ 3.3 ms versus 51.6 $\pm$ 3.0 ms). This difference appears to be statistically significant ($p \leq 0.05$).

No statistical significant age-induced effect for any of the PERG parameters was found. Therefore the data of all the 66 normals could be directly used for comparison with the patient groups.

PATTERN-VEP	mean $\pm$ sd n=66	clinical limits (mean $\pm$ 2 sd)		age effect
Pattern D0 80				
P100 amplitude (μv)	13.9 $\pm$ 4.7	(6.7 - 28.2)	*	
latency (ms)	101.4 $\pm$ 4.4	(92.6 - 110.2)		
Pattern D1 80				
P100 amplitude (μv)	11.0 $\pm$ 4.1	(4.3 - 21.8)	*	
latency (ms)	116.7 $\pm$ 7.4	(101.9 - 131.5)		#
(group < 40 years)	116.0 $\pm$ 6.0	(104.0 - 128.0)		
(group > 40 years)	117.2 $\pm$ 8.1	(101.0 - 133.4)		
Pattern D1 40				
P100 amplitude (μv)	10.0 $\pm$ 3.9	(3.8 - 23.9)	*	
latency (ms)	116.5 $\pm$ 6.8	(102.9 - 130.1)		#
(group < 40 years)	115.7 $\pm$ 5.8	(104.1 - 127.3)		
(group > 40 years)	117.0 $\pm$ 7.4	(102.2 - 131.8)		

Table 8.1: PVEP data of the control group, 66 subjects aged 19 - 77 years (41.6 $\pm$ 17.2 years) for two different check sizes (40' and 80') and two different luminance levels (D0 without and D1 with a one logarithm neutral density filter). * = Clinical limits after logarithmic transformation. # = Statistically significant ($p \leq 0.05$) age-induced effect (Spearman rank correlation test).

PATTERN-ERG		mean ± sd n=66	clinical limits (mean ± 2 sd)
Pattern D0 80			
P50	amplitude (μv)	5.6 ± 1.2	(3.2 - 8.0)
	latency (ms)	49.2 ± 3.3	(42.6 - 55.9)
N95	amplitude (μv)	8.9 ± 1.9	(5.1 - 12.8)
	latency (ms)	96.8 ± 6.4	(84.0 - 109.7)
Pattern D0 40			
P50	amplitude (μv)	5.5 ± 1.3	(3.0 - 8.0)
	latency (ms)	51.6 ± 3.0	(45.7 - 57.5)
N95	amplitude (μv)	8.8 ± 1.9	(5.0 - 12.7)
	latency (ms)	97.5 ± 5.1	(87.4 - 107.7)

Table 8.2: PERG data of the control group, 66 subjects aged 19-77 years (41.6 ± 17.2 years) for two different check sizes (40' and 80'). There are no significant age-induced effects of any of the PERG parameters.

The PVEP and the PERG in the patient groups

The PVEP

As mentioned before three glaucoma groups (OHT, GLAU, NPG), an OGD group and three neuritis groups (ON, MS-, MS+) were compared with a reference group. The results in mean amplitudes and latencies are listed in table 8.3, whereas the numbers of individual cases with normal and abnormal amplitudes and latencies are presented in table 8.4.

The PVEP amplitudes (table 8.3.) are statistically significantly reduced for all check sizes and luminance levels in GLAU, NPG, ON (acute onset and one month later) and MS+. The latencies are also statistically significantly increased in these diseases, furthermore in OHT, OGD, MS- and 6 months after ON. Of the three glaucoma groups the changes in amplitude and/or latency are most prominent in GLAU and the least in OHT. The mean latencies of the OHT group are in between those of the control group and the GLAU/NPG group and reach statistical significance both versus the normal group and the GLAU/NPG groups.
The changes in OGD are rather small and comparable with those of OHT. In ON, amplitudes and latencies are much more disturbed than in all other groups. The changes in ON gradually improve. After 6 months the latencies resemble those of the MS groups. Amplitudes and latencies of the MS+ group are generally more disturbed than those of the MS- group. The recovery of latency and amplitude after ON indicate a temporary function loss during the acute stage, which apart from demyelination may be caused by edema itself or by a compressive factor caused by edema.

The remaining amplitude reduction, very probably points to a definite axon loss, whereas the remaining delay both after ON and in the MS groups is known to be caused by plaques of demyelination. The results obtained with the three check size and luminance parameters are not statistically (or systematically) different from each other in all groups.
Table 8.4 represents the individual data, assessed as normal or abnormal based on 2 sd limits. The results confirm those of table 8.3, i.e. the latencies are more often abnormal than the amplitudes. Individual abnormal amplitude reduction is only seen in acute ON and in MS+. If more advanced cases of glaucoma and NPG were included in this study, more abnormal results would certainly be obtained.

In acute ON, amplitudes are often too low to be measured. Reduced amplitudes were usually more than 50% lowered and in eight patients (27%) the PVEP was not even recognisable. Consequently, in these cases the numerical value of the latencies is unknown, although it is very plausible that they are significantly increased.
Although during the follow-up of ON the mean latencies improve, half a year after the initial ON attack 80% of the individuals still has delayed responses. Thus while the amplitudes in ON quickly recover, most of the latencies remain prolonged. This is in accordance with the results of the patients of the MS+ group of whom 95% demonstrated delayed responses.
It is worth noting that the responses of the contralateral eyes in ON appear to be frequently delayed too. During the acute attack 20% of these eyes had increased latencies and during the follow-up this number increased to 46% after one month and 52% after six months, although these eyes were without clinical complaints. These percentages correspond rather well with those of the patients of the MS-group of whom 62% had statistically significantly delayed PVEP responses.

The PERG
In table 8.5 the mean PERG amplitudes and latencies of all groups are listed. In figure 8.1 the percentual amplitude reductions are presented graphically, while in table 8.6 the numbers of individual normal and abnormal PERG results are given.
In general, the P50 component is lowered in amplitude and prolonged in latency in all three glaucoma groups. Apart from acute ON and OGD (D0 40) these amplitudes are normal in all the other patient groups, whereas the N95 amplitude is decreased in all groups except for the OGD (D0 80) and the MS- group. The results of the N95 latency are variable. Comparing the two check sizes (40' vs. 80'), it appears that the loss in amplitude is somewhat higher for the 40' check size in all cases.
In the three glaucoma groups both the P50 and the N95 amplitudes were statistically significantly lowered (up to almost 50% amplitude reduction). In all the patient groups the N95 amplitudes were more frequently and more severely affected than the P50 amplitudes. Compared to the other patient groups the reduction of the PERG amplitudes in the glaucoma groups was more severe.

PATTERN-VEP	CONTROL GROUP n=66	OHT n=30	GLAU n=30	NPG n=30		OGD n=30
D0 80 A mean	13.9	11.4	8.8 *	9.1 *		13.4
sd	4.7	4.8	4.2	2.9		6.0
L mean	101.4	103.9 *	113.3 *	107.5 *		104.4 *
sd	4.4	6.5	11.0	11.3		6.0
D1 80 A mean	11.0	9.2	7.6 *	7.4 *		10.1
sd	4.1	3.6	3.6	2.8		4.5
L mean	116.7	119.7 *	133.5 *	125.7 *		116.9
sd	7.4	10.1	13.9	14.1		9.6
D1 40 A mean	10.0	8.5	7.0 *	6.7 *		9.1
sd	3.9	3.3	3.5	2.1		4.0
L mean	116.5	121.6 *	134.4 *	130.5 *		120.3 *
sd	6.8	9.4	11.5	14.9		9.8
PATTERN-VEP	CONTROL GROUP n=66	ON n=30	M1 n=26	M6 n=20	MS - n=21	MS + n=21
D0 80 A mean	13.9	5.9 *	9.5 *	10.7	11.0	8.7 *
sd	4.7	3.9	3.3	4.3	4.4	5.3
L mean	101.4	135.8 *	134.7 *	124.5 *	115.5 *	133.9 *
sd	4.4	22.3	16.5	16.9	17.4	26.6
D1 80 A mean	11.0	5.6 *	8.5 *	9.5	9.5	7.4 *
sd	4.1	3.5	3.4	3.9	3.3	4.9
L mean	116.7	149.2 *	146.5 *	136.6 *	129.4 *	135.2 *
sd	7.4	22.1	17.1	13.7	18.4	43.0
D1 40 A mean	10.0	4.3 *	7.7 *	8.1	8.5	6.7 *
sd	3.9	3.3	3.5	3.6	3.4	4.9
L mean	116.5	146.9 *	148.0 *	135.5 *	136.0 *	141.9 *
sd	6.8	24.8	17.9	13.6	21.1	20.0

Table 8.3: Comparison of the Pattern-VEP parameters between the control group and the patient groups.
Patient groups:
OHT= ocular hypertension, GLAU= glaucoma, NPG= Normal pressure glaucoma, OGD= ophthalmic Graves disease, ON= acute optic neuritis, M1 = 1 month after the onset of ON, M6 = 6 months after the acute onset of ON, MS +/ MS - = multiple sclerose with or without a history of ON.
PVEP parameters:
A mean = mean amplitude (microvolts) of three measurements, L mean= mean latency (milliseconds) of three measurements, sd= standard deviation, D0 80= 80 minutes of arc pattern stimulation without neutral density filter, D1 80= 80 minutes of arc stimulation using a one logarithm density filter, D1 40= 40 minutes of arc stimulation also using a one logarithm density filter. *= Statistical significant difference ($P \leq 0.05$) using multiple regression/Mann Whitney U - Wilcoxon Rank Sum W tests.

PVEP Individual cases			Amplitude		Latency		
			normal	lowered (≥ 2 sd)	normal	increased (≥ 2 sd)	
GLAU		(n = 30)	30	-	13	17	(57%)
OHT		(n = 30)	30	-	24	6	(20%)
NPG		(n = 30)	30	-	16	14	(47%)
OGD		(n = 30)	29	1	21	9	(30%)
ON	affected eye						
	onset	(n = 30)	15	15 *	-	22 *	
	1 month	(n = 26)	25	1	1	25	(96%)
	6 month	(n = 20)	19	1	4	16	(80%)
ON	contralat. eye						
	onset	(n = 30)	30	-	24	6	(20%)
	1 month	(n = 26)	25	1	14	12	(46%)
	6 month	(n = 20)	19	1	9	11	(52%)
MS-		(n = 21)	20	1	8	13	(62%)
MS+		(n = 21)	14	7	1	20	(95%)

Table 8.4: Numbers of normal and abnormal individual PVEPs.
Not only the result of the affected eye in ON are presented but also those of the contralateral eye. Limits of normality: Mean values of the reference group ± 2 standard deviations. * = In eight individuals with acute ON the PVEP was not recognizable (see text).

Just like the PVEP latencies, the PERG amplitudes of the OHT group are in between those of the normals and GLAU/NPG groups and differ significantly from the group of normals as well as from the groups of GLAU/NPG. The individual data in table 8.6 confirm these results. In all three glaucoma groups the P50 latencies were prolonged, reaching statistical significance, but different from the PVEP results the PERG latency increase in the OHT group resembles those of the GLAU and NPG groups.
In the OGD group reduced P50 and N95 amplitudes were found too but only for the 40' check size. Its clinical meaning is probably irrelevant, because the number of individual cases with significantly decreased amplitudes is low. The P50 latencies are normal.
Normal mean PERGs are seen in MS-. In ON and MS+ the mean P50 amplitude is also within normal limits, whereas the N95 amplitude is significantly lowered. In the MS+ group a considerable proportion of the individuals had lowered N95 amplitudes (25-30%). In ON this percentage was much lower (±10%). For the N95 component there is not much difference in percentage of individual amplitude loss between check size 80' and 40'. In contrast, almost twice as many individual abnormalities are found for the P50 component, if the smaller pattern element (40') is used.

PATTERN-ERG	CONTROL GROUP n=66	OHT n=30	GLAU n=30	NPG n=30		OGD n=30
D 80 P50 A mean	5.6	4.7 *	3.8 *	3.8 *		5.2
sd	1.2	1.4	1.7	1.1		1.6
L mean	49.2	52.0 *	51.9 *	50.3 *		49.3
sd	3.3	4.1	4.9	4.8		3.0
N95 A mean	8.9	7.3 *	4.9 *	5.9 *		9.0
sd	1.9	2.5	2.7	2.0		2.9
L mean	96.8	98.3	101.5	99.8 *		97.0
sd	6.4	7.6	13.7	8.3		5.8
D 40 P50 A mean	5.5	4.4 *	3.4 *	3.5 *		4.7 *
sd	1.3	1.6	1.7	1.2		1.8
L mean	51.6	53.8 *	54.9 *	54.9 *		52.2
sd	3.0	4.2	5.1	4.9		4.1
N95 A mean	8.8	7.0 *	4.5 *	4.7 *		7.7 *
sd	1.9	2.3	2.2	1.9		3.0
L mean	97.5	100.2	102.5 *	99.7		102.2 *
sd	5.1	6.7	10.2	7.2		6.7
PATTERN-ERG	CONTROL GROUP n=66	ON n=30	M1 n=26	M6 n=20	MS - n=21	MS + n=21
D 80 P50 A mean	5.6	5.2	5.4	5.1	5.5	4.9
sd	1.2	1.6	1.3	1.1	1.9	1.6
L mean	49.2	46.8 *	48.4 *	47.8	49.0	43.0 *
sd	3.3	3.5	4.3	3.5	4.7	3.6
N95 A mean	8.9	7.3 *	7.4 *	7.5 *	8.8	6.7 *
sd	1.9	1.9	1.8	2.0	3.4	2.5
L mean	96.8	96.6	98.4	96.4	96.2	97.1
sd	6.4	14.2	8.8	7.8	8.2	9.9
D 40 P50 A mean	5.5	4.6 *	5.0	5.3	5.5	5.1
sd	1.3	1.3	1.2	1.4	2.2	2.3
L mean	51.6	49.9	50.0	49.4 *	51.4	50.4 *
sd	3.0	3.5	3.1	3.0	4.8	3.3
N95 A mean	8.8	6.9 *	6.6 *	7.3 *	8.4	6.7 *
sd	1.9	1.6	1.6	1.7	2.9	2.5
L mean	97.5	98.0	95.7	102.7 *	97.9	100.4 *
sd	5.1	8.1	7.1	8.9	7.5	9.2

Table 8.5: Comparison of the Pattern-ERG parameters between the control group and the patient groups. For the abbreviations of the patient groups and pattern variables see table 8.3. PERG parameters: P50= PERG positive component at ± 50 msec, N95= PERG negative component at ± 95 msec. *= statistical significant difference ($p \leq 0.05$).

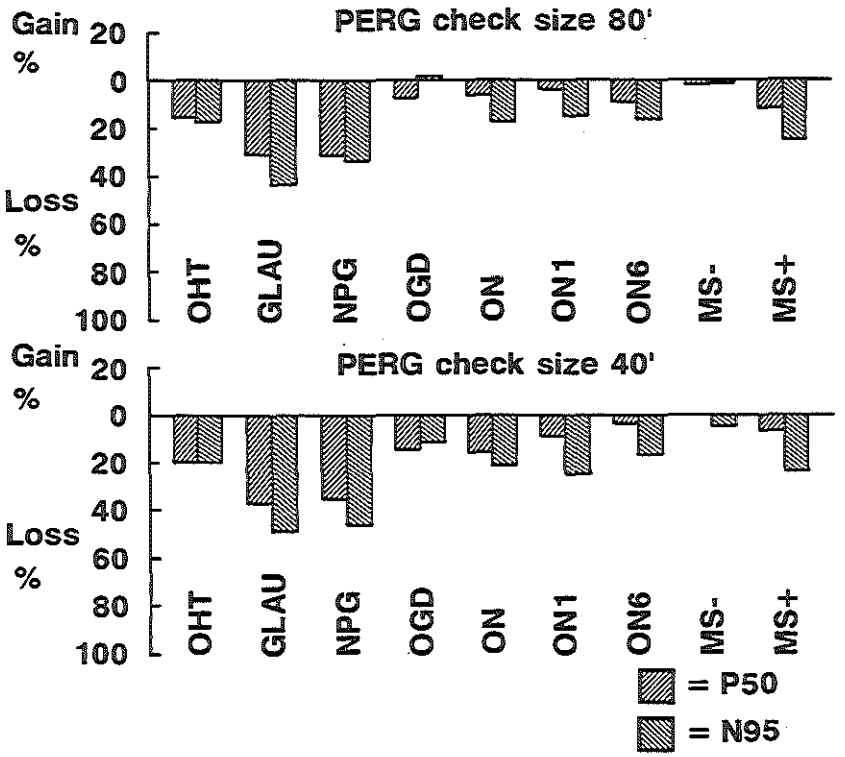

Fig 8.1: Graphical presentation of the percentual changes in amplitude of the PERG P50 and N95 components in the patient groups. The upper figure shows the results for the 80' check size, the lower for the 40' check size. A loss of amplitude is drawn under the base line, an increase of amplitude above the base line. The numbers at the end of the bars are the percentual changes.

PERG abnormalities versus PVEP abnormalities

Whens studying the PERG in optic nerve diseases, an important question is whether abnormal results are running parallel with abnormal results of the PVEP or whether they behave independently. For this purpose four categories were created (table 8.7). In this table the PERG abnormalities refer to amplitudes only because the latencies are too variable and unpredictable to be of individual use. The PVEP abnormalities refer to both amplitudes and latencies. The following categories are listed: 1) Normal PERG and normal PVEP, 2) normal PERG but abnormal PVEP, 3) abnormal PERG but a normal PVEP and 4) abnormal PERG and abnormal PVEP.

Cases with lowered PERG amplitudes		P50 80'		P50 40'		N95 80'		N95 40'	
		n	(%)	n	(%)	n	(%)	n	(%)
OHT	30	3	(10)	6	(20)	6	(20)	7	(23)
GLAU	30	8	(27)	13	(43)	12	(40)	12	(40)
NPG	30	4	(13)	7	(23)	10	(33)	13	(43)
OGD	30	2	(7)	6	(20)	3	(10)	3	(10)
ON	30	1	(3)	3	(10)	3	(10)	5	(17)
1 month	26	2	(8)	1	(4)	2	(8)	2	(8)
6 month	20	1	(5)	2	(10)	1	(5)	1	(5)
MS-	21	2	(10)	4	(19)	3	(14)	2	(10)
MS+	21	1	(5)	2	(10)	6	(29)	5	(24)

Table 8.6: Numbers of cases (n) and percentages (%) with significantly lowered PERG amplitudes. The results of the positive (P50) and negative (N95) PERG component for both check sizes are listed.

PERG vs PVEP	PERG norm and PVEP norm		PERG norm and PVEP abn		PERG abn and PVEP norm		PERG abn and PVEP abn	
OHT	16	(53%)	2	(7%)	8	(27%)	4	(13%)
GLAU	8	(27%)	6	(20%)	4	(13%)	12	(40%)
NPG	10	(33%)	5	(17%)	6	(20%)	9	(30%)
OGD	17	(57%)	4	(13%)	3	(10%)	6	(20%)
ON	-	-	26	(87%)	-	-	4	(13%)
1 month	1	(4%)	23	(88%)	-	-	2	(8%)
6 month	4	(20%)	14	(70%)	-	-	2	(10%)
MS-	6	(28%)	9	(43%)	2	(10%)	4	(19%)
MS+	1	(5%)	9	(43%)	-	-	11	(52%)

Table 8.7: Comparison between PERG and PVEP abnormalities in the patient groups. PVEP abnormalities refer to amplitudes as well as latencies.

In all three glaucoma groups the PERG and PVEP results run parallel in a majority of the individuals (± 65%). This means that in 35% of the patients one of the examinations is normal, while the other is abnormal. In OHT a remarkably high percentage (27%) has abnormal PERGs together with normal PVEPs. In the same category, percentages of 13% and 20% are found for GLAU and NPG respectively. Apparently in the glaucoma groups the PERG can be affected earlier than the PVEP. The high percentage of PERG abnormalities in OHT is interesting. Perhaps these are the individuals at high risk for developing glaucoma.

In OGD the PERG and PVEP in most cases are both normal and in 77% of the cases the PERG and PVEP run parallel. These results are opposite to those of the ON group because here frequently only the PVEP is abnormal (in almost 90% of cases). Furthermore, an abnormal PERG is always accompanied by an abnormal PVEP.
In MS- and MS+ the PVEP is more frequently abnormal than the PERG. It is striking that the PERGs and PVEPs are more frequently affected in MS+ patients than in MS- patients.

In conclusion, the highest PERG abnormalities are seen in the glaucoma groups (>60%) and the MS+ group (>50%). Apart from OHT this could be the result of ganglion cell loss. In glaucoma perhaps a second factor influences the results, which could explain the amplitude decrease in OHT and the higher percentage abnormalities in the glaucoma groups compared to the MS+ group.

Comparison between visual field loss and PVEP and PERG parameters

As mentioned in chapter VII, the visual field was divided over three sectors. In tables 8.8a, 8.8b and 8.8c the correlations between the PVEP/PERG parameters and the visual field loss for each of these three sectors are summarised.

In table 8.8d the same is done for the complete visual field. The disorders with hardly any visual field loss (OGD) or without any visual field loss (inclusion criterium for OHT) are not entered in this table. When the correlation coefficient is not statistically significant, only the sign is noticed, if a statistical significance is reached, not only the sign but also the numerical value of the correlation coefficient is given.

In general, visual field defects are accompanied by a decrease in PVEP and PERG amplitudes and an increase in PVEP latencies. The correlations for the PERG latencies are less consistent as both positive and negative correlations are observed. Strong correlations ($r > 0.5$) are generally not seen, the strongest correlations being found in the ON groups, but even then a statistical significance is only occasionally reached.

For the PVEP the following facts can be observed in tables 8.8a-d. Within the 10° radius the visual field loss is correlated with a PVEP amplitude decrease and a latency increase in all groups and for all stimulus parameters. In the 10°-20° and 20°-30° sectors these correlations are less strong and less consistent, especially for the PVEP amplitudes.

The correlations between PVEP parameters and visual field are almost similar in GLAU and NPG but without statistical significance, whereas in the acute stage of ON a significant level is reached for all stimulus parameters and the central 10° visual field. A remarkable difference was present between the MS- and MS+ groups. In the MS- group the correlation with the visual field was stronger for the PVEP latencies than for the PVEP amplitudes, while the opposite was true for the MS+ group.

Both the P50 and N95 component of the PERG have only a weak correlation with visual field loss. Statistical significance is reached between some of the PERG amplitudes in glaucoma (GLAU/NPG) and some more in the course of ON.
The PERG latencies more frequently have a negative correlation than a positive correlation with visual field loss except for the MS- and the ON (6 months) groups where the opposite is seen. If the MS- and the MS+ group are compared the opposite correlations for the PERG latencies are remarkable. This accounts for all three sectors studied.

In reverse to the PVEPs, better correlations of the PERG components are found with the 10°-20° and 20°-30° than with the central 10° visual field losses. This may be an indication that the PERG as measured in this study reflects more the perifoveal function than the PVEPs do.

r		GLAU	NPG	ON	1 MONTH	6 MONTH	MS -	MS +
PVEP								
D0 80	A	-	-	-0.42	-	-	-	-0.46
	L	+	+	+0.43	+0.54	+	+0.63	+
D1 80	A	-	-	-0.46	-	-	-	-0.47
	L	+	+	+0.62	+0.51	+0.59	+	+
D1 40	A	-	-	-0.49	-	-	+	-0.49
	L	+	+	+0.49	+0.48	+0.40	+0.60	-
PERG								
D0 80								
P50	A	+	-	+	-0.33	-	-	+
	L	-	-	-	-	+	-	-
N95	A	-	-	+	-0.48	-0.33	-	+
	L	-	+	-	-0.43	+	-	-
D0 40								
P50	A	-	-	+	-	-0.43	-	+
	L	-	-	-	+	-	+	-
N95	A	-	-0.49	-	-0.41	-	-	+
	L	-0.51	+	-0.38	-	+	+	-

Table 8.8a) Signs of the correlation coefficient when the PVEP and PERG parameters are compared with the degree of visual field loss in the central 10° radius (Sector A). - and + signs indicate the sign of the correlation found. Those correlations which are high enough to reach statistical significance ($P \leq 0.05$) are printed with their numerical value.

r		GLAU	NPG	ON	1 MONTH	6 MONTH	MS -	MS +
PVEP								
D0 80	A	-	-	-	+	+	-	-0.42
	L	-	-	+	+0.39	+	+0.70	+
D1 80	A	-	-	-	-	+	-	-0.42
	L	+	+	+0.50	+0.34	+	+0.56	+
D1 40	A	-	+	-	+	-	+	-0.44
	L	+	+	+0.49	+0.37	+	+0.57	-
PERG								
D0 80								
P50	A	+	-	+	-0.42	-0.36	-	-
	L	-	-	-	-	-	+	-
N95	A	-0.34	-	+	-0.47	-0.54	-	-
	L	-	+	-	-0.38	+	+	-
D0 40								
P50	A	-	-	-	-	-	-	+
	L	+	-	-	-	+	+	-
N95	A	-0.33	-0.46	-	-0.41	-	-	+
	L	-0.50	+	-	-	+0.45	+0.56	-

Table 8.8b): Signs of the correlation coefficient when the PVEP and PERG parameters are compared with the degree of visual field loss in the 10°-20° radius (Sector B). Those correlations which are high enough to reach statistical significance ($P \leq 0.05$) are printed with their numerical value.

r		GLAU	NPG	ON	1 MONTH	6 MONTH	MS -	MS +
PVEP								
D0 80	A	-	-	+	+	+	-	-
	L	-	+	+	+0.43	-	+0.77	+
D1 80	A	+	-	-	-	+	-	-
	L	+	+	+0.39	+0.40	+	+0.59	+
D1 40	A	-	+	-	+	+	-	-0.41
	L	+	+	+0.46	+0.42	+	+0.69	+
PERG								
D0 80								
P50	A	-	-	-	-0.38	-	-	-
	L	-	-	-	+	+	+	-
N95	A	-0.46	-	+	-0.43	-0.42	-0.31	-
	L	-	-	-	-0.41	-	+	-
D0 40								
P50	A	-0.33	-0.37	-	-	-	-	+
	L	-	-	-	+	+	+	-
N95	A	-	-0.48	+	-0.37	+	-	-
	L	-0.40	+	-	-	+0.40	+0.58	-

Table 8.8c): Signs of the correlation coefficient when the PVEP and PERG parameters are compared with the degree of visual field loss in the 20°-30° radius (Sector C). Those correlations which are high enough to reach statistical significance ($P \leq 0.05$) are printed with their numerical value.

r		GLAU	NPG	ON	1 MONTH	6 MONTH	MS -	MS +
PVEP								
D0 80	A	-	-	-	-	+	-	-0.44
	L	-	-	+	+0.52	+	-0.70	+
D1 80	A	-	-	-	-	+	-	-0.45
	L	+	+	+0.45	+0.47	+	-0.56	+
D1 40	A	+	+	-	-	-	+	-0.48
	L	+	+	+0.42	+0.41	+	-0.57	+
PERG								
D0 80								
P50	A	+	-	+	-0.39	-0.39	-	-
	L	-	-	-	+	+	+	-
N95	A	-0.38	-	+	-0.52	-0.50	-	+
	L	-	+	-	-0.38	+	+	-
D0 40								
P50	A	-	-0.31	-	-0.37	-	-	+
	L	-	-	-	+	+	+	-
N95	A	-0.31	-0.50	+	-0.49	-	-	+
	L	-0.50	+	-	-	+0.42	+0.56	-

Table 8.8d): Signs of the correlation coefficient when the PVEP and PERG parameters are compared with the degree of visual field loss for the total 30° radius (Sector D). Those correlations which are high enough to reach statistical significance ($P \leq 0.05$) are printed with their numerical value.

Visual acuity

In table 8.9 the PVEP/PERG amplitudes and latencies are correlated with the visual acuity. On top of the table the mean visual acuity per patient group is given. When the correlation coefficient is not statistically significant only the sign is noticed, if a statistical significance is reached not only the sign but also the numerical value is given.
Most patient groups have a mean visual acuity $\geq$ 1.0 except for ON (acute onset and one month later), OGD and MS+. As a consequence only a few statistical significant correlations are seen. In the glaucoma groups the mean visual acuity is normal, but individual cases with a decreased visual acuity are present (table 8.10). In percentual terms, the loss of the PERG amplitudes is highest among the glaucoma groups (figure 8.1), for this reason the visual acuity data of these groups are further analysed in table 8.10.

During an acute attack of ON the visual acuity is severely disturbed, but quickly recovers in the following month and is normal six months later. In the OGD group six patients had a lowered visual acuity (four of them $\geq$ 0.7), whereas in the MS+ group six patients had a severely affected visual acuity (0.1 - 0.6) and five patients a slightly lowered visual acuity (0.7- 0.9).

For the PVEP amplitudes a positive correlation with visual acuity is seen for all stimulus parameters. A statistical significance is reached repeatedly in those patient groups with a lowered mean visual acuity. Negative correlations are seen for the PVEP latencies in the glaucoma groups, whereas in the other patient groups no such clear correlations are found. Table 8.10 confirms the PVEP results in the glaucoma groups: Increased PVEP latencies are more frequently seen among patients with a visual acuity $<$ 1.0. However, the absolute numbers of persons with a visual acuity $\leq$ 1.0 are rather small, which makes a careful interpretation of these results necessary.

Like the PVEP amplitudes the PERG amplitudes correlate positively with the visual acuity for all stimulus parameters in all patient groups, but for the PERG, statistical significances appear to be less dependent of the mean visual acuity. In the glaucoma groups the PERG amplitudes are more frequently lowered among patients with a visual acuity of $<$ 1.0 (table 8.10), but again these results have to be carefully interpreted.
The correlations for the PERG latencies are not of any use as both positive and negative correlations are seen without a predilection for certain patient groups.

In OGD orbital irradiation may have influenced the results. Six OGD patients had a lowered visual acuity. Of these six patients four were known to have a history of orbital irradiation. In three of these patients abnormal PVEPs and PERGs were found. Unfortunately no conclusion can be drawn on the basis of this small sample.

		OHT	GLAU	NPG	OGD	ON	M1	M6	MS -	MS +
Visual acuity		1.0	1.0	1.0	0.9	0.4	0.9	1.0	1.1	0.8
PVEP										
D0 80	A	+	+	+	+	+0.55	+	+	+	+0.54
	L	-0.39	-	-	-	+	-	+	-	+
D1 80	A	+	-	+	+	+0.55	+0.37	-	+	+0.51
	L	-	-	-0.44	-	+	+	-	-	+0.47
D1 40	A	+	+	+	+	+0.32	+	+	+	+0.52
	L	-0.37	-	-0.41	+	+	+	+	-	+
PERG										
D0 80										
P50	A	+	+	+	+	-	+0.38	+	+	+
	L	-0.40	+	-	-	+	+	-	-0.41	+
N95	A	+0.35	+	+0.44	+	-	+0.41	+	+	+
	L	+	+	+	-	+	+	-0.65	-	+
D0 40										
P50	A	+	+	+0.41	+	-	+	+0.41	+	+
	L	-	+	-	-	+	+	-	-	+
N95	A	+	+0.42	+	-	+	+0.34	+	+	+
	L	-	+	+	-	+	-	-0.43	-	+

Table 8.9: Correlations between the PVEP/PERG results and the visual acuity. abbreviations: OHT = Ocular hypertension, GLAU = Glaucoma, NPG = Normal pressure glaucoma, OGD = Ophthalmic Graves' disease, ON = Acute optic neuritis, M1 = Optic neuritis one month after the onset, M6 = Optic neuritis six months later, MS- = multiple sclerosis without a previous attack of ON, MS+ = multiple sclerosis with a previous attack of ON, + = positive correlation coefficient, - = negative correlation coefficient. Those correlations reaching statistical significance ($P < 0.05$) are given with their numerical value. The mean visual acuity per patient group is presented on top of the table.

Visual acuity		PVEP lowered amplitudes	PVEP increased amplitudes	PERG lowered P50 amplitudes	PERG lowered N95 amplitudes
OHT					
< 1.0	(n= 4)	0	3	3	3
≥ 1.0	(n=26)	0	3	4	5
GLAU					
< 1.0	(n= 6)	0	5	3	4
≥ 1.0	(n=24)	0	12	10	8
NPG					
< 1.0	(n= 8)	0	5	4	5
≥ 1.0	(n=22)	0	9	3	10

Table 8.10: Distribution of abnormal PVEPs (amplitudes and latencies) as well as abnormal PERGs (P50 and N95 amplitudes) in patients (OHT, GLAU and NPG) with a visual acuity < than 1.0 and patients with a visual acuity ≥ 1.0.

Contrast vision

As explained in chapter VII, the contrast vision was tested at five spatial frequencies. Per spatial frequency 9 steps of decreasing contrast were available. The number of the step with the least amount of contrast seen was noted down per spatial frequency. The results are presented graphically in figure 8.2a and 8.2b, while the intrinsic numerical values are presented in table 8.11.

As can be seen in figure 8.2a and 8.2b, the values of contrast vision in OHT, GLAU and NPG are within the shaded area of normality, but all data are just above the lower limit. The mean visual acuity is similar in all three glaucoma groups, but the OHT patients have a higher contrast vision compared to GLAU and NPG. In this context it should also be kept in mind that the mean age of the OHT group is lower. In all three glaucoma groups individual cases with abnormal contrast sensitivity were present, but a selective loss for any of the spatial frequencies tested could not be established.
In ON a severe and statistically significant reduction of contrast vision for all spatial frequencies was found during the acute attack. In this period the visual acuity was severely reduced too. One month later the contrast vision was still abnormal although a substantial improvement was seen, especially at the lower and higher spatial frequencies. After six months the contrast vision just returned to normal. As can be seen these results are in between those of the MS+ and the MS- groups. In MS-the contrast vision is completely normal, while in MS+ it is lowered for all spatial frequencies except for the highest. In OGD the contrast vision is normal for all spatial frequencies.

Spatial frequency	OHT n=30	GLAU n=30	NPG n=30	OGD n=30	ON n=30	M1 n=26	M6 n=20	MS - n=21	MS + n=21
1.5 c/deg	5.1	4.6	4.9	4.9	2.1	4.4	4.7	4.8	4.2
3.0 c/deg	5.9	5.3	5.6	5.7	2.5	4.9	5.2	5.4	4.6
6.0 c/deg	4.9	4.4	4.3	5.1	1.7	3.9	4.6	4.8	3.4
12 c/deg	3.9	3.0	3.0	4.1	1.0	2.7	3.7	3.9	2.4
18 c/deg	2.4	2.4	1.8	2.6	0.5	2.0	2.9	3.1	1.3
Visual acuity	1.0	1.0	1.0	0.9	0.4	0.9	1.0	1.1	0.8
Mean age	58.3	66.1	64.4	44.9	31.0	30.3	31.6	47.9	42.9

Table 8.11: Contrast vision as determined with the Vistech contrast 6000 test chart. The contrast sensitivity was tested at five different spatial frequencies (1.5, 3.0, 6.0, 12 and 18 cycles/degree).
For each spatial contrast the Vistech chart provided nine steps of decreasing contrast. Per spatial frequency the number of the step with the least amount of contrast seen was note done. This means the higher the number, the better the contrast sensitivity.
At the bottom of this table the mean visual acuity and mean age for each group is given.

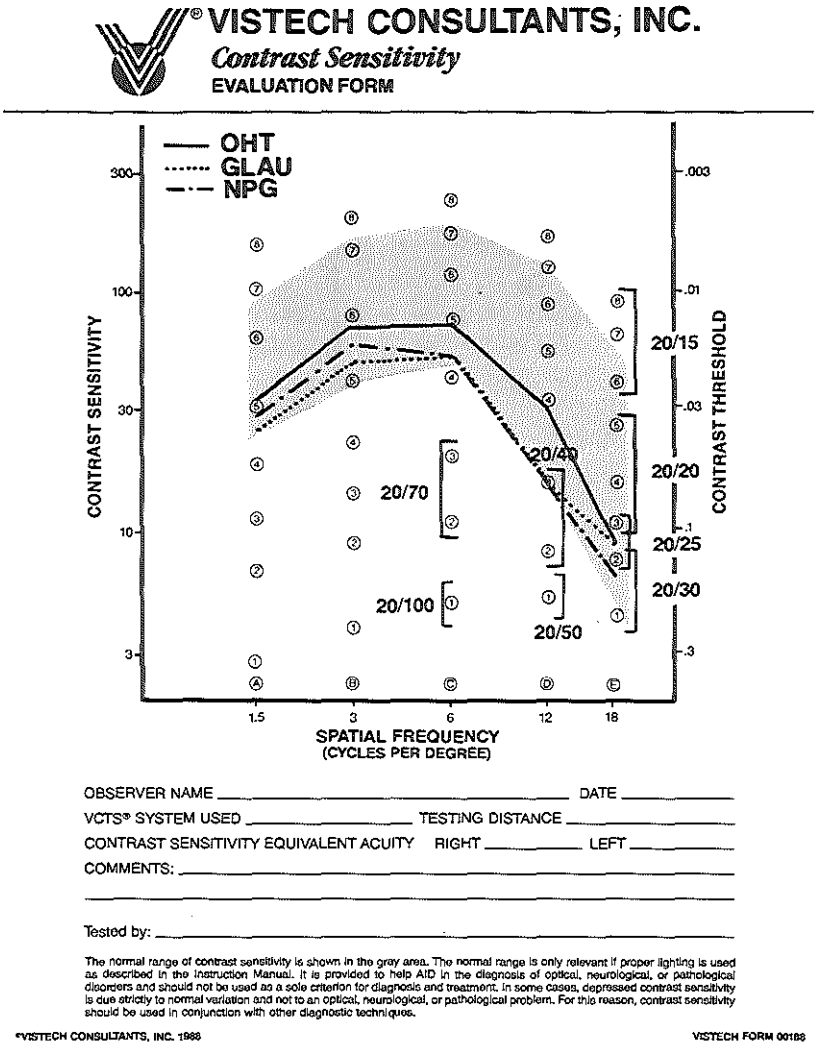

Fig 8.2a: Graphical presentation of the contrast sensitivity of the glaucoma groups studied. At the X-axis the five spatial frequencies are noted. At the left Y-axis the contrast sensitivity and at the right Y-axis the corresponding contrast threshold can be found. The shaded area is the area of normal contrast vision. Per spatial frequency 9 steps of decreasing contrast were available, each corresponding with a contrast sensitivity and a contrast threshold. For each spatial frequency these nine steps (1 - 9) are marked with encircled numbers.

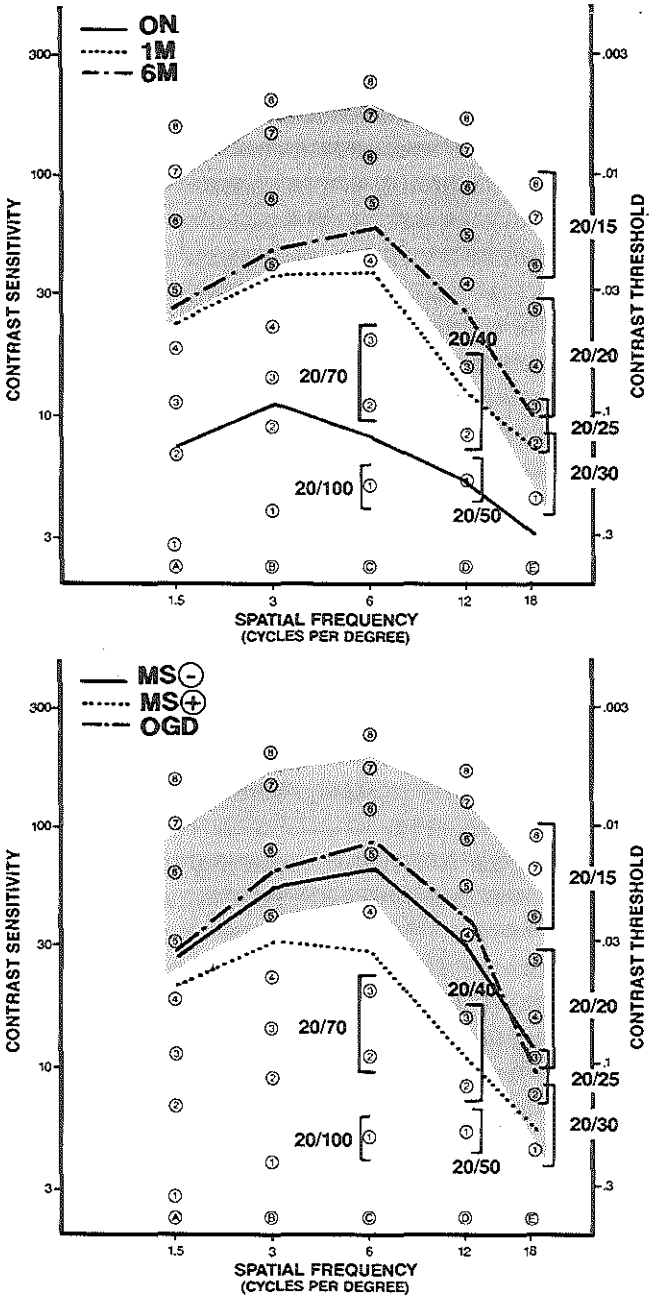

Fig 8.2b: Graphical presentation of the contrast sensitivity of the optic neuritis groups (top) and the MS+/MS- and OGD groups (bottom). For text see figure 8.2a.

Parameters within the patient groups

OHT/GLAU/NPG

In table 8.8 the PVEP/PERG parameters are correlated with the Cup/Disc ratios and the momentary as well as the highest eye pressure measured. Only those correlations which reach statistical significance are shown here. Not many correlations are observed.
In glaucoma, as expected from the literature, significant correlations were found between the C/D ratios (horizontally as well as vertically) and the PVEP parameters. Increased C/D ratios run parallel with lowered PVEP amplitudes and prolonged latencies.
In OHT and NPG a similar tendency was found, but the correlations did not reach statistical significance. The reason probably is that in these groups the C/D ratios did not have much spread.
In the OHT group all C/D ratios were $\leq$ 0.4 (admission criterium) and in the NPG group most of these ratios were between 0.7 and 0.9.

			C/D horiz.			C/D vert.			Eye press.			Highest pr.		
			O	G	N	O	G	N	O	G	N	O	G	N
PVEP														
D0 80		A		-			-							
		Lat												
D1 80		A		-			-			+				
		Lat		+			+				-			
D1 40		A		-			-			+	-		-	
		Lat									-			
PERG														
D0 80	P50	A												
		Lat									-			
	N95	A												
		Lat												
D0 40	P50	A	+											
		Lat								-				
	N95	A	+	-		+	-							
		Lat			-					-				

Table 8.12: Correlations of PVEP/PERG data with Cup/Disc ratios horizontally and vertically as well as with the momentary eye pressure and the highest eye pressure measured.
Abbreviations: O = Ocular hypertension (n=30), G = Glaucoma (n=30) and N = Normal pressure glaucoma (n=30), A = Amplitude, Lat = Latency, + = statistically significant positive correlation ($P \leq 0.05$), - = statistically significant negative correlation ($P \leq 0.05$).

The PERG data are noteworthy. Not only significant correlations with the C/D ratios are seldom seen (except for the D0 40 N95 component), but also opposite correlations were found between groups. For example in glaucoma, a significant negative correlation between C/D ratios and the D0 40 N95 amplitude was found, whereas in OHT there is a significant positive correlation. Perhaps the lack of spread of the C/D ratios in the OHT group attributes to this effect. Statistically significant correlations between the electrodiagnostic results and the momentary or highest eye pressure measured are infrequently seen and are not of any clinical use.

			Notch		Haemorr				Pallor		L.cribr		Rim	
			G	N	G	N			G	N	G	N	G	N
Present			5	3	3	6	(class	a	8	8	9	6	12	11
Absent			25	27	27	24	see	b	5	3	15	19	5	6
							table	c	2	5	6	5	7	11
							7.2)	d	15	14			6	2
PVEP														
D0 80		A												
		Lat			+	+								
D1 80		A												
		Lat											+	
D1 40		A												
		Lat				+							+	
PERG														
D0 80	P50	A									-			
		Lat												
	N95	A												
		Lat								+				
D0 40	P50	A											-	
		Lat	+											
	N95	A											-	-
		Lat								+				

Table 8.13: Statistically significant correlations between PVEP/PERG parameters and various glaucomatous aspects of the optic disc.
Abbreviations: G = Glaucoma (n=30), N = Normal pressure glaucoma (n=30), A = Amplitude, Lat = Latency, Notch = a focal enlargement in the neural rim area of the optic disc, Haemorr = small haemorrhages near or at the margin of the optic disc, Pallor = degree of pallor of the optic disc (a = none, b = one quarter, c = half sided, d = total), L.cribr = the degree of the visibility of the lamina cribrosa (a = not visible, b = just visible, c = visible) , Rim = the degree of absence of neural rim area of the optic disc (a = none, b = 0-2 hours, c = 2-6 hours, d = > 6 hours). + = statistically significant positive correlation ($P \leq 0.05$), - = statistically significant negative correlation ($P \leq 0.05$). On top of the table the numbers of patients are given, categorised according to the classification of table 7.2.

In table 8.13 the PVEP/PERG results are correlated with glaucomatous signs of the optic disc like the presence of notches and optic disc haemorrhages, the degree of pallor of the optic disc, the visibility of the lamina cribrosa and the degree of absence of the neural rim area of the optic disc. The OHT group is left out, because glaucomatous signs are absent in this group (inclusion criterium).
The classification of the parameters can be found in table 7.2 as well as in the legend of table 8.13. The numbers of patients categorised according to this classification are listed on top of the table.

It is remarkable that hardly any significant correlations are present for the glaucomatous signs studied. Significant correlations between the electrodiagnostics and the presence of notches in the neural rim or the presence of haemorrhages at or near the margin of the optic disc were seldom found. Perhaps the small number of patients with these glaucomatous signs can explain this result. Significant correlations with the degree of pallor of the optic disc were absent too, whereas quite a lot of patients had a clear pallor of the optic disc. Therefore small numbers cannot explain this rather negative result. This is also the case with pathologic visibility of the lamina cribrosa or an abnormal degree of excavation. The degree of absence of the neural rim area of the optic disc appears to be the only parameter which significantly correlates with PERG amplitudes (D0 40 N95).

Optic Neuritis/ MS+/ MS-

In table 8.14 the PVEP/PERG parameters are correlated with optic disc pallor and the duration of the disease. The extent of the pallor of the optic disc was classified according to the classification as found in table 7.3. In contrast to the previous tables in this table the signs of all the correlations (- = negative correlation, + = positive correlation) are listed because some interesting facts can be seen. Those correlations which reach statistical significance are specified with their numerical value.
As to pallor of the optic disc, the PVEP demonstrates a decrease in amplitude and an increase in latency for all the patient groups. Sometimes statistical significance is reached.
The PERG results are more complicated. They demonstrate hardly any significant correlation with pallor of the optic disc, except for the MS patients without a previous attack of ON, although in this group only three patients (class d and e) with an obvious pallor of the optic disc were seen. In the MS+ group this frequency was essentially higher, but nevertheless statistical significant results were not found here. The signs of the correlations run parallel between MS- and MS+.
If the plus and minus signs of the correlations in the neuritis groups are studied, a reversal of sign (from plus to minus) can be seen for the PERG amplitudes and latencies a half year

after the initial ON attack. At this time the correlation signs resemble those of the MS+ group.

As to the correlations with the duration of the disease, according to the literature, and to what may be expected, the PVEP amplitudes decrease, whereas the latencies increase. These results resemble those between the PVEP and the degree of pallor of the optic disc.
The PERG results are not consistent. The PERG P50 amplitudes have a tendency to increase with the years, which is opposite to what might be expected in a disease in which progress is normal. The N95 amplitudes show a decrease in the MS- group but an increase in the MS+ group. Statistically significant correlations are absent. For both PERG components and both stimulus parameters the latencies increase with the years without reaching statistical significance (except for P50 D0 80).

Pallor of the optic disc (for classification see table 7.3)								Duration of MS	
Class			ON	M1	M6	MS-	MS+		
		a	20	10	5	13	4		
		b	4	8	10	4	8		
		c	3	0	0	1	1		
		d	2	8	5	2	4		
		e	1	0	0	1	4		
			ON	M1	M6	MS-	MS+	MS-	MS+
PVEP									
D0 80		A	-	-	-0.40	-	-	-0.44	-
		Lat	+	+	+	+	+	+0.27	+
D1 80		A	-	-	-	-	-	-	-
		Lat	+	+0.39	+	+	+	+0.64	+
D1 40		A	-	-	-0.41	-0.42	-	-	-
		Lat	+	+0.38	+	+	+	+0.46	+
PERG									
D0 80	P50	A	+	+	-	-0.48	-	+	+
		Lat	+	+	-	-0.49	-	+	+0.38
	N95	A	+	+0.36	-	-0.70	-	-	+
		Lat	+	+	-0.38	-0.58	-0.58	+	+
D0 40	P50	A	+	+	+	-0.56	-	+	+
		Lat	+	+	-	-0.58	-	+	+
	N95	A	+	+	-	-0.63	-	-	+
		Lat	-	-	-	-	+	+	+

Table 8.14: Correlations between PVEP/PERG data and the extent of pallor of the optic disc in neuritis/MS+/MS- as well as the duration of the disease in MS+/MS-.
Abbreviations: ON = acute optic neuritis (n=30), M1 = one month later (n=26), M6 = six months later (n=20), MS- = multiple sclerosis without a previous attack of ON (n=21), MS+ = multiple sclerosis with a previous attack of ON (n=21). For the other abbreviations see table 8.12.

OGD

In table 8.15 the PVEP/PERG data are correlated with various OGD parameters like pallor of the optic disc, the use of prednisone medication and a history of orbital irradiation. Furthermore the data are correlated with the NOSPECS classification classes 2-6 (for details: see table 6.1).

Like in the other patient groups, the electrodiagnostic results did not statistically significantly correlate with the extent of pallor of the optic disc. Using both classifications of optic disc pallor (listed in table 7.3), not a single statistical significant correlation was found. However, as can be noticed on top of the table not many advanced cases of OGD were present. There were only four patients with obvious optic disc pallor and eight patients with some sight loss, whereas patients with severe sight loss were absent.

						NOSPECS (table 6.1)				
		Pal	Predn	Irrad		CL2	CL3	CL4	CL5	CL6
					0	0	18	13	29	22
					a	17	10	8	1	8
	Yes	4	10	8	b	10	2	8	0	0
	No	26	20	22	c	3	0	1	0	0
PVEP										
D0 80	A		-	-				-		-
	Lat			+		+	+			
D1 80	A		-	-						-
	Lat			+		+				
D1 40	A			-						-
	Lat		+	+						
PERG										
D0 80 P50	A		-					-		-
	Lat			+						
N95	A		-	-				-		-
	Lat									
D0 40 P50	A		-	-			-	-		
	Lat									
N95	A		-	-				-		
	Lat									

Table 8.15: Correlation of the PVEP/PERG data with various OGD parameters as well as with the OGD NOSPECS classification.
Abbreviations: Pal = pallor of the optic disc, Predn = the use of prednisone medication, Irrad = a history of orbital irradiation.
NOSPECS classification: CL2 = Class 2 (Soft tissue involvement), CL3 = Class 3 (Proptosis), CL4 = Class 4 (Extra ocular muscle involvement) CL5 = Class 5 (Corneal involvement) and CL6 = Class 6 (Sight loss). The other abbreviations are listed in table 8.12.

The effects of the use of prednisone medication and a history of orbital irradiation is more clear. The PVEP demonstrates significantly lowered amplitudes and prolonged latencies, whereas the PERG amplitudes of both the P50 and the N95 component are significantly decreased. Six patients had a history of both orbital irradiation and of prednisone medication. Because of the cross sectional aspect of this study a seperation of the effects of prednisone medication and orbital irradiation was statistically impaired.

Some of the parameters of the NOSPECS classification (table 6.1) correlate significantly with the PVEP/PERG results. Extra ocular muscle involvement and sight loss both result in lowered PVEP and PERG amplitudes.

In this chapter the alterations of the PERG and PVEP in affections of the optic nerve have been presented as well as their correlations with various ophthalmic parameters.
The alterations of the PVEP were just as could be expected from the literature. Affections of the optic nerve result in decreased amplitudes and increased latencies. The results of the visual field correlations further emphasize that the PVEP is derived from the central area of the visual field. Pallor of the optic disc also causes a decrease in PVEP amplitude and an increase in PVEP latency.
The PERG results are more complex. In the foregoing chapters we have seen that in literature a unanimous opinion concerning alterations of the PERG in disorders of the optic nerve does not exist as yet. The results of this study demonstrate that the PERG amplitudes are generally lowered, not only in groups but also individually. In almost all groups the negative component is more affected. Remarkable differences are seen for the P50 component between the glaucoma groups and the other groups. In the glaucoma groups the P50 component is significantly lowered in amplitude and decreased in latency which appears to be in contrast to the other patient groups where the P50 amplitude is normal or slightly lowered and where the latency is normal or even somewhat increased. It seems as if a different factor attributes to the changes of the P50 component in glaucoma. The correlations with visual field loss indicate that the PERG is derived from a larger retinal area than the PVEP. The PVEP and PERG results do not always run parallel, especially not in the glaucoma groups. The possible explanations for this finding and their clinical consequences will be discussed in the next chapter.

CHAPTER IX

DISCUSSION

The PVEP in the reference group and the patient groups

The PVEP in the reference group

The PVEP was registered at two luminance levels (D0 and D1) and at two spatial frequencies (40' and 80'). As we have seen in chapter III a lower luminance level results in a latency increase and an amplitude decrease (van Lith and van Marle, 1978). These effects are clearly seen in table 8.1 (D0 80 vs. D1 80). Spatial frequency does not influence PVEP latencies, but changes in amplitude (with a maximum amplitude for check sizes 10'-40') have been reported (Harter and White, 1968; Armington and Gorwin, 1971; Spekreijse, 1973). In this study only two check sizes were applied, making an analysis of PVEP spatial tuning effects impossible. The fact that the PVEP amplitudes are somewhat higher using the 80' check size can be explained by the relatively large field size of the screen (22° x 20°) and the high pattern contrast (87%). The discussion of the stimulus parameters chosen will be given later. A statistically significant increase in PVEP latency with increasing age (especially after the sixth decade) was found for the D1 80 and D1 40 stimulus. This may be explained by a decrease in retinal luminance by ageing processes (e.g. smaller pupil sizes, minor lens opacities), an anatomical change of the nerve fibres and a loss of ganglion cells at older ages (Vrabec, 1965; Dolman et al., 1980). It is logical that the loss of ganglion cells results in a reduction of PVEP amplitudes. Although some reduction of the PVEP amplitude is seen with age a statistically significant difference is not reached. Two explanations are possible. First, the standard deviation of the PVEP amplitude masks statistically significant age-induced effects. Actually, the standard deviations are quite large (up to 35% of the mean PVEP amplitude: table 8.1). Second, the loss of ganglion cells has no linear course during life, but accelerates after 60 years of age (Dolman et al., 1980; Balaszi et al., 1984). Only 20% of our normals were over 60 years old, a percentage probably too low to unmask age-induced effects on the PVEP amplitude.

The PVEP in the patient groups

The groups examined were ocular hypertension (OHT), primary open angle glaucoma (GLAU), normal pressure glaucoma (NPG), ophthalmic Graves' disease (OGD), optic

neuritis during the acute onset (ON), one month later (M1) and six months later (M6), multiple sclerosis with a history of optic neuritis (MS+) and without a history of optic neuritis (MS-). Later in this chapter the PVEP results will be discussed for each disorder separately and related to its underlying pathogenesis. This section contains a comparison of the PVEP results between the patient groups studied in order to be able to evaluate its clinical value in relation to the PERG at a later stage.
Apart from OHT, OGD and MS- all groups had statistically significant increased latencies and lowered amplitudes for all stimulus parameters. In OHT and MS- only the PVEP latencies were statistically significant prolonged, whereas in OGD some, but not all, latencies were increased.
The increase in latency can be explained by a disfunction of the nerve axon or of its surrounding myelin sheath (by demyelination and/or compression), whereas a decrease of amplitude can be the result of loss of axons and of their ganglion cells (atrophic processes). This explains the differences between the patient groups. In ON and the MS groups, demyelination is more prominent than atrophy resulting in more severely affected PVEP latencies compared to the other patient groups. Demyelination itself does not necessarily result in atrophy as reflected in the normal amplitudes in the MS- group. In the MS+ patients the attacks of ON cause significantly reduced amplitudes. The curves of these patients frequently demonstrate multiple peaks, explained by a selective loss of groups of axons of different conduction velocities (Feinsod and Hoyt, 1975). This selectivity is caused by the disease itself and not by the proposition that PVEP components from the central or peripheral field have different latencies (Blumhardt et al., 1989). In ON the temporary edema, inflammation and demyelination cause an almost complete conductive block (Berninger and Heider, 1985, 1989). During the follow-up of ON, the PVEP amplitudes almost completely normalize, whereas the latencies only slightly recover indicating a permanent damage. In the glaucoma groups demyelination is not known and therefore not the cause of the increased latencies. Here other factors like compression and/or ischaemia may be responsible for the optic nerve disfunction. Wijngaarde and van Lith (1979) presume that these factors cause less prolonged PVEP latencies than demyelination does. In the OGD group hypothyroidism and irradiation effects have also very probably contributed.

The results thus far have concerned mean amplitudes and mean latencies. For the clinical use of PVEP in diseases of the optic nerve, the percentage of individual cases with abnormal PVEPs has also been studied (table 8.4). It appears that individually lowered amplitudes (mean amplitude minus two standard deviations) are only seen in ON and MS+, whereas individual cases of abnormal latencies were seen in all patient groups, especially in ON and MS-/MS+. These observations are in agreement with those of many authors mentioned in the chapters IV-VI. The low number of individually lowered amplitudes is explained by the large standard deviation of the mean in combination with the low number of severe cases.
In a PVEP review Sokol (1976) concludes that the major PVEP parameter which is

unequivocally affected in disorders involving the optic nerve is latency. The individual results of table 8.4 support this statement. Based on the results of Halliday et al. (1973), Millner et al. (1974) and Asselman et al. (1975), Sokol came to the conclusion that the most significant PVEP results are reached if patterned stimuli consist of large checks (50'). Our check sizes of 40' and 80' are in this range.
The importance of the PVEP latencies implicates that the use of a slide projector system instead of a television system is a justifiable choice, because the former system has a much smaller variability of the latencies (van Lith and van Marle, 1978).
No consensus exists concerning the optimal temporal frequency to be used. In the literature abnormal PVEP latencies were observed for both low and high pattern reversal frequencies. The choice of the pattern reversal frequency is perhaps not such an important item here although it is for the unpatterned flash VEP. The reason may be that unpatterned flashes provide a complementary means of studying the temporal characteristics of the visual system (different channels) that cannot be offered by patterned stimuli (Sokol, 1976). Later on, data became available that some temporal frequency selectivity is present in pathological conditions. In demyelinating neuropathies PVEPs are affected at low and high temporal frequencies (Riemslag, 1986; Bobak et al., 1988), whereas compressive disorders result in abnormal PVEPs at high reversal frequencies only (Bobak et al., 1988). Our results demonstrate abnormal transient PVEPs for both demyelinating and compressive neuropathies. These abnormalities are less marked for the latter.

Correlations between the PVEP and the psychophysical examinations
The PVEP amplitudes are dominated principally by the cone system of the central visual field and are said to correlate well with psychophysical examinations like visual acuity, visual field, colour vision and contrast sensitivity (Shibasaki and Kurowa, 1982; Plant et al., 1986; Celesia et al., 1986; Sanders et al., 1987). In general, our results do not contradict these findings, but statistically significant relations are not always reached (tables 8.8, 8.9, 8.11). Several authors have pointed to a macular overrepresentation of the PVEP involving the central 3°-15° of the retina depending on the pattern element size used (Harter and White, 1968; Armington and Gorwin, 1971; Regan, 1972; Spekreijse, 1973; Katsumi et al., 1988). The results in tables 8.8a-d underline that the PVEP is dominated by the central part of the visual field. Negative correlations between the PVEP amplitudes and visual field loss are seen, and especially in the case of the central 10°, statistically significant levels are reached. The relatively large check sizes used in this study explain that these correlations were also found towards the midperiphery (sectors 10°-20° and 20°-30°), although these were less obvious. Positive correlations between amplitudes and visual acuity are seen in all patients (table 8.9). That most of these correlations do not reach statistical significance is explained by the normal mean visual acuity in most patient groups and the low numbers of individual cases with severely decreased visual acuity.

The PERG in the reference group and its dependence on stimulus variables

The PERG in the reference group

The PERG is influenced by many factors as discussed in chapter III. Various authors have studied its waveform and have measured the components, all using different recording equipment and stimulus parameters. A direct comparison with the results of others is therefore difficult. Only one paper, the one of Ringens et al. (1986), deals with exactly the same recording equipment and stimulus parameters. Our data (waveform, amplitudes, latencies and standard deviations) correspond very well with those of Ringens et al. (1986). Some authors have used comparable equipment and stimulus parameters (Persson and Wanger, 1982; Trau and Salu, 1984; Adachi-Usami et al., 1987; Veagan and Billson, 1987). Their data are in the same range as ours. The differences with other publications can be explained by the stimulus parameters used. These parameters will be discussed separately now, although the effect of a certain parameter is highly dependent on the choice of other parameters.

Compared to the results of others, our PERG amplitudes for both check sizes are relatively high (P50 $\pm$ 5.5μv, N95 $\pm$ 9μv). In the literature, the P50 amplitude seldom exceeds the range of 1.5-3.0 μv, whereas the N95 amplitude is seldom higher than 6μv. Stimulus parameters, known to influence the PERG amplitudes, are the check size, the pattern reversal frequency, the mean luminance, the pattern contrast and the stimulus field size. Recording variables like the electrode placement and the sort of electrode used also affect the PERG.

The stimulus parameters

The choice of our two check sizes 40' and 80' is not unusual, although most authors prefer smaller check sizes in the range 5'- 40' (e.g. Arden et al., 1982; Dawson and Maida, 1982; Persson and Wanger, 1984; Trau and Salu, 1984; Odom and Norcia, 1984; Celesia and Kaufman, 1985; Mashima and Oguchi 1985; Skrandies and Leipert, 1988). This probably has to do with the fear for a significant luminance contamination of the PERG. According to Bobak et al. (1983) our element sizes would be too large for a true pattern response. Certainly a disturbing luminance contribution has been demonstrated, but only for check sizes over 120' (Mashima and Oguchi, 1985). PERG amplitudes are known to increase with larger check sizes. The difference in amplitude between our two check sizes is only small (0.1μv), whereas the pattern size differs by a factor of two. Similar observations for check sizes in the same range were done by others. The small difference can be explained by a small increase in amplitude for check sizes over 5' (Holopigian et al., 1988; Tan et al., 1989), a saturation effect (Berninger and Schuurmans, 1985) or an optimal check size in between the two check sizes chosen (Yoshii, 1988). The latter author observed an optimal check size for the N95 component at 50'.

Several arguments are available in favour of our choice for the relatively large pattern elements. Elements of this size are easier to concentrate on for the elderly and have lower

optical and perceptual degradation (Korth and Rix, 1984; Thompson and Drasdo, 1989). Not only the P50 component but also the N95 component has been studied. Those authors reporting on the N95 component generally observe larger optimal check sizes for this component in the range of 25' - 60' (Berninger and Schuurmans, 1985; Yoshii 1988; Holopigian et al, 1988; Thompson and Drasdo, 1989). Our relatively large testfield and the inherent stimulation of more peripheral ganglion cells with larger receptive fields cause a shift of the optimal size towards a lower spatial frequency (Celesia and Kaufman, 1985; Thompson and Drasdo, 1987; Ambrosio et al., 1989).

The choice of the pattern reversal frequency remains a controversial item in literature. As discussed in chapters IV - VI, abnormal PERGs are found for both transient and steady-state reversal frequencies, although it appears that abnormalities are more frequently seen with the latter. Some authors report higher PERG amplitudes at high temporal frequencies (Trick and Wintermeyer, 1982; Seiple et al., 1983a; Odom and Norcia, 1984), whereas others observe them for low reversal frequencies as well (Hess and Baker, 1984; Yoshii, 1988). Our special interest in the effects of optic nerve diseases on both the P50 and the N95 component meant that the use of a high reversal frequency was not desirable. The data obtained in this study lead to the conclusion that the N95 component is of greater value than the P50 component. This result combined with the observation that the steady-state PERG is dominated by the N95 component (Berninger and Heider, 1989), explains the higher prevalence of steady-state PERG abnormalities reported.

The luminance level and the PERG amplitude are closely related either linearly (Hess and Baker, 1984; Korth and Rix, 1984; Veagan and Billson, 1987; Lorenz et al., 1989) or logarithmically (Yoshii and Päärman, 1989). Higher mean pattern luminance levels result in higher amplitudes. Indeed the luminance level used here is high (135 cd/m2) compared to the levels of many others (30 -80 cd/m2). In the study of Vaegan and Billson (1987) the mean luminance level is high as well (400 cd/m2) and their results are comparable with ours. Celesia and Kaufman (1985) and Celesia et al. (1987) also apply high luminance levels but their amplitudes are rather low. This is probably caused by a low pattern contrast and the different type and placement of the electrodes.
In contrast to the PVEP we did not utilize the one logarithm filter for the PERG registration. Such a filter would reduce the luminance level by a factor ten. This is not a problem for the PVEPs with their high amplitudes, but from our own clinical experience we know that the use of a one logarithm filter reduces the PERG amplitudes so much that the signal to noise ratio becomes a serious problem. High luminance levels have the inherent risk of a relatively high luminance contribution to the PERG. For this reason the use of some slight filtering (e.g. 0.25 or a 0.5 logarithm filters) is recommended in future tests. The PERG obtained at different luminance levels could provide additional information.

Pattern contrast correlates linearly with PERG amplitudes (Arden et al., 1982; Arden and Vaegan 1983; Mitchell and Howe, 1984; Hess and Baker 1984; Korth et al., 1985; Yoshii, 1988) or logarithmically (Ambrosio et al., 1989). For this reason a high pattern contrast of 85-100% is frequently chosen in the literature. Our pattern contrast of 87% is within this range. Only a few reports with a lower pattern contrast are known to me, resulting in severely reduced PERG amplitudes (Dawson and Maida, 1982; Celesia and Kaufman, 1985; Adachi-Usami, 1987). Although it is inviting to use high pattern contrasts, the risk of a significant luminance contribution increases as well (Odom et al., 1982).

The size of the stimulus field in this study is rather large compared to others (22°x 20°). We have deliberately chosen such a large testfield, because diseases like glaucoma and normal pressure glaucoma affect the paracentral areas first. As the PERG is a retinal summation response with a macular overrepresentation, a larger stimulus field results in higher amplitudes especially if large check sizes are chosen (Vaegan and Arden, 1982; Mitchell and Howe, 1984). If the ganglion cell distribution along the retina is studied, over 50% of the ganglion cells are within the central 13 degrees of the fovea (Dawson and Maida, 1984). With a testfield size of (22°x 20°) this means that at least 50% of the ganglion cells present in the retina is tested.

The PERG electrode placement has repeatedly been mentioned as a contributive factor to the variability and contamination of the PERG (Bodis-Wollner et al., 1984; Yanashima et al., 1984; Berninger and Schuurmans, 1985; Berninger, 1986; Tan et al., 1989). These authors observe cross-contamination from the contralateral eye and/or a PVEP contamination reflected in the amplitude of the N95 component. This would be especially the case at a low reversal frequency in combination with the reference electrode placed at the ipsilateral earlobe, like we did. Others, for example Odom et al. (1987) and Holopigian et al. (1988), were not able to confirm such statistically significant contaminations. Odom et al. applied a DTL electrode, but Holopigain et al. used almost identical circumstances as Berninger and Schuurmans before and was not able to demonstrate a PVEP contamination of the N95 component. Yet, the use of the ipsilateral ear as a reference instead of the ipsilateral temple increased the N95 amplitude and reduced the variability by almost 50%. Most authors do not take this larger variability into consideration when using the ipsilateral temple which is probably caused by muscle activity. Different spatial and temporal tuning of the PERG and PVEP provide further evidence that the PVEP does not contaminate the PERG (Odom and Norcia, 1984).
From our own clinical experience we can report completely normal PERGs in MS- patients with highly abnormal or absent PVEPs. This observation is not compatible with the idea that the PERG is significantly contaminated by the PVEP, if the ipsilateral ear is used as a reference.

Although in the literature a tv-system is frequently applied, in this study a projector system was chosen. The advantages for the PVEP registration have already been discussed. As to the PERG, only a few authors have compared both systems. Ringens et al. (1986) observed better amplitudes for the projector system. This finding was confirmed by Yoshii (1988). Furthermore, the latter author made the important observation that the use of a projector system instead of a tv-system reveals a better spatial tuning of the N95 component (with an optimum at check size 50'). This is noteworthy because of our special interest for the changes of the N95 component and the check sizes chosen (40' and 80'). With this observation, the relatively high amplitudes at check size 40' can probably be explained.

The usual PERG recording in literature consists of a single recording in which 64, 128 or 254 counts are averaged. Repeated recordings are seen occasionally (e.g. Ryan and Arden, 1988), whereas interrupted stimulation is unusual and does not result in a lower variability of the PERG (Holopigian et al., 1988).
In this study 64 or 128 counts were averaged for each measurement, depending on the signal to noise ratio. Each measurement was repeated twice. The best as well as the mean of the three measurements was noted. In chapter III several factors were mentioned which lower the PERG amplitudes and influence the PVEP results as well (e.g. refractive errors, medial opacities, pupil size). Concentration and awareness of the patient are important for the registration of the PVEP. Brain activity (e.g. alpha rhythm) interferes with the response evoked by the moving pattern and can result in higher PVEP amplitudes. Except for a possible PVEP interference of the N95 component (Tan et al., 1989) and eye movements or blinking (Ryan and Arden, 1988), no other factors which result in artificially increased PERG amplitudes could be traced in the literature. Therefore we were interested to see whether the use of the best of three measurements instead of the mean would result in better and/or more frequent statistically significant correlations. Of course the use of the best out of three measurements results in higher PERG amplitudes, but with these measurements we were not able to demonstrate any of the effects searched for. Therefore in chapter VIII only the calculated means of three measurements are presented, leaving the only advantage of a lower variability of the PERG as the number of counts increases (Holopigian et al., 1988).

The effect of age on the PERG results is an interesting item for discussion. The fact that nerve fibres and ganglion cells are lost during life (Vrabec, 1965; Dolman et al., 1980; Quigley et al., 1982a, 1982b; Balaszi et al., 1984) would explain the significant decrease in PERG amplitudes. Indeed such observations have been reported for steady-state stimulation (Trick, 1987; Porciatti et al., 1988), but not for transient stimulation (Arden et al., 1984; Wanger and Persson, 1985, 1987). Our study demonstrates negative correlations between age and transient PERG amplitudes without reaching statistical significances. Our group of normals is quite large (n=66, 19-77 years of age) with only a few individuals over 70 years old. This is somewhat different from the study of Trick (1987) in which nine elderly adults

(70-80 years of age) are compared with nine younger ones (20-30 years of age). In this study nothing can be said about the moment (decade) at which the PERG amplitudes begin to decline and the course of the decline. The same argument applies to the study of Porciatti et al., 1988). Wanger and Persson (1985) used a control group for their transient PERGs which is to young (21-40 years of age) to be age-matched with our control group. Later Wanger and Persson (1987) found a non-significant decrease in amplitude in an older group of normal subjects (57-77 years of age). In the paper of Arden et al. (1984) some decline in PERG amplitude in the subjects over 70 years of age can be noticed.
From these results it can be concluded that the PERG is sensitive for age-induced changes, but not until the eight decade is reached (70-80 years of age). Only a few of our normals and patients are within this range of age, which explains for the non-significant decrease in PERG amplitudes found in this study.

The PERG in disorders of the optic nerve

This topic will be dealt with on the basis of four questions: 1) Is the origin of the PERG proximal from that of the luminance ERG; 2) if so, is the PERG a ganglion cell response; 3) is the PERG influenced by disorders of the optic nerve; 4) if this is the case, is the abnormal PERG caused by a retrograde ganglion cell degeneration or are there other factors explaining the PERG abnormalities? These questions will be discussed using our clinical results in correlation with basic observations from the literature.

Is the origin of the PERG proximal from the luminance ERG?
The luminance ERG has several components with a different origin in the retina. The a-wave originates in the inner segments of the rods and the cones (Brown and Wiesel, 1961), the b-wave is derived from the bipolar cell layer (Granit, 1947, 1963; Noell, 1954, 1963) and the c-wave has its origin in the pigment epithelium layer (Noell, 1954, 1963). The luminance ERG does not involve the ganglion cells at all (Granit, 1963). We did not examine the luminance ERGs in our patient groups, but they are reported to be normal in glaucoma (Dodt, 1987; Skrandies and Leipert, 1988), in MS/ON (Seiple et al., 1983; Galloway et al., 1986), in dysthyreoidism (Ladenson et al., 1984) and in optic nerve compression (Mizota et al., 1988). The oscillatory potentials (OPs) have their origin proximal in the bipolar cell layer (Heynen and van Norren, 1985). Clinical literature on this subject is difficult to interpret since a quantative evaluation of the OPs is difficult and only really possible according to the method of van der Torren (1991). The fact that the PERG is sensitive for isoluminant chromatic contrast (coloured patterns: Riggs et al., 1966; Korth and Rix, 1984) and that the amacrine cells are not colour coded means the PERG is not thought to have its origin in these cells (Arden et al., 1982).

These observations make it understandable that some authors, among others Maffei and Fiorentini (1981), came to the more specific hypothesis that the PERG derives from ganglion cells or at least reflects ganglion cell activity.

Is the PERG a ganglion cell response?

Ganglion cells are relatively insensitive to changes in stimulus luminance as such, but are particulary responsive to changes in spatial contrast (Enroth Cugell and Robson, 1966). The cat experiment of Maffei and Fiorentini (1981) was the first study in which ganglion cell activity and PERG alterations were linked. The fact that, after the sectioning of the optic nerve the PERG disappeared at the moment that ganglion cells were lost, due to retrograde degeneration, provided a strong argument for the origin of the PERG in the ganglion cells. In the years after, anatomical, physiological and clinical evidence became available to support this hypothesis.

Anatomically, a retrograde ganglion cell degeneration was demonstrated in various animal species (Van Buren et al., 1963; Radius et al., 1978; Maffei and Fiorentini, 1981; Porciatti et al., 1985), but whether these results are applicable to the human situation remains unclear (Hess et al., 1986). Traumatic accidents of the optic nerve in humans with a complete loss of visual function are very instructive for the anatomical and physiological origin of the PERG, since in these instances a severe or total loss of the optic nerve fibres can be expected. Completely absent steady-state PERGs were reported by Fiorentini et al. (1981), May et al. (1982) and Yanashima et al. (1984). The observation of Fiorentini was not confirmed by Sherman (1982) who found completely normal steady-state PERGs (high contrast, high luminance) in a patient with complete traumatic optic nerve atrophy. Reductions between 40 and 60% in patients with optic canal fracture are reported by Mashima and Oguchi (1985) using both a transient and steady-state stimulus. In all these studies there was no absolute evidence of complete transection of the optic nerve. Harrison et al. (1987) report a patient with lowered but not absent PERGs after surgical resection of the optic nerve. It is stressed that these reports concern the positive PERG component only.

From a physiological point of view a lot of effort was made to demonstrate the spatial tuning effects of the P50 component. This would further support the ganglion cell hypothesis. Some authors did observe such spatial tuning effects but others did not (see chapter III). Those authors who were not able to find spatial tuning effects explained their findings by saturation effects (Groneberg, 1980), a luminance response dominating over the contrast response (Trick and Wintermeijer, 1982; Korth 1983, Van den Berg et al., 1988) or a complete absence of a contrast response (Spekreijse et al., 1973; Riemslag, 1986).

Clinically, PERG P50 disturbances were found in retinal, macular and optic nerve disorders, but these observations were not always confirmed by others. The PERG is dependent on a complex interactive network of stimulus, registration and patient variables. Many of the discrepancies found can be explained by the lack of standardization of the PERG.

Another aspect of the PERG is the N95 component. A clear spatial selectivity for this component was demonstrated (Berninger and Schuurmans, 1985; Korth, 1985; Yoshii, 1988) as well as a selectivity for disorders of the optic nerve (Holder, 1987, 1991; Ryan and Arden, 1988). These authors considered the P50 component mainly or completely as a pure luminance response. The use of small check sizes and a low pattern luminance would leave the true N95 contrast response, whereas the P50 luminance response completely disappears (Schuurmans and Berninger, 1985).
Based on the facts presented; it is best concluded that the PERG and the ganglion cell activity are linked. To my best knowledge no micro electrode studies are available proving that the PERG is derived from the ganglion cells themselves. An origin in the proximal part of the bipolar cell layer can not be excluded as yet. Therefore it is better to speak about loss of ganglion cell activity instead of loss of ganglion cells.

Is the PERG affected by disorders of the optic nerve?
The differences between the P50 and N95 component necessitate their being dealt with separately.
The positive PERG component has been compared in various disorders of the optic nerve (Fiorentini et al., 1981; Arden et al., 1982; Seiple et al., 1983; Celesia and Kaufman, 1985; Galloway et al., 1986; Lorenz et al., 1989). Unfortunately, in these papers only a few patients with each disorder were examined. Significantly lowered or even absent PERGs were seen. In contrast, Ota and Myake (1986) demonstrated normal or slightly abnormal steady-state PERGs in a larger group of patients with various optic nerve diseases. In their study a contact lens electrode is used instead of a gold foil and the affected eye is compared with the contralateral eye. A considerable number of their patients suffered from optic neuritis or MS and therefore subclinical damage to the contralateral eye is not excluded. The moment of examination of ON/MS patients probably also explains the differences found. The amount of time that has elapsed since the onset of the ON is an important factor in the PERG outcome, as has already been demonstrated by Arden et al. (1982).
Alterations of the P50 latency are reported by Lorenz et al. (1989). A decrease in latency is observed which they presumed to be due to a selective loss of the pattern specific response, leaving a luminance response of shorter peak time.
Holder (1987) presents a comparative study (36 patients) of various disorders of the optic nerve studying both positive and negative PERG components. The N95 component is selectively affected in 81% of the patients with definite optic nerve involvement (glaucoma patients not included), whereas the P50 component is abnormal in only 19% of these cases. In patients with glaucoma (n=3) Holder observes abnormalities of the P50 component only. In 1991 Holder extends the patient group with optic nerve demyelination (n=141) and reports similar results. The observation that optic nerve disorders affect the N95 component more frequently and more severely is confirmed by Ryan and Arden (1988).

In chapters IV-VI the literature for the patient groups examined in this study has been reviewed. Most of the papers in these chapters deal with one or two disorders only. Frequently the combination of GLAU/OHT or ON/MS is chosen. Although PERG abnormalities for all these patient groups have been demonstrated some comments have to be made. In OHT/GLAU PERG abnormalities are more seen with steady-state stimulation than with transient state stimulation. The fact that the N95 ganglion cell response dominates the steady-state response can explain this finding (Berninger and Heider, 1985). Those authors who report on the N95 component observe lowered amplitudes (Howe and Mitchell, 1985; Weinstein et al., 1988; Hawlina et al., 1989).

If our results are compared with the observations in the previous paragraph, the conclusion is that our findings correspond best with those of Holder (1987, 1991). We could confirm that in disorders of the optic nerve the N95 component is more frequently and more severely affected than the P50 component.
The P50 component can not easily be interpreted as a pure ganglion cell activity, as significant abnormalities are only seen in the glaucoma groups. Our check sizes predominantly stimulate the midperiphery of the retina, an area which is known to be primarily affected by glaucoma. This can explain the alterations of the P50 component found in the glaucoma groups, which is even more the case for the N95, since the decrease in terms of percentage of this component is more marked than for the P50 component. In the other patient groups the ganglion cell activity is, apparently, not sufficiently diminished to cause a significant decrease in P50 amplitudes. That the N95 component is more frequently and more severely affected than the P50 component in disorders of the optic nerve, confirms the view that the P50 component is dominated by a luminance component and becomes abnormal only if large numbers of ganglion cells are lost. Further support for this view is found in the P50 latencies. In our patient groups the P50 latencies tend to decrease (except for glaucoma) and sometimes statistical significant delays are seen confirming the observation of Lorenz et al. (1989) that after selective loss of the pattern response the shorter peak time of the luminance response remains.

A luminance contribution to the N95 component can not be excluded. As discussed before our high pattern contrast, the relatively large check size and the low reversal frequency create the risk of an substantial luminance contamination. If the results of the PVEP and the psychophysical examinations are included in the evaluation of the N95 component, it has to be concluded that our patient groups are characterized by only slight to moderate optic nerve involvement. The fact that in these patient groups N95 amplitude reductions are seen up to 40-45% (GLAU/NPG), makes a major luminance contribution improbable. In MS+ the reduction is only $\pm$ 25% but here the choice of our stimulus parameters (i.e. the relatively large check sizes) probably explains the difference with the glaucoma groups (see later).

Is the abnormal PERG caused by a retrograde ganglion cell degeneration?
The axon of a retinal ganglion cell has no collaterals which means that any damage between the retinal ganglion and the chiasm results in a complete retrograde degeneration (Kupfer, 1963). In humans, this degeneration is completed at six months or later, while the distance between the site of the damage and the ganglion cell has no influence on this delay (Radius and Anderson, 1978). Pallor of the optic disc and ganglion cell degeneration are related in some way, but it is important to know that pallor can precede the degeneration (Radius and Anderson, 1978).
Primary involvement of the optic nerve with damage to the ganglion cells and/or their axons has been demonstrated for OHT/GLAU/NPG (et al., 1980 - 1989; Anderson, 1983; Airaksinen et al., 1984, 1989), for MS (Gartner, 1953; McDonald, 1974; Frisén and Hoyt, 1974; Walsh and Hoyt, 1982; Lidegaard et al., 1983) as well as for OGD (Trokel and Jacobiec, 1981; Kennerdel et al., 1981; Ossoinig, 1984). In these diseases we observed lowered PERG N95 amplitudes. Normal N95 amplitudes were seen in those groups in which a retrograde ganglion cell degeneration was not very likely at the moment of examination (ON/MS-). Based on these results, it is logical to conclude that the N95 component predominantly reflects ganglion cell activity and that the loss of amplitude can be caused by a retrograde ganglion cell degeneration.

Although it is tempting to attribute any significant PERG amplitude reduction to a retrograde degeneration of the ganglion cells there are other factors which can cause a (temporary) amplitude loss of the PERG. Each of our patient group has its own underlying mechanisms resulting in optic nerve disfunction or definite optic nerve damage. The most important mechanisms and factors are: compression (OHT/GLAU/NPG/OGD), ischaemia (OHT/GLAU/NPG/OGD), inflammation and edema (ON/MS-/MS+), demyelination (ON/MS-/MS+), thyroid hormone levels (OGD) and irradiation (OGD). Permanent damage to the nerve fibres is not always the pattern, for instance during the acute onset of ON lowered PERGs have been reported which later appeared to recover (Berninger and Heider, 1985; Holder, 1991). Here a temporary edema of the optic nerve is probably responsible. In OHT/GLAU a recovery of the PERG amplitudes has been observed after treatment of high eye pressure (Papst et al., 1984; Ringens et al., 1986). This recovery can be explained by the relief of the ischaemia and compression. In OGD the electrodiagnostical results appear to be dependent on the thyroid levels (Holder and Condon, 1989). Each of the mechanisms mentioned will be dealt with in the next paragraphs more extensively.
Thus far, the best conclusion is that the N95 component reflects ganglion cell activity but that a decrease in amplitude is not necessarily caused by a retrograde ganglion cell degeneration. Only if the PERG amplitudes during the follow-up and in spite of treatment of the patients do not return to normal or even get worse can one conclude that the retrograde ganglion cell degeneration is the more important factor.

The PERG versus the PVEP

One of the aims of this study is to compare the PERG and the PVEP results in order to evaluate their clinical value. For a meaningful discussion of this subject not only group differences (tables 8.3 and 8.5) and percentages of individual abnormalities (tables 8.4 and 8.6) are essential, but also the figures with regard to the parallel run of both electrodiagnostics have to be considered (table 8.7). These tables not only indicate that in general the PVEP is more frequently abnormal than the PERG, but also that two types of abnormality are present.

The first type of abnormality is seen in those optic nerve diseases, in which aspects like inflammation, demyelination and/or compression are prominent (ON, MS- and MS+). Here the PVEP is abnormal in the vast majority of individual cases (up to 95%), whereas the PERG is abnormal only in a minority of cases. Furthermore, abnormal PERGs run parallel with abnormal PVEPs, but the reverse is not the case. These results are in agreement with those of various authors comparing PVEPs and PERGs in similar disorders (Kirkham and Coupland, 1983; Bobak et al., 1983; Persson and Wanger, 1984; Boschi et al., 1984; Celesia et al., 1986; Plant et al., 1986; Kaufman et al., 1988; Holder 1991). The fact that the PVEP is more severely affected than the PERG in ON, MS- and MS+ is probably explained by the pathogenesis. Temporary edema (ON) and clinical or subclinical demyelination (MS+/MS-) are responsible for a conductive disorder reflected in the PVEP abnormalities. Histological studies have confirmed myelin sheath defects in ON/MS, but have also demonstrated normal axons being affected in late stages of the disease only. If the PERG represents a ganglion cell activity becoming abnormal after a retrograde degeneration of the axon and ganglion cell, the absence of significant PERG alterations may be explained by the fact that in most of our cases this degeneration has not, as yet occured. Consequently our conclusion has to be that the PERG does not contribute to the diagnosis of ON or MS.
Another aspect of the PERG is whether it provides any additional information on ON/MS. Some authors have pointed to this aspect. Celesia et al. (1986) and Kaufman et al. (1988) observe a prognostic value with regard to the visual outcome after an episode of ON. During a two-years follow-up patients with abnormal PERGs correlated closely with failure of visual recovery and the eventual development of severe optic atrophy. In this study the ON patients were examined during the acute onset, one month later and after six months. Although we observe positive correlations between visual acuity and PERG amplitudes, statistical significances are not reached. On the one hand this absence is explained by the fact that visual acuity returned to normal in almost all patients, on the other, our follow-up might have been too short to demonstrate clearly a ganglion cell dysfunction by means of the PERG. A clear judgement concerning the predictive value of the PERG in ON is therefore not possible. The OGD group is a more distinct group. Optic nerve edema or demyelination are not likely to play a major role in the pathogenesis. Other factors like optic nerve compression,

hypothyroidism or a history of orbital irradiation probably explain for the PVEP abnormalities. These factors will be discussed in the paragraph concerning the OGD patients.

The second type of abnormality is seen in the glaucoma groups. In these groups the incidence of PVEP and PERG abnormalities is more or less equal (± 50% of the cases), but these abnormalities do not have a parallel run since in about a third of the individual cases only one of the electrodiagnostics is abnormal. The percentage of OHT patients with normal PVEPs but abnormal PERGs (27%) is remarkable. Two factors attribute to the difference in results between the glaucoma groups and the other patient groups; the anatomical site of damage and the localization of ganglion cell loss.
In ON/MS the anatomical site of damage is primary in the optic nerve caused by inflammation, demyelination and compression of the optic nerve fibres. As explained before, the PVEP is a sensitive tool for such damage, reflected in the high percentage of abnormal PVEPs observed in these groups. In those cases were axons are lost the PERG is affected as well. In glaucoma the anatomical site of damage is within the lamina cribrosa of the eye (chapter IV). The damage to the nerve fibres either caused by direct compression (bending and strangulation of the fibres) or by vascular (ischaemic) influences. As will be discussed in the next section, several arguments are available to prove that glaucoma not only has an optic nerve component but a retinal component too. The selective amplitude loss of the P50 component in glaucoma can be explained by such a retinal component.
Compared to ON/MS the type of visual field loss is different in glaucoma. In ON/MS the nerve fibres from the central area of the visual field (papillomacular bundle) are predominantly affected. The PVEP is derived from this area and dominates over the PERG which represents a larger part of the retina. In contrast, glaucoma is known for its early paracentral scotomas, an area dominated by the PERG. In addition, several authors point to a (subclinical) damage of the central part as well. Therefore it is likely that glaucoma in general affects a larger retinal surface area than ON/MS does. Depending on the exact location of nerve fibre damage within the visual field, the PERG can be abnormal, while the PVEP is abnormal and vice versa. As demonstrated in table 8.7 both situations occur.
In 1983 et al. estimated that in glaucoma 25-50% of the ganglion cells can be lost before visual field defects are detected by dynamic perimetry (Goldmann perimetry). Modern static computer perimetry with the Octopus or Humphrey Allergan equipment has improved the sensitivity significantly. Depending on the location of damage, a loss of 20% of the ganglion cells is detectable in the central area, whereas in the periphery visual field defects can be seen after a loss of 5% (et al., 1989). In this study the visual field was tested by means of static perimetry (Humphrey Allergan, central 30 degrees, full threshold). In 27% of the OHT patients without visual field defects the PERG was abnormal. Based on these figures it is logical to conclude that the PERG is able to detect a small loss of ganglion activity. Therefore in contrast to ON/MS, the PERG is a useful tool in the early detection of glaucomatous damage especially in combination with the PVEP.

The patient groups

OHT/GlAU/NPG

In all three patient groups the mean PVEP amplitudes are lowered, whereas the mean latencies are increased. A statistical significance is reached for all stimulus variables. The results of the OHT group are in between those of the normals and the GLAU/NPG groups. Due to the large standard deviation of the PVEP amplitudes the PVEP latencies are of greater value for clinical purpose than the amplitudes. All these results are in agreement with those of others as presented in chapter IV.

We tried to correlate the PVEPs with visual acuity, contrast vision, visual field loss as well as with various optic disc parameters like pallor of the optic disc and the cup/disc ratio. Several authors reported significant correlations (Towle et al., 1983; van Lith et al., 1984). Our results are not inconsistent with these observations, but can not confirm them either because only a few statistically significant differences are seen. This finding is probably explained by the fact that most patients were in a comparable and moderate stage of their disease. Potential differences remain hidden because of such uniformity of patients.

The PERGs in the OHT/GLAU/NPG groups are more severely and more frequently affected compared to the other patient groups. In fact P50 amplitude reductions are seen almost exclusively in these groups. It is remarkable that in OHT the P50 and N95 amplitudes are significantly reduced, since in literature transient state PERGs are frequently reported to be normal in OHT (Papst et al., 1984; Wanger and Persson 1985, 1987; Weinstein et al., 1988; Marx et al., 1988; Hawlina et al., 1989; Korth et al., 1989). Although no significantly reduced mean amplitudes were found by these authors, they all report abnormal individual cases. Our patient and reference group are substantially larger which may be the reason for the differences found. Another explanation may be the check size used, because most of the authors applied smaller elements (around 25') predominantly testing the central part of the retina. If the first damage in OHT is localized in the paracentral areas, then it is plausible that the use of a somewhat larger check size will detect this damage at an earlier stage. In this context the choice of a check size of 40' is preferred over 80', since the 80' check size is probably too large, as demonstrated in table 8.6 by the higher percentages of individuals with abnormal PERGs using the 40' stimulus. Additional support is found in tables 8.8a-d. The best correlation between the amplitude of the N95 40' component and the visual field is seen in the 10°-20° sector, whereas this is the case for the N95 80' component in the 20°-30° sector.

It is estimated that 3 - 35% of the OHT patients will develop glaucoma (Armaly, 1969; Perkins, 1973 and Shields 1982). Table 8.6 reveals that the N95 component is abnormal in 20% (80') and 23% (40') of our OHT patients. In this study only screening of the OHT patients took place, therefore a follow-up over many years will be necessary to determine, whether the OHT patients with abnormal PERGs are those patients at risk for developing

glaucoma. As discussed before, the computer static perimetry greatly improved the sensitivity of visual field testing, but still a minimum loss of 5 - 20% of the ganglion cells is required before visual field defects become detectable (er al., 1989). The fact that in more than 20% of our OHT patients PERG abnormalities are seen is promising for the PERG as a tool of early detection of glaucoma.
The changes of the PERG P50 component in OHT/GLAU/NPG need further comment as these changes are not seen in the other optic nerve disorders. The significantly lowered P50 amplitudes and the prolonged latencies have been observed under similar circumstances by others (van Lith et al., 1984; Howe and Mitchell, 1984). The differences with the other optic nerve diseases raise questions with regard to the site of damage in glaucoma and the physiological origin of the PERG P50 component. Anatomical, physiological and clinical observations allow two scenarios for the specific P50 reduction in the glaucoma groups.

In the first scenario the primary site of damage in glaucoma is at the level of the lamina cribrosa. The loss of retinal ganglion cells is secondary to this damage and is caused by a retrograde degeneration, in which case glaucoma is a pure optic nerve disorder. The significant P50 amplitude decrease is explained by a much greater loss of ganglion cells and thus ganglion cell activity in glaucoma compared to the other optic nerve disorders. In ON/MS inflammation and demyelination are more prominent than the loss of axons (Wanger and Persson, 1984; Kaufman et al., 1988). In those MS cases where axons and subsequently ganglion cells are lost, the central part of the retina (papillomacular bundle) is predominantly affected. In glaucoma not only a significant reduction of ganglion cells has been demonstrated but also a more diffuse pattern of loss of these cells. In the macular area ganglion cells of all sizes are affected but in the paracentral and peripheral areas the loss evidently shifts towards the larger Y-ganglion cells (et al., 1989). The selective retrograde loss of these large Y-cells with their large fast conducting axons explains for the increase in P50 latency as the smaller and slower conducting X-cells are left.

The second scenario is that glaucoma has two primary sites of damage, not only at the level of the lamina cribrosa but also at the level of the retinal ganglion cells. The retrograde degeneration of axons is accompanied by a functional impairment of the retinal ganglion cells probably due to ischaemia. Even an antegrade degeneration can not be excluded (Zrenner et al., 1988). Electrodiagnostic observations provide us with some clues as to the depth localization of this damage in the retina, because the luminance ERG is frequently reported to be normal in glaucoma (May et al., 1982; Bobak et al., 1983; van Lith et al., 1984; Porciatti and von Berger, 1984; Wanger and Persson, 1984; Marx et al., 1986; Zrenner et al., 1988). This normal luminance ERG in glaucoma does not support substantial damage in the distal retina or more specifically the distal part of the bipolar cell layer.
Apart from both scenarios, the intraocular eye pressure (IOP) is an important aspect of glaucoma. Elevated IOPs undoubtedly cause compressive damage to the eye, but can not

explain for the glaucomatous damage seen in NPG. Even at IOPs as low as 10-15 mm Hg a progressive visual field loss is seen in this group. The degree of tissue oxygenation depends not only on the IOP but also on the blood pressure (BP). The perfusion pressure (BP minus IOP) appears to be a more useful parameter in glaucoma (Grehn and Prost, 1983; Ross et al., 1985; Siliprandi et al., 1988, Novack et al., 1990)). In animal experiments a lowered perfusion pressure results in a lowered firing rate of the ganglion cells and in a decrease of the PERG. Clinical observations confirm that retinal ischaemia affects the PERG P50 component (Arden et al., 1986; Porciatti, 1987; Siliprandi et al., 1988). The fact that lowered PERG P50 amplitudes with prolonged latencies are also seen in macular and retinal diseases (Celesia and Kaufman, 1985; Ryan and Arden, 1988; Lorenz et al., 1989) further supports the view that the P50 both reflects retinal and optic nerve damage. Glaucoma has a more or less unique position with both factors present.

If the P50 peak also has a luminance component, it is even more clear why abnormalities of the P50 peak are seen almost exclusively in glaucoma. Very probably our relatively large check sizes cause a substantial luminance response. Therefore P50 abnormalities are seen, if large numbers of ganglion cells are lost (scenario 1) or if both optic nerve and retinal ganglion cell damage affect the relative pattern contribution to the PERG P50 component (scenario 2).

Various parameters of the optic disc were correlated with the PERG variables (table 8.13). Hardly any statistically significant correlations were found. A plausible explanation for this observation is that most patients were in a comparable and moderate stage of their disease. This holds especially true for glaucomatous signs like the presence of notches and optic disc haemorrhages which were seldomly seen and for cup disc ratios in GLAU/NPG which were mostly about 0.8. Other glaucomatous signs, however, were seen more frequently (e.g. optic disc pallor and absence of the neural rim) or had a larger spread in their values (e.g. the eye pressure). Other arguments explain the lack of significant correlations for these parameters. The estimation of the degree of optic disc pallor is not easy and like all other optic disc parameters it is sensitive to intra and inter observer variability. The physiologic variation in color and excavation of the optic disc, the background colour of the retina and opacities of the lens or cornea hamper a correct assessment. The influence of opacities is negligible because of our admittence criteria. Photography of the optic disc is an alternative in overcoming the other problems of ophthalmoscopy. These photographs allow an evaluation of the degree of optic disc pallor and can be of help in measuring the C/D ratio and the degree of absence of the neural rim (photogrammetry). Yet optic disc photography has its own problems. Even after the best standardization, a variation of at least 6% remains (Schwartz et al., 1985), whereas other disadvantages are the relatively high cost, the requirement of a skilled professional and the individual eye magnification (Airaksinen, 1989). Perhaps the degree of pallor is not such a useful parameter in glaucoma as cupping and pallor

of the optic disc progress rather independently (Schwartz, 1973; Kitazawa and Matsubara, 1989). An increase in C/D ratio does not necessarily indicate that nerve fibres are lost because loss of supportive glia tissue also causes enlargement of the C/D ratio (Schwartz, 1973). An even more important observation is that optic disc pallor does not directly reflect nerve fibre loss, but can precede optic nerve degeneration (Radius and Anderson, 1978).

Several authors pointed to the aspect of the neuroretinal rim area as a more useful parameter in glaucoma evaluation (Balaszi et al., 1984; Airaksinen et al., 1985; Kitazawa and Matsubara, 1989). The neuroretinal rim correlates better with visual function than the C/D ratio and is less dependent on the natural size of the optic disc (Balaszi et al., 1984). Thus far, positive correlations between the neuroretinal rim area and the PERG amplitudes have been demonstrated by Korth et al. (1989). In this study statistically significant correlations were found for the PERG amplitudes and the degree of absence of the neuroretinal rim area but not for the degree of pallor or the C/D ratio. Therefore our results are not in contradiction with the view that the neural rim area is a better measure for glaucomatous damage than optic disc pallor or the C/D ratio.

The PERG data were also correlated with the intraocular pressure (IOP) at the moment of examination. In animal experiments, the ganglion cell response appears to be resistent to acute intraocular eye pressures as high as 50 mm HG (Linsenmeijer 1990). However, these experiments deal with normal animals with a normal vascular system and concern acute pressure rises only. As discussed before, the perfusion pressure is probably more important than the intraocular eye pressure. Histologically, a loss of ganglion cells after a period of elevated eye pressures has been confirmed (Geijer and Bill, 1979). In the literature, PERG amplitude reductions are reported in IOPs over 26 - 30 mm Hg (Papst et al., 1984; Hawlina et al., 1989). Hawlina et al. report that the PERG is less sensitive to a longstanding rise in the IOP than to an acute rise. In our study the IOPs of the OHT and GLAU patients were below 30 mm Hg, whereas those of the NPG patients were below 20 mm Hg. Perhaps this explains the absence of a significant correlation between the PERG and the IOP at the moment of examination.

ON/MS-/MS+

During the acute stage of ON, the PVEP is severely decreased in amplitude and increased in latency. This appears to be partly a temporary effect, as during the follow-up the mean amplitudes return to almost normal, whereas the latencies remain prolonged. Six months after the attack of ON some decrease in latency towards normal values is seen, but at that moment still some 80% of the patients has abnormal latencies resembling the results of the MS groups. These data confirm earlier observations as presented in chapter V (Halliday, 1972; Bornstein, 1975; Wildberger and van Lith, 1976; Sherman, 1982; Engell et al., 1987; Kaufman et al., 1988). Not only the clinically-affected eyes in ON have abnormal PVEPs,

but a substantial number of the contralateral eyes also demonstrates abnormal PVEPs (table 8.4). In the literature this fact has been reported before (Wildberger and van Lith, 1976; van der Poel, 1985; Berninger and Heider, 1985; Engell et al., 1987). After six months about half of our ON patients has bilateral abnormal PVEP latencies. As known from the literature, approximately 50% of the patients with an ON will eventually develop MS (Compston et al., 1978; Hely et al., 1986; Bradley and Whitty 1968; van der Poel, 1985). Further prospective study is necessary to determine, whether these patients have a higher risk for MS compared to those with normal latencies of the contralateral eye. The results of the clinically non-affected contralateral eyes in ON manifest the more general character of ON. It is a logical thought that patients with both eyes affected have a greater risk of contracting MS because then at least two separate places of demyelination are present (van Lith and van Vliet, 1979; van der Poel, 1985).

The PERG shows a slight but statistically significant P50 40' amplitude reduction during the acute stage of ON (Fiorentini et al., 1981; Bobak et al., 1983; Berninger and Heider, 1985, 1989; Gottlob and Heider, 1988; Holder, 1991). A temporary edema of the optic nerve or a central vascular retinal disfunction is a possible explanation for this temporarily amplitude decrease. This is contradictory to our normal P50 80' result, confirming the results of others using transient stimulation (Arden et al., 1982; Ringens et al., 1986; Kaufman et al., 1988). The difference is probably explained by the larger check size and the moment of examination. Only half of the patients were seen during the first week of the attack, the others in the two weeks following. A recovery of the peripheral visual field before the recovery of the central visual field is not unusual in ON. The PERG 80' amplitude normalizes earlier than the 40' PERG amplitude as the 80' PERG amplitude is more generated in the retinal midperiphery. The N95 amplitudes are statistically significantly lowered at all three examinations (15-20%)

In conclusion, during the acute stage of ON the 40' check size PERG P50 amplitudes as well as the N95 amplitudes are disturbed. During our six-month follow-up the lowered P50 amplitudes return to normal, whereas the N95 amplitudes remain abnormal. Seiple et al. (1983) observe the first P50 PERG changes after a minimum of four months and Kaufman et al. (1988) only after 6-16 months in a two-year follow-up. Perhaps our follow-up is too short for a permanent decrease in ganglion cell activity. However, it is doubtful whether a longer follow-up would have revealed more significant amplitude reductions, since the PERG amplitudes of the ON group after six months only slightly differ from those of the MS+ group. In both groups the amplitudes of the P50 component are normal, whereas the amplitudes of the N95 component are slightly but statistically signicantly lowered. Our finding that within the MS+ group significant correlations between the PERG data and the time elapsed since the onset of the disease are absent (table 8.14) further supports the idea that our follow-up was probably not too short.

In the MS+ group 33% of the patients has significantly decreased PVEP amplitudes and almost 30% has lowered PERG N95 amplitudes. In the MS- group only one individual with an abnormal PVEP amplitude is seen and the percentage of abnormal PERG amplitudes is lower (10-14%) compared to the MS+ group (30%). The PVEP latencies are prolonged in all except one of the MS+ individuals and in 62% of the MS- patients. The results of the MS+ group are easily explained by the history of an attack of ON, as they resemble those of the ON group six months after the attack. The percentage of abnormal PVEP latencies observed in the MS- group is remarkably high. The prolonged PVEP latencies seen in the non-affected contralateral eyes of ON and the visualization of brain lesions by means of CT-scans (Lidegaard et al., 1983) and MRI (Sartucci et al., 1989) provide serious arguments for the possibility in these patients of insidious and unremarked nerve damage along the optic tract.

In comparison with the glaucoma groups, the changes of the PERG N95 and especially the P50 component are relatively small in ON/MS, whereas the changes of the PVEP latencies are more marked for these groups. MS is a disease in which the axons are initially spared (Wanger and Persson, 1984), although optic atrophy has been demonstrated as demyelination proceeds (Frisén and Hoyt, 1974; Feinsod and Hoyt, 1975; Boschi et al., 1984).
During an episode of ON, inflammation with a vascular involvement (Lightman et al., 1987) and edema (Berninger and Heider, 1985) cause a temporary disfunction of the optic nerve. The underlying histopathologic mechanism is probably an obstructed axoplasm transport (Rao et al., 1981; Walsh and Hoyt, 1982). After the inflammation has ceased the transport of action potentials is restored resulting in the improvement of the electrodiagnostic results. The definitely-increased PVEP latencies indicate permanent damage (plaques).

A difference in PVEP and PERG N95 amplitudes is seen between MS patients with and without a history of ON. Several patients of our MS+ group had suffered recurrences of ON and had lowered PVEP and PERG amplitudes. Apparently these recurrences not only result in demyelination but also cause optic nerve atrophy.
The axonal damage in ON/MS+ causes a decrease of the N95 amplitude but seems too small to reduce the P50. If the P50 component not only has an optic nerve contribution but, as discussed before, also has a retinal and/or a luminance contribution then the absence of significant P50 amplitude reductions is explained.

The PVEP and PERG results of the ON/MS-/MS+ groups are correlated with several psychophysical tests like the visual acuity and the visual field. In literature significant positive correlations between the PVEP amplitudes and the visual acuity are reported (Shibasaki and Kurowa, 1982; van Lith et al., 1982; Plant et al., 1986; Celesia et al., 1986), but not for the PERG (Berninger and Heider, 1985; Adachi-Usami, 1987). These findings are in agreement with ours, although significant correlations are only seen for the PVEP amplitudes in MS+

and ON (acute onset). The fact that the PVEP amplitudes do not correlate well for MS- or ON during the follow-up is explained either by the low numbers of individuals with a lowered visual acuity or by the uniformity of these patient groups. As to the visual field, tables 8.8a-d reveal that the PERG reflects a more perifoveal function than the PVEP does. For the PVEP the strongest correlations with the degree of visual field loss are seen for the central 10° radius which emphasizes the macular overrepresentation of the PVEP.

Pallor of the optic disc in ON/MS-/MS+ causes a decrease in PVEP amplitude and an increase in PVEP latency, but statistical significant differences are only occasionally seen. The PERG results are more complex, as negative correlations between pallor and amplitudes are only seen in the MS groups and in ON six months after the attack. The reversal of sign (from plus to minus) during the follow-up of ON can be interpreted as the beginning of a decrease in ganglion cell activity. Nerve fibre layer (NFL) defects with some predilection for the papillomacular bundle have been demonstrated (Frisén and Hoyt, 1974; Feinsod and Hoyt, 1975; Boschi et al., 1984). The papillomacular bundle represents the axons of the macular area. This may be an explanation for the better correlation of optic disc pallor with the PVEP than with the PERG. Another aspect is that according to the authors mentioned above, the NFL defects are not always correlated with the degree of pallor of the optic disc. Perhaps pallor of the optic disc in ON/MS is not such a sensitive sign for the beginnings of a loss of axons. It is likely that in the more advanced stages of MS optic disc pallor reflects axon loss better.

OGD

Compared to the other patient groups, not many alterations of the PERG and PVEP are seen in OGD. The psychophysical tests (visual acuity, perimetry and contrast vision) are almost normal as well. The reason is that our OGD patient group is a selection of patients who are not severely affected by the disease. Patients with advanced stages of OGD are seldom seen in our clinic because of therapeutic intervention. On top of table 8.15 the OGD patients are classified according to the NOSPECS system. Most patients have only minor signs of OGD and advanced cases with a severe loss of vision (classes 6c and 6d) are not present in our group. That not one of our 30 patients has a severe loss of vision is not in contradiction with the estimation that only five percent of the OGD patients develops a severe optic neuropathy (Trobe, 1981; Wiersinga et al., 1989). Although a severe loss of vision was infrequently seen by these authors, they did observe a minor loss of vision in about a third of their patients. In our study eight patients (class 6a; 27%) have a minor loss of vision which is in the same range.

As to the PVEP, the amplitudes are normal, whereas the latencies are somewhat prolonged in 30% of the individuals. These results confirm earlier observations of normal or slightly prolonged PVEP latencies in OGD (Wijngaarde and van Lith, 1979; van Lith et al., 1982;

Ouwerkerk et al., 1985a, 1985b). Compression of the optic nerve is one of the explanations for the increased latencies. Although compression can result in optic nerve degeneration (De Vita et al., 1987), significantly increased PVEP latencies are only reported in cases of direct pressure on the optic nerve, in contrast to orbital compression which hardly influences PVEP latencies (Halliday et al., 1976; Wijngaarde and van Lith, 1979; van Lith et al., 1982). The results of the present study are in agreement with this view. Perhaps a selective loss of nerve fibres in OGD is responsible for the slight increase of the PVEP latency. This possibility was suggested by Flanagan and Harding (1988) as well as by Bobak et al. (1988). These authors propose a selective loss of fast-conducting magnocellular nerve fibres at the periphery of the optic nerve in OGD. In an animal experiment such a selective loss has been demonstrated (Burke et al., 1986). According to Flanagan and Harding the PVEP alterations will be seen clearest, when large pattern elements are used (Larger than 50'), whereas Bobak advocates the use of high reversal temporal frequencies. Although the pattern elements used in this study are quite large, our pattern reversal frequency is rather low. If future anatomical and clinical experiments confirm the selective loss of magnocellular nerve fibres in OGD, the use of high reversal frequency PVEPs has surely to be recommended.

The PVEP latency is not only influenced by compression, the thyroid hormone level probably plays a role too. Hyperthyroidism seems to have no influence on PVEP latency and therefore can not account for the increase found (Takahashi and Fujitani, 1970; Mitchell et al., 1988). The opposite is true for hypothyroidism in which a reversible latency increase has been reported (Nishitani et al., 1968; Mastaglia et al., 1978; Ladenson et al., 1984). In this context it is interesting that hypothyroidism appears to affect the myelin synthesis (Bhat et al., 1981). In our OGD group only two patients were known with a hypothyroidism at the moment of examination. Indeed in these patients the PVEP latencies were prolonged. The other patients with a latency increase had normal thyroid levels, therefore hypothyroidism can only partly be held responsible for the PVEP latency increase.

Another factor which should be considered in the evaluation of the PVEP in OGD patients is a history of irradiation of the orbit. Damage to ocular and extraocular structures encompassed in the radiation field has been described, although the adult retina (including the ganglion cells) appears to be relatively tolerant to large doses of irradiation (Pinchera et al., 1984; Hurbli et al., 1985). It is only logical to think that irradiation eventually causes some (subclinical) damage to the optic nerve. The observation of Ouwerkerk et al. (1985) of a PVEP latency increase of 11 msec in the first year after irradiation is a support for this view. In table 8.15 the factor irradiation is correlated with our PVEP and PERG results. Eight patients had a history of orbital irradiation, seven of them having prolonged PVEP latencies, whereas six of them had lowered PERGs. Significant correlations for the PVEP latencies and the PERG amplitudes were found. Perhaps (subclinical) damage to the optic nerve is first reflected in a change of the PVEP latencies and PERG amplitudes. If that is the

case, both electrodiagnostics are useful tools in the early diagnosis of irradiation damage and can probably help us to determine a safe irradiation dose schedule for OGD patients.
A vascular component in OGD is likely. In their discussion Day and Caroll (1962) provide arguments to show that the optic nerve may be subject to the same vascular changes which have been reported in the other tissues of the orbit. Circulatory disturbances due to mechanical pressure are more likely to occur in vessels already narrowed by vascular changes like in the elderly (Wijngaarde and van Lith, 1979; Trobe, 1981). This view is further supported by the age distribution of the patients in this study because the average age of the nine patients with prolonged latencies was higher if compared to the rest of the patients (52 compared to 40 years of age).
Pallor of the optic disc was only seen in four patients. Therefore no correlation between pallor of the optic disc and any PERG parameter was found. Probably pallor of the optic disc is not such a good measure for optic neuropathy in OGD, because in the literature it is reported that in patients with optic neuropathy the optic disc is mostly completely normal and can even be hyperaemic (Trobe, 1981; Neigel et al., 1988).

During the last phase of this thesis we were able to increase our patient group to 40 patients. Again, statistically significant correlations between the PVEP latencies and hypothyroidism or orbital irradiation were found, whereas OGD patients without these factors had normal PVEPs (van Houwelingen and van Lith, 1992). We therefore conclude that in OGD patients with hardly any damage of the visual functions like the acuity and the fields, irradiation previous to the moment of examination or hypothyroidism at the moment of examination may cause abnormal PVEPs.

SUMMARY

In ophthalmology, electrodiagnostics provide additional objective information about the function of the visual system. Three basic methods are at our disposal: The electro-oculogram (EOG), the electroretinogram (ERG) and the visually evoked potentials (VEP). The ERG and the VEP are elicited by either luminance or by patterned stimuli (PERG and PVEP). In this thesis the PERG is studied in relation to the PVEP in disorders of the optic nerve.

The PVEP, being a cortical response evoked by patterned stimuli, represents the central retinal area. The exact dimensions of this area are determined by the size of the pattern elements. Thanks to the clinical work of Halliday et al. (1972, 1973 and 1976) the PVEP has become an accepted electrodiagnostic tool with well-defined clinical applications. Various disorders of the visual pathway result in lowered amplitudes (atrophic diseases), prolonged latencies (compression and/or demyelination) or a combination of both.
The PERG still belongs to a research area in progress. Offering a pattern and subsequently registering the evoked potential from the lower fornix of the eye results in a signal with a positive component at 50 msec (P50) and a negative component at 95 msec (N95). Originally the PERG was introduced by Riggs et al. (1964) in an attempt to develop a local or local foveal ERG. Due to complicated technical aspects and disappointing clinical results Rigg's technique was ignored. In 1981 the cat experiment of Maffei and Fiorentini renewed interest in the PERG. Immediately after the sectioning of the optic nerve of a cat, the luminance ERG and the PERG were normal. Four months later the PERG totally disappeared, while the luminance ERG was still present without any changes. Histologically, a retrograde ganglion cell degeneration was demonstrated, suggesting that the PERG is a ganglion cell response and not a local foveal ERG. In the subsequent years numerous basic and clinical studies were published. No consensus was reached on two related fundamental questions: A) is the PERG a luminance or a contrast response or a mixture of both, B) Is the PERG generated in the ganglion cells exclusively or are other cell structures involved as well.

The ganglion cell hypothesis is supported by various histopathological observations. Physiological (i.e. spatial tuning effects of both components) and clinical support are not

unequivocal. A major reason for this ambiguity is that both the pattern and the luminance contribution to the PERG are highly dependent on the stimulus parameters chosen. This concerns in particular the reversal frequency and the pattern element size. A second reason is the lack of large comparative studies. In order to meet this last issue we started such a study in optic nerve disorders. Although the pathogenesis is different in these disorders, a loss of axons and ganglion cells has been demonstrated in anatomical studies in all of them.

Seven optic nerve disorders were studied. The groups examined were ocular hypertension (OHT), primary open angle glaucoma (GLAU), normal pressure glaucoma (NPG), ophthalmic Graves' disease (OGD), optic neuritis (ON) at the acute moment as well as one and six months later, multiple sclerosis with a history of optic neuritis (MS+) and multiple sclerosis without such a history (MS-). Most groups contained 30 patients except for the two MS groups which contained 20 subjects each. In all patients the PVEP and the PERG were registered. A slide-projector pattern reversal system was used with a low pattern reversal frequency (2 rev/s), for we wanted to study both the PERG P50 and N95 component. Two check sizes (40 and 80 minutes of arc) with high contrast (87%) were applied. The PERG and PVEP results were correlated with various psychophysical test like visual acuity (Snellen chart), visual field (Humphrey Allargan full threshold central 30-2 program) and contrast vision (Vistech 6000 chart). Furthermore, the electrodiagnostic results were correlated with the degree of optic disc pallor as this pallor can be a manifestation of nerve fibre loss. In each group the PERG and PVEP results were correlated with various parameters inherent to the disorder itself like the cup/disc ratio in OHT/GLAU/NPG, the duration of the disease in ON/MS-/MS+ and the NOSPECS classification system in OGD.

The mean PVEP latencies are significantly increased in all the patient groups except in OGD. High percentages of individually prolonged latencies are seen in ON/MS+ (95%), MS- (62%) and in GLAU/NPG (50%). Almost 50% of the contralateral eyes of ON has prolonged latencies too. The mean PVEP amplitudes are lowered in GLAU, NPG, ON and MS+, but individually this is only the case in ON and MS+. Our results are in agreement with the findings of many others. Furthermore, they confirm the view that increased latencies are especially seen in inflammation and demyelination (ON/MS) and are less severe in compression or ischaemia (GLAU/NPG). The latency increase in about half of the contralateral eyes affected by ON, supports the more general inflammatory and demyelinative aspect of ON. The abnormalities seen in MS- are explained by a gradual demyelination, which is supported by CT and MRI observations in the literature. In OGD occasionally abnormal latencies are seen which are explained by hypothyroidism at the moment of examination or by a history of orbital irradiation.
The small percentual decrease of the PVEP amplitudes in most patient groups is probably explained by a minimal loss of axons in that part of the retina represented by the PVEP. The large standard deviations of the PVEP amplitudes, result in the clinical value of the PVEP

latencies being higher than that of the PVEP amplitudes.
In the literature, the PVEP is known to correlate well with the psychophysical tests. Our results are not in contradiction with this view, although not many statistical significances are to be seen. This is explained by the low incidence of severe cases and/or the uniformity of some patient groups. The same argument applies for the lack of statistical significances for the NOSPECS classification system in OGD. The correlations with the visual field make it clear that the PVEP is derived from a much smaller area than the PERG.

The PERG N95 amplitudes are significantly lowered in all groups except for the groups MS- and OGD. The N95 amplitudes are more severely and more frequently affected than those of the P50 component. The percentual reduction of the N95 is more or less equal for both check sizes and is approximately 40% in the GLAU/NPG groups and about 20% in the other groups.
The results of the P50 component are remarkable as abnormalities are seen in OHT, GLAU and NPG exclusively. There are two scenarios possible. The first scenario is that the P50 component is affected by optic nerve damage alone. In that case the abnormalities seen in glaucoma are explained by a greater loss of ganglion cell activity than in the other disorders examined. The fact that due to our stimulus parameters the PERG is derived from a relatively large retinal area supports this view. Glaucoma affects nerve fibres derived from both paracentral and central areas, whereas in the other disorders this is more the case for nerve fibres representing the central part of the visual field. The second scenario is that the PERG P50 component is not only affected by optic nerve damage but also by damage at the level of the retina. In that case the site of glaucomatous damage is more diffuse than in the other diseases. The PERG latencies support this latter view as they are increased in the glaucoma groups and decreased in the other groups. In the literature an increase of the P50 latency is reported for various retinal disorders.
For both scenarios an additional luminance contribution to the P50 component can not be excluded as our stimulus parameters (relatively large check sizes, a high contrast and luminance) induce such a contribution and since a total loss of P50 amplitude is seldom seen.
Not many significant correlations between the PERG and the psychophysical tests are observed. Like in the PVEP the absence of severe cases is a major cause.
Optic disc pallor probably is not such a good measure for the amount of ganglion cell loss. Estimation of the degree of pallor is hampered by several factors and is subject to inter and intra observer variability. Furthermore, optic disc pallor can precede axon loss, whereas reversely nerve- fibre-layer defects are not always reflected in pallor of the optic disc. In glaucoma, the aspect of the neural rim of the optic disc better correlates than the cup/disc ratio or the degree of pallor. Several authors report upon this aspect with similar results. In MS the papillomacular bundle is predominantly affected, in which case the pallor is not diffuse but localized, whereas in OGD even a hyperaemia of the optic disc is reported in severe optic neuropathy.

As to the clinical applications of the PVEP and PERG, in the demyelinative disorders the PVEP is more frequently and more severly affected than the PERG. Abnormal PERGs run parallel with abnormal PVEPs, but the reverse is not seen. During the half year follow-up of ON only minor changes of the PERG are seen. One could suppose that a longer follow-up is needed before a judgement can be given as to the visual prognosis. The PERG results in the MS+ group, however, do not support this view, since the results of patients with a longstanding MS are comparable with those of our ON patients at six months.
In the glaucoma groups the PVEP and PERG abnormalities do not run parallel. Especially in ocular hypertension PERG abnormalities are seen with normal PVEPs. The first damage in glaucoma is frequently reported in the paracentral area, which is better represented by the PERG than the PVEP. Based on our results, we can conclude that the PERG is able to detect early loss of ganglion cell activity, even in those cases in which the visual field is still normal (OHT).

In conclusion our PVEP results are in full agreement with the literature. The PERG N95 component better reflects ganglion cell activity than the P50 component does. The latter probably has an essential luminance contribution and perhaps a retinal contribution as well. In the demyelinative disorders, the PVEP has more clinical value than the PERG. In glaucoma and especially in ocular hypertension the PERG is a promising method. In these disorders the registration of both the PERG and the PVEP is recommended.

SAMENVATTING

In de oogheelkunde is de electrodiagnostiek een objectief hulpmiddel om de functie van het visuele systeem nader te analyseren. De drie hoofdpijlers zijn: Het electro-oculogram (EOG), het electroretinogram (ERG) en de visual evoked potentials (VEP). Het ERG en het VEP kunnen worden opgewekt door luminantie of door patroon stimuli (PERG en PVEP). In dit proefschrift wordt het PERG onderzocht in relatie tot het PVEP bij aandoeningen van de nervus opticus.

Het Patroon VEP is een corticale respons op het aanbieden van patronen en vertegenwoordigt het centrale deel van het netvlies. De grootte van dit gebied wordt bepaald door de grootte van de patroon elementen. Dankzij het werk van Halliday en anderen (1972, 1973 en 1976) is het PVEP uitgegroeid tot een erkend onderzoek met een scala aan klinische toepassingen. Afwijkingen van de visuele baan resulteren in verlaagde amplituden (bij atrofie), in verlengde latentietijden (bij compressie en of demyelinisatie) of in een combinatie van beiden.

Het Patroon ERG bevindt zich nog deels in een onderzoeksstadium. Een patroon stimulus wekt in het oog een electrisch signaal op, dat door middel van een electrode kan worden afgeleid bij het onderste ooglid. De aldus verkregen curve bevat een positieve piek na 50 msec (P50) en een negatieve piek na 95 msec (N95). In 1964 is het PERG geintroduceerd door Riggs in een poging een locaal foveaal ERG te ontwikkelen, maar door technische problemen en tegenvallende resultaten verschuift het PERG naar de achtergrond.
In 1981 kwam er hernieuwde interesse in het PERG door een experiment van Maffei en Fiorentini. Direkt na het doorsnijden van de nervus opticus van een kat bleek zowel het luminantie als het patroon ERG normaal te zijn. Vier maanden later was het PERG verdwenen, terwijl het luminantie ERG onveranderd was gebleven. Histologisch werd een retrograde ganglion cel degeneratie aangetoond, er op wijzend dat er een verband bestaat tussen ganglion cel activiteit en veranderingen van het PERG. In de jaren daarop volgden er talrijke fundamentele en klinische studies, waarin onduidelijkheid bleef bestaan ten aanzien van twee belangrijke vragen: A) Is het PERG een luminantie of een contrast respons of een combinatie van beide en B) Wordt het PERG alleen in de ganglion cellen opgewekt of zijn er ook andere cel structuren bij betrokken?

De ganglion cel hypothese wordt vervolgens ondersteund door een aantal histopathologische observaties. Fysiologische ondersteuning, zoals het vinden van de optimale schaakblok grootte, en klinische ondersteuning worden verschaft door verscheidene auteurs, maar weer tegengesproken door anderen. Een belangrijke reden voor deze tegenstelling is het feit, dat de luminantie en patroon bijdrage aan het PERG sterk afhankelijk zijn van de gekozen stimulus parameters. Dit betreft speciaal de omkeer frequentie en de schaakblok grootte. Een tweede reden is het ontbreken van grote vergelijkende studies. Dit laatste was het doel van de huidige studie. Hiertoe hebben wij een groot vergelijkend onderzoek opgezet bij aandoeningen van de oogzenuw. Alhoewel de pathogenesis verschillend is voor deze aandoeningen, is een verlies van axonen en ganglion cellen in anatomische studies voor elk van hen aangetoond.

Zeven aandoeningen van de nervus opticus werden bestudeerd. De onderzochte groepen waren oculaire hypertensie (OHT), primair open kamerhoek glaucoom (GLAU), normale druk glaucoom (NPG), de ziekte van Graves (OGD), neuritis optica (ON) zowel in de acute fase als een maand en zes maanden later, multiple sclerose met een voorgeschiedenis van neuritis optica (MS+) en multiple sclerose zonder zo'n voorgeschiedenis (MS-). Vrijwel alle groepen bestonden uit 30 patienten behalve de MS groepen, die elk uit 20 personen bestonden.
Een diaprojector patroon omkeer systeem werd gebruikt met een lage omkeer frequentie (2 rev/s), omdat wij zowel de PERG P50 als de N95 component wilden bestuderen. Twee schaakblok grootten (40 en 80 boogminuten) met een hoog contrast (87%) werden gepresenteerd. De PERG en PVEP resultaten werden gecorreleerd met verscheidene psychofysische testen, zoals de visus (Snellen kaart), het gezichtsveld (Humphrey Allergan volledige gevoeligheid van het centrale 30-2 gebied) en het contrast zien (Vistech 6000 kaart). Verder werden de electrodiagnostische resultaten gecorreleerd met de mate van bleekheid van de oogzenuw, daar deze een maat voor het verlies van zenuwvezels kan zijn. In elke groep werden de PERG en PVEP resultaten gecorreleerd met een aantal parameters inherent aan de aandoening zelf, zoals de cup/disc ratio in OHT/GLAU/NPG, de ziekteduur in ON/MS-/MS+ en de NOSPECS classificatie in OGD.

De gemiddelde PVEP latentietijden zijn statistisch significant toegenomen in alle groepen behalve in OGD. Hoge percentages van individueel afwijkende waarden worden gezien in ON/MS+ (95%), MS- (62%) en in GLAU/NPG (50%). Bijna 50% van de niet aangedane ogen in neuritis optica laat eveneens verlengde latenties zien. De gemiddelde PVEP amplituden zijn verlaagd in GLAU, NPG, ON en MS+, maar individueel is dit alleen het geval in ON en MS+. Deze resultaten zijn in overeenstemming met die van vele auteurs. Onze resultaten bevestigen dat verlengde latenties vooral gezien worden in ontsteking en demyelinisatie (ON/MS) en in mindere mate in compressie of ischaemie (GLAU/NPG). De toename van de latentietijd in de klinisch niet aangedane ogen in ON onderstreept het

algemene ontstekings- en demyelinisatie aspect van een neuritis optica. De afwijkingen gezien in MS- worden verklaard door een sluipende demyelinisatie, hetgeen in de literatuur door CT en MRI afwijkingen wordt ondersteund. De enkele verlengde latenties in OGD kunnen worden verklaard door hypothyreoidie op het moment van onderzoek of door een voorgeschiedenis van orbita bestraling.
De in de meeste groepen geconstateerde kleine procentuele afname van de PVEP amplituden wordt waarschijnlijk verklaard door een minimaal verlies aan axonen in dat deel van de retina, waaruit het PVEP afkomstig is. De in vergelijking met de latentietijden grote standaard deviaties van de PVEP amplituden maken, dat deze in de kliniek een kleinere rol spelen dan de latentietijden.
In de literatuur staat het PVEP bekend om zijn goede correlaties met de psychofysische testen. Onze resultaten spreken dit niet tegen, alhoewel er niet veel statistische significanties worden gezien. Dit wordt enerzijds verklaard door de lage aantallen van ernstige gevallen bij ons onderzoek en anderzijds door de uniformiteit van sommige groepen. Hetzelfde argument is van toepassing op de correlaties met het NOSPECS classificatie systeem in OGD. De correlaties met het gezichtsveld geven aan dat het PVEP van een kleiner retina gebied afkomstig is dan het PERG.

De PERG N95 amplituden zijn statistisch significant verlaagd in alle groepen behalve in MS- en OGD. De amplituden van de N95 component zijn vaker en ernstiger aangedaan dan die van de P50 component. De procentuele afname van de N95 is voor de beide door ons gekozen blokgrootten hetzelfde en bedraagt ongeveer 40% in de GLAU/NPG groepen en rond de 20% in de andere groepen. De resultaten van de P50 component zijn opmerkelijk, daar afwijkingen hiervan alleen voorkomen in de glaucoom groepen. Hiervoor zijn twee verklaringen mogelijk. De eerste verklaring houdt in dat de P50 component alleen gevoelig is voor schade van de nervus opticus. In dit geval worden de afwijkingen bij glaucoom verklaard door een groter verlies aan ganglion cel activiteit vergeleken met de andere onderzochte groepen. Het feit, dat het PERG door onze stimulus parameters afkomstig is van een relatief groot retina oppervlak, ondersteunt dit standpunt. Glaucoom immers tast zenuwvezels aan afkomstig van zowel paracentrale als centrale gebieden, terwijl in de andere aandoeningen dit meer het geval is voor de zenuwvezels afkomstig uit het centrum. De tweede verklaring houdt in, dat de PERG P50 component niet alleen gevoelig is voor schade aan de opticus maar ook voor schade op retinaal niveau. In dit laatste geval is de localisatie van de schade bij glaucoom meer diffuus dan bij de andere aandoeningen. De PERG latentietijden kunnen hiervoor een ondersteuning zijn, omdat ze verlengd zijn in de glaucoom groepen, terwijl ze juist afnemen in de overige groepen. In de literatuur wordt een toename van de P50 latentietijd bij retinale aandoeningen herhaaldelijk gemeld. Voor beide verklaringen geldt dat een bijkomende luminantie component niet is uitgesloten, omdat onze stimulus parameters (vrij grote blokken, hoog contrast en luminantie) zo'n luminantie bijdrage in de hand werken en omdat een totaal verdwijnen van de P50 zelden wordt gezien.

Er worden slecht weinig significante correlaties gezien tussen het PERG en de psychofysische testen. Net zoals in het PVEP is de afwezigheid van ernstige gevallen bij ons onderzoek hiervoor een goede verklaring.

De mate van bleekheid van de oogzenuw is waarschijnlijk niet zo'n goede maat voor de hoeveelheid verlies aan ganglion cellen. Verschillende verklaringen zijn mogelijk. De inschatting van de mate van bleekheid wordt bemoeilijkt door diverse factoren en is onderhevig aan inter- en intra- waarnemer variabiliteit. Bleekheid van de oogzenuw kan vooruit lopen op het werkelijke axonen verlies en omgekeerd blijkt bleekheid niet altijd te correleren met zenuwvezellaag defecten. In glaucoom blijkt dat de 'neural rim' beter correleert met het PERG dan de cup/disc ratio of de mate van bleekheid. Verschillende auteurs hebben hierover gerapporteeerd met gelijkluidende conclusies. In MS wordt hoofdzakelijk de papillomaculaire bundel aangedaan, waardoor de bleekheid niet diffuus maar meer gelocaliseerd is, terwijl in OGD zelfs een hyperaemie wordt gezien in gevallen van een ernstige opticus neuropathie.

Wat betreft de klinische toepassingsmogelijkheden van het PVEP en het PERG kan worden geconcludeerd dat in de demyeliniserende aandoeningen het PVEP vaker en ernstiger is aangedaan dan het PERG. Abnormale PERGs gaan altijd vergezeld van abnormale PVEPs, terwijl het omgekeerde bij demyeliniserende aandoeningen niet het geval is. De follow-up van ON gedurende een half jaar liet geen veranderingen zien van het PERG. Mischien is een langere follow-up noodzakelijk om een uitspraak te kunnen doen over de prognostische waarde van het PERG ten aanzien van de visus. De resultaten van de MS+ groep wijzen echter niet in deze richting, daar de resultaten van patienten met reeds lang bestaande MS vergelijkbaar zijn met die van onze ON groep na zes maanden.
In de glaucoom groepen lopen PERG en PVEP afwijkingen niet gelijk op. Vooral in OHT worden afwijkende PERGs gezien met normale PVEPs. De eerste schade in glaucoom wordt vaak paracentraal gezien, een gebied dat beter door het PERG dan door het PVEP wordt vertegenwoordigd. Op basis van onze resultaten concluderen wij dat het PERG in staat is om al in een vroege fase glaucomateuze schade te detecteren, zelfs in die gevallen waar het gezichtsveld nog normaal is (OHT).

Concluderend kan gezegd worden dat de PVEP resultaten in goede overeenstemming zijn met de literatuur gegevens. De PERG N95 component reflecteert beter de ganglion cel activiteit dan de P50. Deze laatste heeft dan ook waarschijnlijk een essentiele luminantie component en misschien ook wel een retinale component. In de demyeliniserende aandoeningen heeft het PVEP meer klinische waarde dan het PERG. In glaucoom en vooral in oculaire hypertensie zijn de resultaten van het PERG veel belovend en wordt de registratie van zowel het PVEP als het PERG aanbevolen.

REFERENCES

Abe H, Hasegawa S, Iwata K. Contrast sensitivity and pattern visual evoked potentials in patients with glaucoma. Doc Ophthalmol 1987; 65: 65-70.

Adachi-Usami E. Facially distributed pattern evoked potentials in multiple sclerosis. Doc Ophthalmol 1987; 65: 259-269.

Airaksinen PJ. Retinal nerve fiber layer and neuroretinal rim changes in ocular hypertension and early glaucoma. Surv Ophthalmol 1989; 33 suppl: 413-414.

Airaksinen PJ, Drance SM, Douglas GR, Mawson DK, Nieminen H. Diffuse and localized nerve fiber loss in glaucoma. Am J Ophthalmol 1984; 98: 566.

Airaksinen PJ, Drance SM, Douglas GR, Schulzer M. Neuroretinal rim areas and visual field indices in glaucoma. Am J Ophthalmol 1985; 99: 107-110.

Alder VA, Constable IJ. Effect of hypoxia on the maintained firing rate of retinal ganglion cells. Invest Ophthalmol Vis Sci 1981; 21: 450-456.

Ambrosio G, Andreoni A, Colasanti A. Pattern specific and luminance response: a temporal differentiation. Clin Vision Sci 1989; 4: 333-340.

Ambrosio G, Arienzo G, Aurilia P, Colasanti A, Fusco R. Pattern electroretinograms in ocular hypertension. Doc Ophthalmol 1988; 69: 161-165.

Anctil JL, Anderson DR. Early foveal involvement and generalized depression of the visual field in glaucoma. Arch Ophthalmol 1984; 102: 363-370.

Anderson DR. What happens to the optic disc and retina in glaucoma? Ophthalmology 1983; 90: 766-770.

Anderson RL, Tweeten JP, Patrinely JR, Garland PE, Thiese SM. Dysthyroid optic neuropathy without extraocular muscle involvement. Ophthalmic Surg 1989; 20: 568-574.

Anmarkrud N, Sletness ON. Uncomplicated retrobulbar neuritis and the development of multiple sclerosis. Acta Ophthalmol 1989; 67: 306-309.

Arden GB, Banks JLK. Foveal electroretinogram as a clinical test. Br J Ophthalmol 1966; 50: 740.

Arden GB, Barrada A. Analysis of the electrode-oculogram of a series of normal subjects. Br J Ophtalmol 1962; 46: 468-482.

Arden GB, Carter RM, Hogg C, Siegel IM, Margolis S. A gold foil electrode: extending the horizons for clinical electroretinography. Invest Ophthalmol Vis Sci 1979; 18: 421-426.

Arden GB, Carter RM, McFarclan A. Pattern and Ganzfield electroretinograms in macular disease. Br J Ophthalmol 1984; 68: 887-884.

Arden GB, Hamilton AMP, Wilson-Holt J, Ryan S, Yudkin JS, Kurtz A. Pattern electroretinograms become abnormal when background diabetic retinopathy detoriates

to a preproliferative stage: possible use as a screening test. Br J Ophthalmol 1986; 70: 330-335.

Arden GB, Kelsey JH. Some observations on the relationship between the standing potential of the human eye and the bleaching and regeneration of visual purple. J Physiol 1962; 161: 205-226.

Arden GB, Vaegan. Electroretinograms in man by local uniform or patterned stimulation. J Physiol 1983; 341: 85-104.

Arden GB, Vaegan, Hogg CR. Clinical and experimental evidence that the pattern electroretinogram (PERG) is generated in more proximal retinal layers than the focal electroretinogram (FERG). Ann NY Acad Sci 1982: 580-601.

Armaly MF. Ocular pressure and visual fields: A ten year follow-up study. Arch Ophthalmol 1969; 81: 25.

Armaly MF. Glaucoma. Arch Ophthalmol 1973; 90: 485.

Armington JC. Spectral sensitivity of simultaneous electroretinograms and occipital responses. Vision Res 1966; suppl 1: 225-233.

Armington JC. The electroretinogram, the visual evoked potentials, and the area-luminance relation. Vision Res 1968; 8: 263-276.

Armington JC, Corwin TR, Marsetta R. Simultaneously recorded cortical responses to patterned stimuli. J Opt Soc Amer 1971; 61: 1514-1521.

Armington JC, Tepas D. Electroretinograms from non corneal electrodes. Invest Ophthalmol 1962; 1: 784.

Asselman P, Chadwick DW, Marsden CD. Visual evoked responses in the diagnoses and management of patients with multiple sclerosis. Brain 98; 1975: 261-282.

Atkin A, Bodis-Wollner I, Wolkstein M,Moss A, Podos SM. Abnormalities of central contrast sensitivity in glaucoma. Am J Ophthalmol 1979; 88: 205-211.

Bach M, Hiss P, Röver J. Check-size specific changes of pattern electroretinogram in patients with early open-angle glaucoma. Doc Ophthalmol 1988; 69: 315-322.

Bach M, Speidel-Fiaux A. Pattern electroretinogram in glaucoma and ocular hypertension. Doc Ophthalmol 1989; 73: 173-181.

Balaszi AG, Drance SM, Schulzer M, Douglas GR. Neuroretinal rim area in suspected glaucoma and early chronic open angle glaucoma. Arch Ophthalmol 1984; 102: 1011-1014.

Balaszi AG, Rootman J, Drance SM, Schulzer M, Douglas GR. The effect of age on the nerve fiber population of the human optic nerve. Am J Ophthalmol 1984; 97: 760-766.

Bartl G, Lith GHM van, Marle GW van. Cortical potentials evoked by a TV pattern reversal stimulus with varying check sizes and stimulus field. Br J Ophthalmol 1978a; 62: 216-219.

Bartl G, Lith GHM van, Marle GW van. Cortical potentials evoked by a TV pattern reversal stimulus varying check sizes and position of the stimulus field. Ophthalmic Res 1978b; 10: 295-301.

Becker-Schaffer. Diagnosis and therapy of the glaucomas. Sixth edition, The CV Mosby Company, St Louis 1989.

Bellizzi M, Cardia L, Lamorgese C, Pomes L, Sorrento G, Ferrante G. Pattern visual evoked potentials in early diagnosis of open-angle glaucoma. Glaucoma 1988; 10: 60-61.

Bengtsson B. Characteristics of manifest glaucoma at early stages. Graefe's Arc Clin Exp Ophthalmol 1989; 227: 241-243.

Berg TJTP vd, Boltjes B, Spekreijse H. Pattern electroretinogram can be more than the sum of local luminance responses. Doc Ophthalmol 1988; 69: 307-314.

Berg TJTP vd, Riemslag FCC, Vos GWGA de, Verduyn-Lunel HFE. Pattern ERG and glaucomatous visual field defects. Doc Ophthalmol 1986; 61: 335-341.

Berninger TA. The pattern electroretinogram and its contamination. Clin Vision Sci 1986; 1: 185-190.

Berninger T, Arden GB. The pattern electroretinogram. Eye 1988; 2(suppl): 257-283.

Berninger T, Heider W. Verlaufsuntersuchung bei patienten mit akuter neuritis nervi optici. Fortschr Ophthalmol 1985; 82: 295-600.

Berninger T, Heider W. Electrophysiology and perimetry in acute retrobulbar neuritis. Doc Ophthalmol 1989; 71: 293-305.

Berninger T, Schuurmans RP. Spatial tuning of the pattern ERG across temporal frequency. Doc Ophthalmol 1985; 61: 17-25.

Bhat NR, Shanker G, Pieringer RA. Investigations on myelination in vitro: regulation of 2,3'-cyclic nucleotide 3'-phosphohydrolase by thyroid hormone in cultures of dissociated brain cells from embryonic mice. J neurochem 1981; 37: 695-701.

Blumhardt LD, Barrett G, Halliday AM, Kriss A. The effect of field size on the pattern reversal visual evoked potential (PRVER). Clin Vision Sci 1989; 4: 27-40.

Bobak P, Bodis-Wollner I, Harnois C, Maffei L, Mulin L, Podos S, Thornton J. Pattern electroretinograms and visual evoked potentials in glaucoma and multiple sclerosis. Am J Ophthalmol 1983, 96: 72-83.

Bobak P, Friedman R, Brigell M, Goodwin J, Anderson R. Visual evoked potentials to multiple temporal frequencies. Arch Ophthalmol 1988; 106: 936-940.

Bodis-Wollner I, Bobak P, Harnois C, Mylin L. Methodological aspects of signal to noise evaluation of simultaneous pattern electroretinogram and visual evoked potential recordings. Doc Ophthalmol Proc Series 1984; 40: 39-48.

Bornstein Y. The pattern evoked responses (VER) in optic neuritis. Greafe's Arch Clin Exp Ophthalmol 1975; 197: 101-106.

Boschi MC, Frosini R, Menucci R, Sodi A. The influence of early diabetes on the pattern electroretinogram. Doc Ophthalmol 1989; 72: 369-374.

Boschi MC, Frosini R, Scaioli V. Correlations among clinical data, pattern electroretinogram, visual evoked potential, and retinal fiber layer findings in multiple sclerosis. Doc Ophthalmol Proc Ser 1984; 40: 133-141.

Bradley WG, Whitty CWM. Acute optic neuritis: prognosis for development of multiple sclerosis. J Neurol Neurosurg Psychiatry 1968; 31: 10-18.

Bron AJ, Gardner ID, Ross JE, Reeves BC. Detection of optic nerve damage in ocular hypertension. Chibret Int J Ophthalmol 1987; 5: 20-23.

Brown KT, Murakami M. A new receptor potential of the monkey retina with no detectable latency. Nature 1964; 201: 626-628.

Brown KT, Wiesel TN. Analysis of the intraretinal electroretinogram in the intact cat eye. J Physiol 1961; 158: 229-256.

Brown KT, Wiesel TN. Localization of origins of the electroretinogram components by intraretinal recording in the intact cat eye. J Physiol 1961; 158: 257-280.

Buren JM van. The retinal ganglion cell layer. Springfield III Charles C Thomas 1963a.

Buren JM van. Trans-synaptic retrograde degeneration in the visual system of primates.

J Neurol Neurosurg Psychiatry 1963b; 26: 402-409.
Burke W, Cottee LJ, Garvey J, Kumarasinghe R, Kyriacou C. Selective degeneration of optic nerve fibres in the cat produced by a pressure block. J Physiol 1986; 376: 461-476.
Campbell FW, Kulikowski JJ. Orientational selectivity of the human visual system. J Physiol 1966; 187: 437-445.
Cant JS, Wilson TM. The ocular and orbital circulations in dysthyroid ophthalmopathy. Trans Ophthalmol Soc UK 1974; 94:416-429.
Caton R. The electric currents of the brain. Br Med J 1875; 2: 278.
Celesia GC, Daly RF. Effects of aging on visual evoked responses. Arch Neurol 1977; 34: 403-407.
Celesia GC, Kaufman D. Pattern ERGs and visual evoked potentials in maculopathies and optic nerve diseases. Invest Ophthalmol Vis Sci 1985; 26: 726-735.
Celesia GC, Kaufman D, Cone S. Simultaneous recording of pattern electroretinography and visual evoked potentials in multiple sclerosis. Arch Neurol 1986; 43: 1247-1252.
Celesia GC, Kaufman D, Cone S. Effects of age and sex on pattern electroretinograms and visual evoked potentials. Electroenceph Clin Neurophysiol 1987; 68; 161-171.
Cleland BG, Dubin MW, Levick WR. Sustained and transient neurones in the cat's retina and lateral geniculate nucleus. J Physiol 1971; 217: 473-496.
Cleland BG, Levick WR. Brisk and sluggish concentrically organized ganglion cells in the cat's retina. J Physiol 1974: 240: 421-456.
Cobb WA, Morton HB. A new component of the electroretinogram. J Physiol 1954; 123: 36.
Cobb WA, Morton HB, Ettlinger G. Cerebral potentials evoked by pattern reversal and their suppresion in visual rivalry. Nature 1967; 216: 1123-1125.
Cohen MM, Lessell S, Wolf PA. A prospective study of the risk of developing multiple sclerosis in uncomplicated optic neuritis. Neurology 1979; 29: 208-213.
Compston DAS, Batchelor JR, Earl CJ, McDonald WI. Factors influencing the risk of multiple sclerosis developing in patients with optic neuritis. Brain 1978; 101: 495-511.
Dalen JTW van, Spekreijse H. Comparison of visual field examination and visual evoked cortical potentials in multiple sclerosis patients. Doc Ophthalmol 1981; 27: 139-147.
Davson H. Electrophysiology of the retina. In: Physiology of the eye. London; Churchill Livingstone, 1980: 243-297.
Dawson WW, Maida TM. Human pattern-evoked retinal responses are altered by optic atrophy. Invest Ophthalmol Vis Sci 1982; 22: 796-803.
Dawson WW, Maida TM. Relations between the human retinal cone and ganglion cell distribution. Ophthalmologica 1984; 188: 216-221.
Dawson WW, Trick GL, Litzkow CA. Improved electrode for electroretinography. Invest Ophthalmol Vis Sci 1979; 18: 988-991.
Day RM, Carroll FD. Optic nerve involvement associated with thyroid disfunction. Arch Ophthalmol 1962; 67: 43-51.
DeVita E, Johnson B, Sadun AA. Optic nerve degeneration in tract hemianopsia. Invest Ophthalmol Vis Sci 1987; ARVO abstracts no 67: 32.
Dodt E. The electrical response of the human eye to patterned stimuli: clinical observations. Doc Ophthalmol 1987; 65: 271-286.

Doesschate G ten, Doesschate J ten. The influence of the state of adaptation on the resting potential of the human eye. Ophthalmologica 1956; 132: 308-320.

Dolman CL, McGormick AQ, Drance SM. Aging of the optic nerve. Arch Ophthalmol 1980; 98: 2053-2058.

Drance SM. Some factors in the production of low tension glaucoma. Br J Ophthalmol 1972; 56: 229-242.

Drance SM, Airaksinen PJ, Price M, Schulzer M, Douglas GR, Tansley B. The use of psychophysical, structural, and electrodiagnostic parameters to identify glaucomatous damage. Graefe's Arch Clin Exp Ophthalmol 1987; 225: 365-368.

Drance SM, Fairclough M, Butler DM, Kottler MS. The importance of disc hemorrhage in the prognosis of chronic open angle glaucoma. Arch Ophthalmol 1977; 95: 226.

Drasdo N, Cox W, Thompson DA. The effects of image degradation on retinal illuminance and pattern responses to checkerboard stimuli. Doc Ophthalmol 1987; 66: 267-275.

Drasdo N, Thompson D. Distortion of spatial selectivity by pattern onset stimulation. Doc Ophthalmol 1989; 72: 1-8.

Elenius V, Lehtonen J. Spectral sensitivity of the standing potential of the human eye. Acta Ophthalmol 1962; 40: 559-566.

Engell T, Andersen PK. The frequency of periphlebitis retinae in multiple sclerosis. Acta Neurol Scand 1982; 65: 601-608.

Engell T, Trojaborg W, Raun NE. Subclinical optic neuropathy in multiple sclerosis. Acta Ophthalmol 1987; 65: 735-740.

Enroth-Cugell C, Robson JG. The contrast sensitivity of retinal ganglion cells of the cat. J Physiol 1966; 187: 517-552.

Feinsod M, Hoyt WF. Subclinical optic neuropathy in multiple sclerosis. J Neurol Neurosurg Psychiatry 1975; 38: 1109-1114.

Feldon SE, Muramatsu S, Weiner JM. Clinical classification of Graves' ophthalmopathy. Arch Ophthalmol 1984; 102: 1469-1472.

Feldon SE, Weiner JM. Clinical significance of extraocular muscle volumes in Graves' ophthalmopathy. Arch Ophthalmol 1982; 100: 1266-1269.

Fiorentini A, Maffei L, Pirchio M, Porciatti V, Spinelli D. Pattern ERG in patients with unilateral alterations of the retinal ganglion cells. Doc Ophthalmol Proc Series 1982, vol 31: 131-133.

Fiorentini A, Maffei L, Pirchio M, Spinelli D, Porciatti V. The ERG in response to alternating gratings in patients with diseases of the peripheral pathways. Invest Ophthalmol Vis Sci 1981; 21: 490-493.

Flanagan JG, Harding GFA. Multi-channel visual evoked potentials in early compressive lesions of the chiasm. Doc Ophthalmol 1988; 69: 271-281.

Fleishman JA, Beck RW, Linares OA, Klein JW. Deficits in visual function after resolution of optic neuritis. Ophthalmlogy 1987; 94: 1029-1035.

François J. Premiers essais d'électro-rétinographie clinique. Bull Acad Royale Méd Belgique 1952; 17: 67-80.

François J, Verriest G, Rouck de A. Modification of the amplitude of the human electro- oculogram by light and dark adaptation. Br J Ophthalmol 1955; 39: 398-408.

Frisén L, Claesson M. Narrowing of the retinal arterioles in descending optic atrophy. Ophthalmology 1984; 91: 1342-1346.

Frisén L, Hoyt WF. Insidious atrophy of retinal nerve fibres in multiple sclerosis. Arch Ophthalmol 1974; 92: 91-97.

Fujimoto N, Adachi-Usami E. Comparison of automated perimetry and pattern visually evoked cortical potentials in optic neuritis. Doc Ophthalmol 1988; 69: 263-269.

Galloway NR, Tolia J, Barber C. The pattern evoked response in disorders of the optic nerve. Doc Ophthalmol 1986; 63: 31-36.

Gartner S. Optic neuropathy in multiple sclerosis. Am Arch Ophtalmol 1953; 50: 718-726.

Geijer C, Bill A. Effects of raised intraocular pressure on retinal, prelaminar and retrolaminar optic nerve blood flow in monkeys. Invest Ophthalmol Vis Sci 1979; 18: 1030-1042.

Gloster J. Incidence of optic disc haemorrhages in chronic simple glaucoma and ocular hypertension. Br J Ophthalmol 1981; 65: 452-456.

Gorman CA, Bahn RS. Pathogenesis of Graves' ophthalmopathy. Dev Ophthalmol 1989; 20: 1-7.

Gottlob I, Heider W. Effect of hypothermia on pattern visual evoked potentials and pattern electroretinograms in optic neuritis. Clin Vis Sci 1988; 2: 227-283.

Gouras P, Carr RE. Light-induced DC responses of monkey retina before and after central retinal artery interuption. Invest Ophthalmol Vis Sci 1965; 4: 310-317.

Granit R. Sensory mechanisms of the retina. London 1947: Oxford University Press.

Granit R. Sensory mechanisms of the retina. New York 1963: Hafner-Publishing Co.

Grehn F, Stange D. The influence of short term IOP elevation and hypoxia on the impulse conduction in the nerve fibre layer of the cat retina. Doc Ophthalmol Proc Ser 1977; 14: 147.

Grehn F, Prost M. Function of retinal nerve fibres depends on prefusion pressure: Neurophysiologic investigations during acute intraocular pressure elevation. Invest Ophthalmol Vis Sci 1983; 24: 347-353.

Groneberg A. Simultaneously recorded retinal and cortical potentials elicited by checkerboard stimuli. Doc Ophthalmol Proc Series 1980; 23: 255-262.

Grounauer PA. The new single use ERG corneal contact lens electrode and its clinical application. Doc Opthalmol Proc Ser 1982; 31: 89-93.

Grunwald JE, Riva CE, Stone RA, Keates EU, Petrig BL. Retinal autoregulation in open-angle glaucoma. Ophthalmology 1984; 91: 1690-1694.

Grunwald JE, Sinclair SH, Riva CE. Autoregulation of the retinal circulation in response to decrease of intraocular pressure below normal. Invest Ophthalmol Vis Sci 1982; 23: 124-127.

Guthauser U, Flammer J, Niesel P. The relationship between the visual field and the optic nerve head in glaucomas. Graefe's Arch Clin Exp Ophthalmol 1987; 225: 129-132.

Hall R, Kirkham K, Doniach D, El Kabir D. Ophthalmic Graves' disease, diagnosis and pathogenesis. Lancet 1970; 1: 375-378.

Halliday AM, Halliday E, Kriss A, McDonald WI, Mushin J. The pattern-evoked potential in compression of the anterior visual pathways. Brain 1976; 99: 357-374.

Halliday AM, McDonald WI, Mushin J. Delayed visual evoked response in optic neuritis. Lancet 1972; II: 982-985.

Halliday AM, McDonald WI, Mushin J. Visual evoked response in diagnosis of multiple sclerosis. Br Med J 1973; 4: 661-664.

Hamburger HA, Leutcher WM, Thompson R. Visual evoked potentials in the diagnosis of multiple sclerosis. Ann Ophthalmol 1984; 16: 752-755.

Hamilton HE, Schultz RO, De Gowin EL. The endocrine eye lesion in hyperthyroidism: Its incidence and course in 165 patients treated for thyrotoxicosis with iodine. Arch

Intern Med 1960; 105: 675.
Harrison JM, O'Connor PS, Young RSL, Kincaid M, Bentley R. The pattern ERG in man following surgical resection of the optic nerve. Invest Ophthalmol Vis Sci 1987; 28: 492-499.
Harter MR. Evoked cortical responses to checkerboard patterns: effect of check size as a function of retinal eccentricity. Vision Res 1970; 10: 1365-1376.
Harter MR, White CT. Effects of contour sharpness and check size on visually evoked cortical potentials. Vision Res 1968; 8: 701-711.
Hawlina M, Strucl M, Stirn-Kranjc B, Finderle Z, Brecelj J. Pattern electroretinogram recorded by skin electrodes in early ocular hypertension and glaucoma. Doc Ophthalmol 1989, 73: 183-191.
Hayreh SS. Blood supply of the optic nerve head and its role in optic atrophy, glaucoma, and oedema of the optic disc. Br J Ophthalmol 1969; 53: 721.
Hayreh SS. Pathogenesis of optic nerve damage and visual field defects in glaucoma. Doc Ophthalmol Proc Series 1980; 22: 89-110.
Heinrichs IH, McLean DR. Evolution of visual evoked potentials in optic neuritis. Can J Neurol Sci 1988; 15: 394-396.
Hely MA, McManis PG, Doran TJ, Walsh JC, McLeod JG. Acute optic neuritis: a prospective study of risk factors for multiple sclerosis. J Neurol Neurosurg Psychiatry 1986; 49: 1125-1130.
Henkes HE. ERG in circulatory disturbance of the retina. Arch Ophthalmol 1954; 51: 42-53 and 52: 30-41.
Henkind P. Radial peripapillary capillaries of the retina. Br J Ophthalmol 1967; 51: 115-123.
Henkind P, Bellhorn R, Rabkin M, Murphy ME. Optic nerve transections in cats, effects on vessels of the optic nerve head and lamina cribrosa. Invest Ophthalmol Vis Sci 1977; 16: 442-446.
Hess RF, Baker CF. Human pattern evoked electroretinogram. J Neurophysiol 1984; 51: 939-951.
Hess RF, Baker CF, Zrenner E, Schwarzer E. Differences between electroretinograms of cat and primate. J Neurophysiol 1986; 56: 747-768.
Heynen HGM, Norren D van. Origin of the electroretinogram in the intact macaque eye: II. Current source density analysis. Vision Res 1985; 25: 709-715.
Heynen H, Wachtmeister L, Norren D van. Origin of the Oscilatory potentials in the primate retina. Vision Res 1985; 25: 1365-1373.
Hiromatsu Y, Fukazawa H, Guinard F, Salvi M, How J, Wall JR. A thyroid cytotoxic antibody that cross-reacts with an eye muscle cell surface antigen may be the cause of thyroid associated ophthalmopathy. J Clin Endocrinol Metab 1988; 67: 565-570.
Hitchings RA, Spaeth GL. Fluorescein angiography in chronic simple and low tension glaucoma. Br J Ophthalmol 1977; 61: 126-132.
Holder GE. The effects of chiasmal compression on the pattern visual evoked potential. Electroenceph Clin Neurophysiol 1978; 45: 278-280.
Holder GE. Significance of abnormal pattern electroretinography in anterior visual pathway disfunction. Br J Ophthalmol 1987; 71: 166-171.
Holder GE. The incidence of abnormal pattern electroretinography in optic nerve demyelination. Electroenceph Clin Neurophysiol 1991; 78: 18-26.

Holder GE, Condon JR. Pattern visual evoked potentials and pattern electroretinograms in hypothyroidism. Doc Ophthalmol 1989; 73: 127-131.

Holder GE, Huber MJE. The efffects of miosis on pattern and flash electroretinogram and pattern visual evoked potential. Doc Ophthalmol 1984; 40: 109-116.

Holopigian K, Snow J, Seiple W, Siegel I. Variability of the pattern electroretinogram. Doc Ophthalmol 1988; 70: 103-115.

Houwelingen AMW van, Wijngaarde R, Sorel-van Daalen M, Lith GHM van. Pattern visual evoked potentials (PVEP) in patients with ophthalmic Graves' disease (OGD) without a clear optic neuropathy, submitted.

Howe JW, Mitchell KW. Visual evoked cortical potential to paracentral retinal stimulation in chronic glaucoma, ocular hypertension, and age matched group of normals. Doc Ophthalmol 1985; 42: 37-43.

Hurbli T, Char DH, Harris J, Weaver K, Greenspan F, Sheline G. Radiation therapy for thyroid eye diseases. Am J Ophthalmol 1985; 99: 633-637.

Hutchinson WM. Acute optic neuritis and the prognosis for multiple sclerosis. J Neurol Neurosurg Psychiatry 1976; 39: 283-289.

Hutchinson M, Martin EA, Maguire P, Glynn D, Mansfield M, Feighery C. Visual evoked responses and immunoglobin abnormalities in the diagnosis of multiple sclerosis. Acta Neurol Scand 1983; 68: 90-95.

Jacobs GM. Receptive field in visual system. Brain Res 1969; 14: 553-573.

Jacobson DH, Gorman CA. Endocrine ophthalmopathy: current ideas concerning etiology, pathogenesis, and treatment. Endocrine Ophtalmopathy Update 1984; 5: 200-220.

Johansson JO. Inhibition of retrograde axoplasmic transport in rat optic nerve by increased IOP in vitro. Invest Ophthalmol Vis Sci 1983; 24: 1552-1558.

Kalvin NH, Hamasaki DI, Gass JDM. Experimental glaucoma in monkeys. Arch Ophthalmol 1966; 76: 82-103

Karpe G. The basis of clinical electroretinography. Acta Ophthalmol 1945; suppl 24: 1.

Katsumi O, Hirose T, Tsukada T. Effect of number of elements and size of stimulus field on recordability of pattern reversal visual evoked response. Invest Ophthalmol Vis Sci 1988; 29: 922-927.

Kaufman DI, Lorance RW, Woods M, Wray SH. The pattern electroretinogram: A long term study in acute optic neuropathy. Neurology 1988; 38: 1767-1774.

Kennerdell S, Rosenbaum AE, El-Hoshy MH. Apical optic nerve compression of dysthyroid optic neuropathy on computed tomography. Arch Ophthalmol 1981; 99: 807-809.

Kinnunen E. The incidence of optic neuritis and its prognosis for multiple sclerosis. Acta Neurol Scand 1983; 68: 371-377.

Kirkham TH, Coupland SG. The pattern electroretinogram in optic nerve demyelination. Can J Neurol Sci 1983; 10: 256-260.

Kitazawa J, Matsubara K. Optic disc changes in early glaucoma. Surv Ophthalmol 1989; 33 suppl: 417-418.

Kornzweig AL, Eliasoph I, Feldstein M. Selective atrophy of the radial peripapillary capillaries in chronic glaucoma. Arch Ophthalmol 1968; 80: 969-702.

Korth M. Human fast retinal potentials and the spatial properties of a visual stimulus. Vision Res 1981; 21: 627-630.

Korth M. Pattern-evoked responses and luminace evoked response in the human electroretinogram. J Physiol 1983; 337: 451-469.

Korth M. Kontrast und Ortsfrequenzselektivität des Musterwechsel-ERGs. Fortschr Ophthalmol 1985; 82: 402-403.

Korth M, Horn F, Storck B, Jonas J. The pattern-evoked electroretinogram (PERG): Age related alterations and changes in glaucoma. Graefe's Arch Clin Exp Ophthalmol 1989; 227: 123-130.

Korth M, Ilschner S. The spatial organization of retinal receptive fields in light and darkness as revealed by the pattern electroretinogram. Doc Ophthalmol 1986; 63: 142-149.

Korth M, Rix R. The pattern electroretinogram under different conditions of stimulus luminance ad contrast. Doc Ophthalmol Proc Series 1984; 40: 21-26.

Kuffler SW. Discharge patterns and functional organization of mammalian retina. J Neurophysiol 1953; 16: 37-68.

Kupfer C. Retinal ganglion cell degeneration following chiasmal lesions in man. Arch Ophthalmol 1963; 70: 256.

Ladenson PW, Stakes JW, Ridgway EC. Reversible alteration of the visual evoked potential in hypothyroidism. Am J Med 1984; 77: 1010-1014.

Lawwill T. Pattern stimuli for clinical ERG. Doc Ophthalmol Proc Series 1974; 4: 353-362.

Lawwill T, Walker C, Crockett S. The scotopic and photopic bar-pattern ERG - contributions of the central and peripheral retina. Doc Ophthalmol Proc Series 1977; 13: 287-291.

Leone CR, Bajandas FJ. Inferior orbital decompression for dysthyroid optic neuropathy. Ophthalmolgy 1981; 88: 525-532.

Leipert KP, Gottlob I. Pattern electroretinogram: effects of miosis, accommodation and defocus. Doc Ophthalmol 1988; 67: 335-346.

Lidegaard O, Gyldensted C, Juhler M, Zeeberg I. CT findings in acute MS. Acta Neurol Scand 1983; 68: 77-83.

Lightman S, McDonald WI, Bird AC, Francis DA, Hoskins A, Batchelor JR, Halliday AM. Retinal venous sheating in optic neuritis. Brain 1987; 110: 405-414.

Linsenmeier RA. Electrophysiological consequences of retinal hypoxia. Graefe's Arch Clin Exp Ophthalmol 1990; 228: 143-150.

Lith GHM van, Henkes HE. The relationship between ERG and VER. Ophthalmic Res 1970; 1: 40-47.

Lith GHM van, Henkes HE. The local electric response of the central retinal area. In: Advances in electrophysiology and -pathology of the visual system: Proc 6th Isceg Symp, Erfurt 1967: ed by Schmöger, Leipzig, Thieme 1968: 163-170.

Lith GHM van, Marle GW van, Dok-Mak GTM van. Variation in latency times of visually evoked cortical potentials. Br J Ophthalmol 1978, 62: 220-222.

Lith GHM van, Vijfvinkel-Bruinenga, Graniewski-Wijnands. Pattern evoked cortical potentials and compressive lesions along the visual pathways. Doc Ophthalmol 1982; 52: 347-353.

Lith GHM van, Vliet AGM van, Dok-Mak GTM van. Value of pattern evoked cortical potentials for the diagnosis of multiple sclerosis. Doc Ophthalmol 1979; 46: 345-351.

Lith GHM van, Ringens P, Heer LJ de. Pattern electroretinogram and glaucoma. Dev Ophthalmol 1984; 9: 133-139.

Loebl M, Schwartz B. Fluorescein angiographic defects of the optic disc in ocular hypertension. Arch Ophthalmol 1977; 95: 1980-1984.

Lorenz R, Dodt E, Heider W. Pattern electroretinogram peak times as a clinical means of discriminating retinal from optic nerve disease. Doc Ophthalmol 1989; 71: 307-320.
Lovasik JV, Konietzny EA. The effect of retinal image quality on steady-state pattern ERGs and VEPs. Clin Vis Sci 1989; 4: 41-50.
Maffei L, Fiorentini A. Electroretinographic responses to alternating gratings before and after section of the optic nerve. Science 1981; 211: 953-955.
Maffei L, Fiorentini A. Electroretinographic responses to alternating gratings in the cat. Exp Brain Res 1982; 48: 327-334.
Maffei L, Fiorentini A, Bisti S, Holländer A. Pattern ERG in the monkey after section of the optic nerve. Exp Brain Res 1985; 59: 423-425.
Marx MS, Bodis-Wollner I, Lustgarten JS, Podos SM. Electrophysiological evidence that early glaucoma affects foveal vision. Doc Ophthalmol 1988; 67: 281-301.
Marx MS, Podos SM, Bodis-Wollner I, Howard Williams JR, Siegel M, Teitelbaum CS, Maclin EL, Severin C. Flash and Pattern electroretinograms in normal and laser induced glaucomatous primate eyes. Invest Ophthalmol Vis Sci 1986; 27: 378-386.
Marx R, Zrenner E. Sensitivity distribution in the central and midperipheral visual field determined by pattern electroretinography and harmonic analysis. Doc Ophthalmol 1990; 73: 347-357.
Mashima Y, Oguchi Y. Clinical study of the pattern electroretinogram in patiens with optic nerve damage. Doc Ophthalmol 1985; 61: 91-96
Mastaglia FL, Black JL, Collins DWK, Gutteridge DH, Yuen RWM. Slowing of conduction in visual pathway in hypothyroidism. Lancet 1978; febr 18: 388-389.
Maumenee AE. Causes of optic nerve damage in glaucoma. Ophthalmology 1983; 90: 742-752.
May JG, Ralston JV, Reed JL, Dyk HJL van. Loss in pattern elicited electroretinograms in optic nerve disfunction. Am J Ophthalmol 1982; 93: 418-422.
McAlpine D. The benign form of multiple sclerosis: Results of a long term study. Br Med J 1964; 2: 1029-1032.
McDonald WI. Pathophysiology in multiple sclerosis. Brain 1974; 97: 179-196.
Meyers IL. Electronystagmography. A graphic study of the active currents in nystagmus. Arch Neurol and psychiatry 1929; 21: 901.
Millner BA, Regan D, Heron JR. Differential diagnosis of multiple sclerosis by visual evoked potential recording. Brain 1974; 97: 755-772.
Millodot M, Riggs LA. Refraction determined electrophysiology: responses to alternation of visual contour. Arch Ophthalmol 1970; 84: 272-278.
Minckler DS. Histology of optic nerve damage in ocular hypertension and early glaucoma. Surv Ophthalmol 1989; 33 suppl: 401-402.
Minckler DS, Bunt AH, Klock IB. Radioautographic and cytochemical ultrastructural studies of axoplasmic transport in the monkey optic nerve head. Invest Ophthalmol Vis Sci 1978; 17: 33-50.
Minckler DS, Tso MOM, Zimmerman LE. A light microscopic, autoradiographic study of axoplasmic transport in the optic nerve head during ocular hypotony, increased intraocular pressure, and papilledema. Am J Ophthalmol 1976; 82: 741-757.
Mitchell KW, Howe JW. Parallel pattern generated electroretinogram and visual evoked cortical potential. Doc Ophthalmol Proc Series 1984; 40: 69-77.
Mitchell KW, Wood CM, Howe JW. Pattern visual evoked potentials in hyperthyroidism. Br J Ophthalmol 1988; 72: 534-537.

Mizota A, Adachi-Usami E, Kakisu Y, Asanagi K. Pre- and postoperative findings of pattern VECPs and ERGs in patients of orbital tumors. Doc Ophthalmol 1988; 69: 41-49.

Mourits MPh, Koornneef L, Wieringa WM, Prummel MF, Berhout A, Gaag R vd. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. Br J Ophthalmol 1989; 73: 639-644.

Neigel JM, Rootman J, Belkin RI, et al. Dysthyroid optic neuropathy. The crowded orbital apex syndrome. Ophthalmology 1988; 95: 1515-1521.

Nikoskelainen E. Symptoms, signs and early course of optic neuritis. Acta Ophthalmol 1975; 53: 254-271.

Nikoskelainen E, Riekkinen P. Optic neuritis - A sign of multiple sclerosis or other diseases of the central nervous system. Acta Neurol Scand 1974; 50: 690-718.

Nishitani H, Kooi KA. Cerebral evoked responses in hypothyroidism. Electroenceph Clin Neurophysiol 1968; 24: 554-560.

Noback CR. The human nervous system. New York; Mc Craw-Hill, 1967: 181.

Noell WK. The origin of the electroretinogram. Am J Ophthalmol 1954; 38: 78-90.

Novack RL, Stefansson E, Hatchell DL. Intraocular pressure effects on optic nerve head oxidative metabolism measured in vivo. Graefe's Arch Clin Exp Ophthalmol 1990; 228: 128-133.

Odom JV, Maida TM, Dawson WW. Pattern evoked retinal response in human: effects of spatial frequency, temporal frequency, luminance and defocus. Curr Eye Res 1982; 2: 99-107.

Odom JV, Maida TM, Dawson WW, Hobson R. Pattern electroretinogram: effects of reference electrode position. Doc Ophthalmol 1987; 65: 297-306.

Odom JV, Norcia AM. Retinal and cortical potentials: spatial and temporal characteristics. Doc Ophthalmol Proc Series 1984; 40: 29-38.

Oishi M, Yamada T, Dickins QS, Kimura J. Visual evoked potentials by different check sizes in patients with multiple sclerosis. Neurology 1985; 35: 1461-1465.

Ossoinig KC. Ultrasonic diagnosis of Graves' ophthalmopathy. In: The eye and orbit in thyroid disease edited by Gorman CA et al. Raven press, New York, 1984; 203-205.

Ota I, Miyake Y. The pattern electroretinogram in patients with optic nerve disease. Doc Ophthalmol 1986; 62: 53-59.

Ouwerkerk BM van. Immunological aspects of Graves' disease (dissertation). Rotterdam, The Netherlands; Erasmus University Rotterdam, 1985.

Ouwerkerk BM van, Wijngaarde R. Henneman G, Andel JG van, Krenning EP. Radiotherapy of severe ophthalmic Graves' disease. J Endocrinol Invest 1985; 8:241-247.

Papst N, Bopp M, Schnaudigel OE. Pattern electroretinogram and visualy evoked cortical potentials in glaucoma. Graefe's Arch Clin Exp Ophthalmol 1984; 22: 29-33.

Papst N, Bopp M, Schnaudigel OE. The pattern evoked electroretinogram associated with intraocular pressure. Graefe's Arch Clin Exp Ophthalmol 1984; 22: 34-37.

Percy AK, Nobrega FT, Kurland KT, Minn R. Optic neuritis and multiple sclerosis. Arch Ophthalmol 1972; 87: 135-139.

Perkins ES. The bedford glaucoma survey. I: Long term follow-up of borderline cases, II Rescreening of normal population. Br J Ophthalmol 1973; 57: 179-192.

Perry VH, Oehler R, Cowey A. Retinal ganglion cells that project to the dorsal lateral geniculate nucleus in the macaque monkey. Neuroscience 1984; 12: 1101.

Persson HE, Wanger P. Pattern-reversal electroretinograms in squint amblyopia, artificial anisometropia and simulated eccentric fixation. Acta Ophthalmol 1982; 60: 123-132.

Persson HE, Wanger P. Pattern-reversal electroretinograms and visual evoked cortical potentials in multiple sclerosis. Br J Ophthalmol 1984; 68: 760-764.

Pickett JE, Terry SA, O'Conner PS, O'Hara M. Early loss of central visual acuity in glaucoma. Ophthalmology 1985; 92: 891-896.

Pierelli F, Pozzessere G, Stenao E, Martelli M, Rizzo PA, Morocutti C. Pattern visual evoked potentials and flash electroretinogram in clinically definite multiple sclerosis. Eur Neurol 1985; 24: 324-329.

Pinchera A, Bartalena L, Chiovato L, Marcocci C. Radiotherapy of Graves' ophthalmopathy. In: The eye and orbit in thyroid disease edited by Gorman CA et al. Raven press, New York, 1984; 304-305.

Plant GT, Hess RF, Thomas SJ. The pattern evoked electroretinogram in optic neuritis. Brain 1986; 109: 469-490.

Poel JC van der. Visual function in optic neuritis in relation to multiple sclerosis (dissertation). Rotterdam The Netherlands; Erasmus University Rotterdam, 1985.

Porciatti V. Non-linearities in the focal ERG evoked by pattern and uniform-field stimulation. Invest Ophthalmol Vis Sci 1987; 28: 1306-1313.

Porciatti V, Falsini B, Brunori S, Colotto A, Moretti G. Pattern electroretinogram as a function of spatial frequency in ocular hypertension and early glaucoma. Doc Ophthalmol 1987; 65: 349-355.

Porciatti V, Falsini B, Scalia G, Fadda A, Fontanesi G. The pattern electroretinogram by skin electrodes: effect of spatial frequency and age. Doc Ophthalmol 1988; 70: 117-122.

Porciatti V, Francesconi W, Bagnoli P. The pigeon pattern electroretinogram is not affected by massive loss of cell bodies in the ganglion cell layer induced by chronic section of the optic nerve. Doc Ophthalmol 1985; 61: 41-47.

Porciatti V, Von Berger GP. Pattern electroretinogram and visual evoked potential in optic nerve disease: early diagnosis and prognosis. Doc Ophthalmol proc series 1984; 40: 117-126.

Price MJ, Drance SM, Price M, Schulzer M, Douglas GR, Tansley B. The pattern electroretinogram and visual-evoked potential in glaucoma. Graefe's Arch Clin Exp Ophthalmol 1988, 226: 542-547.

Quigley HA, Addicks EM. Regional differences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damagage. Arch Ophthalmol 1981; 99: 137-143.

Quigley HA, Addicks EM. Optic nerve damage in human glaucoma. Arch Ophthalmol 1982a; 100: 135-146.

Quigley HA, Addicks EM. Quantitative studies of retinal nerve fiber layer defects. Arch Ophthalmol 1982b; 100: 807-814.

Quigley HA, Addicks EM, Green WR, Maumenee AE. Optic nerve damage in human glaucoma; the site of injury and susceptibility to damage. Arch Ophthalmol 1981; 99: 635-649.

Quigley HA, Anderson DR. The dynamics and location of axonal transport blockade by acute intraocular pressure elevation in primate optic nerve. Invest Ophthalmol 1976; 15: 606-616.

Quigley HA, Anderson DR. The histologic basis of optic disc pallor in experimental optic atrophy. Am J Ophthalmol 1977; 83: 709-717.

Quigley HA, Dunkelberger GR, Green WR. Chronic human glaucoma causing slectively greater loss of large optic nerve fibres. Ophthalmology 1988; 95: 357-363

quigley HA, Dunkelberger GR, Green WR. Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. Am J Ophthalmol 1989; 107: 453-464.

Quigley HA, Hohman RM, Addicks EM. Quantitive study of optic nerve head capillaries in experimental optic disc pallor. Am J Ophthalmol 1982; 93: 689-699.

Quigley HA, Miller NR, George T. Clinical evaluation of nerve fiber layer atrophy as an indicator of optic nerve damage. Arch Ophthalmol 1980; 98: 1564-1571.

Quigley HA, Sanchez RM, Dunkelberger GR, L'Hernault NL, Baginski TA. Chronic glaucoma slectively damages large optic nerve fibres. Inv Ophthalmol Vis Sci 1987; 28: 913-920.

Radius RL, Anderson DR. Retinal ganglion cell degeneration in experimental optic atrophy. Am J Ophthalmol 1978; 86: 673-679.

Radius RL, Anderson DR. The mechanism of disc pallor in experimental optic atrophy. Arch Ophthalmol 1979; 97: 532-535.

Radius RL, Anderson DR. Rapid axonal transport in primate optic nerve. Arch Ophthalmol 1981; 99: 650-654.

Rao NA, Guy J, Sheffield PS. Effects of chronic demeylination on axonal transport in experimental allergic optic neuritis. Inv Ophthalmol Vis Sci 1981; 21/4: 606-611.

Regan D. Sensory information processing and evoked potentials. In: Evoked potentials in psychology, sensory physiology and clinical medicine. London; Chapman and Hall ltd, 1972: 31-133.

Regan D. Evoked potentials in psychology, sensory physiology and clinical medicine. London 1985, Chapman and Hall ltd.

Renard JP. Study of latency of visual evoked potentials in primary open-angle glaucoma: A preliminary report. Chibret Int J Ophthalmol 1987; 5: 2-9.

Riemslag FCC. Retinal and occipital pattern evoked potentials (dissertation) Amsterdam 1986; University of Amsterdam.

Riemslag FCC, Ringo JL, Spekreijse H, Verduyn-Lunel H. The distinction between luminance and spatial contrast components in the pattern ERG. Doc Ophthalmol Proc Series 1983; 37: 255-263.

Riggs LA, Johnson EP, Schick AML. Electrical responses of the human eye to moving stimulus patterns. Science 1964; 144: 567.

Riggs LA, Johnson EP, Schick AML. Electrical responses of the human eye to changes in wavelength of the stimulus of light. J Optom Soc Am 1966; 56: 1621-1627.

Ringens PJ, Lith GHM van, Poel H vd. The pattern-elicited electroretinogram. Ophthalmologica 1986; 192: 217-219.

Ringens PJ, Lith GHM van, Vijfvinkel-Bruinenga S. A standardized method for recording pattern-elicited electroretinograms in normal human subjects. Ophthalmologica 1984; 188: 106-110.

Riva CE, Sinclair SH, Grunwald JE. Autoregulation of retinal circulation in response to decrease of perfusion pressure. Invest Ophthalmol Vis Sci 1981; 21: 34-38.

Robert Y, Steiner D, Hendrickson Ph. Papillary circulation dynamics in glaucoma. Graefe's Arch Clin Exp Ophthalmol 1989; 227: 436-439.

Ross JE, Bron AJ, Reeves BC, Emmerson PG. Detection of optic nerve damage in ocular hypertension. Br J Ophthalmol 1985; 69: 897-903.

Rundle FF, Wilson CW. Lancet 1945; i: 51.

Ryan S, Arden GB. Eelcetrophysiological discrimination between retinal and optic nerve disorders. Doc Ophthalmol 1988; 68: 247-255.

Sakaue H, Katsumi O, Mehta M, Hirose T. Simultaneous pattern reversal ERG and VER recordings. Invest Ophthalmol Vis Sci 1990; 31: 506-511.

Salvi M, Zhang ZG, Haegert D, Woo M, Liberman A, Cadarso L, Wall JR. Patients with endocrine ophthalmopathy not associated with overt thyroid disease have multiple thyroid immunological abnormalities. J Clin Edocrinol Metab 1990; 70: 89-94.

Sanders EACM, Lith GHM van. Optic neuritis, confirmed by visual evoked response, and the risk for multiple sclerosis: a prospective survey. J Neurol Neurosurg Psychiatry 1989; 52: 799-800.

Sanders EACM, Volkers ACW, Poel JC vd, Lith GHM van. Visual function and pattern visual evoked response in optic neuritis. Br J Ophthalmol 1987; 71: 602-608.

Sartucci F, Scardigli V, Murri L. Visual evoked potentials and magnetic resonance imaging in the evaluation of pre- and retrochiasmic lesions in multiple sclerosis. Clin Vis Sci 1989; 4: 229-238.

Schadé OH. Optical and photoelectric analogy of the eye. J Opt Soc Amer 1956; 46: 721-739.

Schuurmans RP, Berninger T. Luminance and contrast responses in man and cat. Doc Ophthalmol 1985; 59: 187-197.

Schwartz B. Cupping and pallor of the optic disc. Arch Ophthalmol 1973; 89: 272-277.

Schwartz B. Changes of the optic disc in ocular hypertension and glaucoma. Jpn J Ophthalmol 1986; 30: 143-153.

Schwartz B, Rieser JC, Fishbein SL. Fluorescein angiographic defects of the optic disc in glaucoma. Arch Ophthalmol 1977; 95: 1961-1974.

Schwartz B, Takamoto T, Nagin P. Measurements of reversibility of optic disc cupping and pallor in ocular hypertension and glaucoma. Ophthalmology 1985; 92: 1396-1407.

Seiple WH, Price MJ, Kupersmith M, Siegel IM, Carr RE. The pattern electroretinogram in optic nerve disease. Ophthalmology 1983a; 90: 1127-1132.

Seiple WH, Siegel IM. Recording the pattern electroretinogram: a cautionairy note. Invest Ophthalmol Vis Sci 1983b; 24: 796-798.

Serra G, Carreras M, Tugnoli V, Manca M, Cristofori MC. Pattern electroretinogram in multiple sclerosis. J Neurol Neurosurg Psychiatry 1984; 47: 879-883.

Shaw NA, Cant BR. Age dependent changes in the latency of the pattern visual evoked potential. Electroenceph Clin Neurophysiol 1980; 48: 237-241.

Sherman J. Simultaneous pattern reversal electroretinograms and visual evoked potentials in diseases of the macula and optic nerve. Ann NY Acad Sci 1982: 214-226.

Shields MB. A study guide for glaucoma. Baltimore: Williams & Wilkins, 1982.

Shibasaki H, Kuroiwa Y. Pattern reversal visual evoked potentials in Japanese patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 1982; 45: 1139-1143.

Siliprandi R, Bucci MG, Canella R, Carmignoto G. Flash and pattern electroretinograms during and after intraocular pressure elevation in cats. Invest Ophthalmol Vis Sci 1988; 29: 558-565.

Skrandies W, Leipert KP. Pattern ERG and VEP topography evoked by lateral eccentric pattern reversal stimulation. Intern J Neuroscience 1988a; 39: 137-146.

Skrandies W, Leipert KP. Visual field defects are not accompanied by electrophysiological evidence of transynaptic retrograde degeneration. Clin Vis Sci 1988b; 3: 45-57.

Sokol S. An electrodiagnostic index of macular degeneration. Arch Ophthalmol 1972; 88: 619-624.

Sokol S. Visually evoked potentials: Theory, techniques and clinical applications. Surv Ophthalmol 1976; 21: 18-44.

Sokol S, Domar A, Moskowitz A, Schwartz B. Pattern evoked potential latency and contrast sensitivity in glaucoma and ocular hypertension. Doc Ophthalmol Proc Series 1981; 27: 79-86.

Spekreijse H, Tweel LH van der, Zuidema Th. Contrast evoked responses in man. Vision Res 1973; 13: 1577-1601.

Spencer WH. Ophthalmic pathology, an atlas and textbook. Third ed., vol I. WB Saunders Company Philadelphia, 1985.

Strucl M, Prevec TS, Zidar I. Dependence of electroretinogram and visual evoked potential on retinal area stimulated by pattern shift. Doc Ophthalmol Proc Series 1984; 40: 79-84.

Tagami Y. Atrophy of maculopapillar bundles in recovered optic neuropathies. Jpn J Ophthalmol 1979; 23: 301-309.

Takahashi K, Fujitani Y. Somatosensory and visual evoked potentials in hyperthyroidism. Electroenceph Clin Neurophysiol 1970; 29: 551-556.

Tan CB, King PJL, Chiappa KH. Pattern ERG: effects of reference electrode site, stimulus mode and check size. Electroenceph Clin Neurophysiol 1989; 74: 11-18.

Taub RG, Rucker CW. The relationship of retrobulbar neuritis to multiple sclerosis. Am J Ophthalmol 1954; 37: 494-497.

Thompson DA, Drasdo N. Computation of the luminance and pattern components of the bar pattern electroretinogram. Doc Ophthalmol 1987; 66: 233-244.

Thompson DA, Drasdo N. Distortion of spatial selectivity by pattern onset stimulation. Doc Ophthalmol 1989; 72: 1-8.

Torren K van der. OP-power in diabetic retinopathy (dissertation). Rotterdam The Netherlands; Erasmus University Rotterdam, 1985.

Towle VL, Moskowitz A, Sokol S, Schwartz B. The visual evoked potential in glaucoma and ocular hypertension: Effects of check size, field size, and stimulation rate. Invest Ophthalmol Vis Sci 1983; 24: 175-183.

Trau R, Salu P. Simultaneous pattern electroretinograms and visual evoked response recording in clinical conditions. Doc Ophthalmol proc series 1984; 40: 93-99.

Trick GL. Retinal potentials in patients with primary open-angle glaucoma: Physiological evidence for temporal frequency tuning deficits. Inv Ophthalmol Vis Sci 1985; 26: 1750-1758.

Trick GL. PRRP abnormalities in glaucoma and ocular hypertension. Invest Ophthalmol Vis Sci 1986; 27: 1730-1736.

Trick GL, Burde RM, Gordon MO, Kilo C, Santiago JV. Retinocortical conduction time in diabetics with abnormal pattern reversal electroretinograms and visual evoked potentials. Doc Ophthalmol 1988; 70: 19-28.

Trick GL, Trick LR. An evaluation of variation in pattern reversal retinal potential characteristics. Doc Ophthalmol 1984; 40: 57-67.

Trick GL, Wintermeyer DH. Spatial and temporal frequency tuning of pattern reversal retinal potentials. Invest Ophthalmol Clin Sci 1982; 23: 774-779.

Trick LR. Age-related alterations in retinal function. Doc Ophthalmol 1987; 65: 35-43.
Trobe JD. Optic nerve involvement in dysthyroidism. Ophthalmology 1981; 88: 488-492.
Trokel SL, Hilal SK. Submillimeter resolution CT scanning of orbital diseases. Ophthalmology 1980; 87: 412-417.
Trokel SL, Jacobiec FA. Correlation of CT scanning and pathologic features of ophthalmic Graves' disease. Ophthalmology 1981; 88: 553.
Vaegan, Arden GB, Hogg CR. Properties of normal electroretinograms evoked by patterned stimuli in man. Doc Ophthalmol Proc Series 1982; 31: 111-129.
Vaegan, Billson FA. The differential effect of optic nerve disease on pattern and focal electroretinograms. Doc Ophthalmol 1987; 65: 45-55.
Vrabec F. Senile changes in the ganglion cells of the human retina. Br J Ophthalmol 1965; 49: 561-572.
Vrabec F. Glaucomatous cupping of the human optic disc. Graefe's Arch Clin Exp Ophthalmol 1976; 198: 223-234.
Vrijland HR, Lith GHM van. The value of preoperative electro-ophthalmological examination before cataract extraction. Doc Ophtalmol 1983; 55: 153-156.
Walsh and Hoyt. Clinical neuro-ophthalmology. Williams & Wilkins, Baltimore/London, fourth edition, 1982.
Wanger P, Persson HE. Pattern reversal electroretinograms in unilateral glaucoma. Invest Ophthalmol Vis Sci 1983; 24: 749-753.
Wanger P, Persson HE. Pattern-reversal electroretinograms in ocular hypertension. Doc Ophthalmologica 1985; 61: 27-31.
Wanger P, Persson HE. Pattern-reversal electroretinograms from normotensive, hypertensive and glaucomatous eyes. Ophthalmologica 1987; 195: 205-208.
Weinstein GW, Arden GB, Hitchings RA, Ryan S, Calthorpe CM, Odom JV. The pattern electroretinogram (PERG) in ocular hypertension and glaucoma. Arch Ophthalmol 1988; 106: 923-928.
Werner SC. Classification of the eye changes of Graves' disease. J Clin Endocrinol Metab 1969; 29: 782.
Werner SC. Modification of the classification of the eye changes of Graves' disease: recommendations of the ad hoc committee of the american thyroid association. J Clin Endocrinol Metab 1977; 44: 203-204.
Wiersinga WM, Smit T, Gaag R vd, Mourits M, Koornneef L. Clinical presentation of Graves' Ophthalmopathy. Opthalmic Res 1989; 21: 73-82.
Wiesel TN, Hubel DH. Spatial and chromatic interactions in the lateral geniculate body of the rhesus monkey. J Neurophysiol 1966; 29: 1115-1156.
Wildberger H, Bär RP. A comparative study of visual evoked potentials and of retinal nerve fiber layer photography in neuropathies of the optic nerve. Doc Ophthalmol 1990; 133-138.
Wildberger HGH, Lith GHM van. Color vision and visually evoked response (VECP) in the recovery period of optic neurtitis. Mod Probl Ophthal 1976; 17: 320-324.
Wijngaarde R, Lith GHM van. Pattern EPS in endocrine orbithopathy. Doc Ophthalmol 1979; 48,2: 327-332.
Yanashima K, Inagaki Y, Okisaka S. Simultaneous recording of electroretinograms and visually evoked potentials on the scalp by means of flash and patterned stimuli. Doc Ophthalmol 1984; 40: 85-92.

Yoshii M. Pattern reversal electroretinograms: TV or projector system? Fortschr Ophthalmol 1988; 85: 304-307.

Yoshii M, Päärmann A. Hemiretinal stimuli elicit different amplitudes in the pattern electroretinogram. Doc Ophthalmol 1989; 72: 21-29.

Zimmerman LE, Venecia de G, Hamasaki DI. Pathology of the optic nerve in experimental acute glaucoma. Invest Ophthalmol 1967; 6: 109-125.

Zrenner E, Ziegler R, Voss B. Clinical applications of pattern electroretinography: Melanoma, retinal detachement and glaucoma. Doc Ophthalmol 1988; 68: 283-292.

LIST OF ABBREVIATIONS

A	= Amplitude
BP	= Blood pressure
C/D	= Cup / disc ratio
dB	= Decibels
D0	= PVEP registration without a one logarithm filter
D1	= PVEP registration with a one logarithm filter
EOG	= Electro oculogram
ERG	= Electro retinogram
ERP	= Early receptor potential
GLAU	= Primary open angle glaucoma
IOP	= Intraocular pressure
L	= Latency
LRP	= Late receptor potential
mm Hg	= Eye pressure in millimeters mercury
ms	= Milliseconds
MS	= Multiple Sclerosis
MS-	= Multiple Sclerosis without a history of optic neuritis
MS+	= Multiple Sclerosis with a history of optic neuritis
M1	= Group of optic neuritis patients one month after the initial attack
M6	= Group of optic neuritis patients six months after the initial attack
n	= Number
NFL	= Nerve fibre layer
NMR	= Nuclear magnetic resonance
NPG	= Normal pressure glaucoma
N95	= Negative component of the pattern ERG at 95 milliseconds
OGD	= Ophthalmic Graves' disease
OHT	= Ocular hypertension
ON	= Optic neuritis
OPs	= Oscillatory potentials
PERG	= Pattern electroretinogram
PMB	= Maculopapillar bundle
PVEP	= Pattern visually evoked potentials
P50	= Positive component of the pattern ERG at 50 milliseconds
sd	= Standard deviation
TM	= Trademark
VEP	= Visually evoked potentials
40'	= Pattern element size of 40 minutes of arc
80'	= Pattern element size of 80 minutes of arc
μv	= Microvolts

CURRICULUM VITAE

De schrijver van dit proefschrift werd geboren op 24 augustus 1961 te Schiedam. Na het behalen van het VWO diploma aan het Stedelijk Gymnasium te Schiedam werd hij in 1982 ingeloot voor de studie geneeskunde aan de Erasmus Universiteit Rotterdam. In september 1986 werd het doctoraal examen behaald. Na het co-schap oogheelkunde in het Oosterschelde Ziekenhuis te Goes startte hij in het Oogziekenhuis Rotterdam onder leiding van prof.dr. G.H.M. van Lith een keuze onderzoek naar de effecten van neuritis optica op het patroon-ERG. Tevens werd de basis gelegd voor een prospectief onderzoek naar de invloeden van diverse geleidingsstoornissen van de oogzenuw op het patroon-ERG. Na het behalen van het artsexamen in december 1988 kreeg hij, ondersteund door de Rotterdamse Vereniging Blindenbelangen, de Flieringa stichting en het Haagsch Oogheelkundig Fonds een AGNIO aanstelling met als taak dit onderzoek te verrichten. Delen van dit onderzoek werden gepresenteerd op bijeenkomsten van het ISCEV (International Society for Clinical Electrophysiology of Vision) en het NOG (Nederlands Oogheelkundig Gezelschap). In november 1990 startte hij met de opleiding Oogheelkunde in het Oogziekenhuis Rotterdam (opleider: drs. G.S. Baarsma, oogarts).