AN ELECTRO-OPHTHALMOLOGICAL STUDY OF AFFECTIONS OF THE OPTIC PATHWAY

PROEFSCHRIFT

door

JOHANNES PAUL DE HAAS

geboren te Arnhem in 1939

PROMOTOR: PROF. DR. H. E. HENKES

CO-REFERENTEN: PROF. DR. M. W. VAN HOF
                            PROF. DR. A. STAAL

Aan

    Hanka,

    Marija, Chantal,

    Janno en Annemée

ACKNOWLEDGEMENTS

CONTENTS

whether the method is of value in cases in which a diagnosis could not be established with certainty by conventional techniques. In addition to patients with a disorder of the visual pathway, we studied patients in whom a lesion of the optic cortex had been diagnosed.

Given the objectives of our study, the emphasis came to be placed especially on the recording and interpretation of the VER. In the majority of cases the VER was recorded in the following two ways, always together with an ERG:

1. after local photic stimulation of the central fovea, in light adapted state;

2. after photic stimulation of the largest possible area of the retina, in light adapted and/or dark adapted state.

What exactly do we mean by the central fovea? This has been precisely defined by DEUTMAN (1970): "The central fovea is the fairly dark, oval-shaped retinal area localized some 3.5 papilla diameters (pd) temporal to the disc, and 0.8 mm below the horizontal meridian, and the outline of which is visible at ophthalmoscopy as a bright oval-shaped reflex: the foveal margin reflex". According to POLYAK (1941), the foveal diameter is about 1.5 mm (1500 μ), which corresponds to about 5° in the visual field. The fovea encompasses some 110.000 cones. (The total number of cones in the retina is about 6.3 to 6.8 million, ØSTERBERG, 1935). Within the fovea a rodless area exists, which meas-
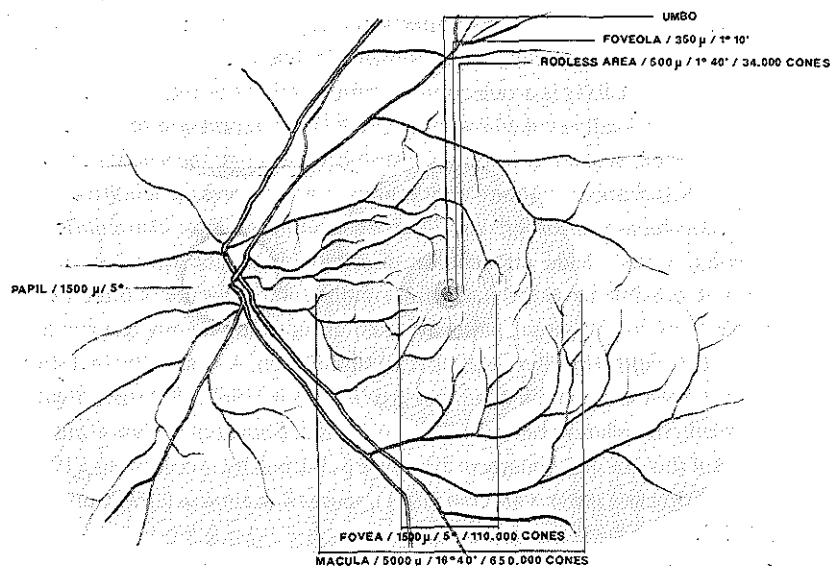
Fig. 1

The central retinal area, (POLYAK 1941).

2

ures 0.5 mm (500 μ) in diameter and comprises some 34.000 cones. This area is about as large as the avascular central retinal area, and corresponds to 1°40′ of the visual field. (See Fig. 1, after POLYAK 1941).

In our study, local stimulation was applied to a circular retinal area centered on the central fovea. The ERG elicited in this way will be refered to as Fovea ERG (FERG). Local stimulation was applied, because transmission disorders of the visual pathway, on which our study focuses, are often characterized by a central relative or absolute scotoma in the visual field. The FERG made it possible to establish objectively whether the simultaneously recorded VER had been evoked by exclusive stimulation of the central retina.

We also recorded the VER after full field stimulation in light adapted as well as in dark adapted state. The results of these investigations should be regarded as supplemental to the data on transmission in the visual pathway obtained by recording the VER after local (foveal) stimulation of the retina. Even this VER, recorded after full field stimulation, is largely determined by the central fovea, as was demonstrated among others by VAN HOF (1960) and COPENHAVER (1964). In our study it was sometimes impossible to obtain information on transmission in the visual pathway by recording the "foveal" VER. For this purpose certain demands were made on the patient's cooperation, and these demands were sometimes not met. In these cases, the recording of the VER after full field stimulation was the only possibility to collect data on transmission in the visual pathway, because this type of examination required little or no cooperation on the part of the patient.

VISUALLY EVOKED (CORTICAL) RESPONSES IN MAN

ADRIAN & MATTHEWS were the first to demonstrate, in 1934, that potential variations following repetitive photic stimuli can be transcranially derived. They referred to "photic driving of the alpha rythm". GREY WALTER (1946) considered the influence of repetitive photic stimuli on the EEG in clinical EEG studies. He used a stroboscope as light source and demonstrated the importance of this type of examination in the diagnosis of subclinical epilepsy. In this affection, a spikes-and-waves complex could be evoked by photic stimulation. The technique he used has remained part of EEG studies until this very day.

It was not until later that the VER could be introduced as a diagnostic aid, for the potential variation evoked by a photic stimulus was hardly recognizable as such amidst the spontaneous cortical activity. A better signal-to-noise ratio was therefore required in order to ensure more selective recording of the VER. Various averaging techniques were used for this purpose, of which Dawson's superimposition technique (1954) was one of the first. By averaging responses, it is possible to select the initially unidentifiable specific response from the totality of spontaneous electric activity. VAN BALEN, who in 1962 devoted a study to the VER and its significance in ophthalmological diagnosis, made use of Dawson's superimposition technique as well as of a mathematical method of integration. With the advance of computer technology, completely automated averaging devices became available for use in research. We mention as an example the Computer of Average Transients, which has long been the most widely used of these devices.

The shape of the visually evoked (cortical) response

MONNIER was among the first investigators who attempted to analyse the con-stellation of waves which constitute the VER and to identify the components which can be found in every normal individual. In reports published in 1952, MONNIER described the specific cortical response to photic stimulation as con-sisting of two surface-positive waves (b-wave and d-wave) which are separated by a single negative wave (c-wave). This description was based on a study of three subjects, using a stroboscope as light source; the stimulus frequency used was not specified. Potential differences between vertex and inion were recorded.

4

VAN HOF (1959) observed duplication of the surface-negative c-wave of MONNIER upon photic stimulation at a frequency exceeding 3 cps. He mentioned in his brief communication that stimulus frequencies used ranged from 3/sec to 11/sec.

VAN BALEN (1962) believed on account of his findings that the occurrence of a single or duplicate surface-negative c-wave should be related to the "attention" factor. At low intensities of the photic stimulus he found both a c1-wave and a c2-wave when recording "with attention", whereas only the c2-wave was found "without attention". At higher flash intensities, he found the c1/c2 ratio to be higher "with attention" than "without attention". He believed that the change in c1/c2 ratio expresses the inhibitory influence of the foveal on the extrafoveal system, assuming that the c1-wave represents the former system in response, and the c2-wave the latter system. VAN BALEN made use of a stroboscope set at a flash frequency of 1 per 2 seconds.

CIGANEK (1958, 1961) gave a different description of the wave complex which constitutes the VER. He used a stroboscope, with stimulus frequencies ranging from 1 per 3 seconds to 35 per second. The responses were averaged by means of Dawson's superimposition technique. Schematically, the specific (cortical) response looks as follows according to CIGANEK:
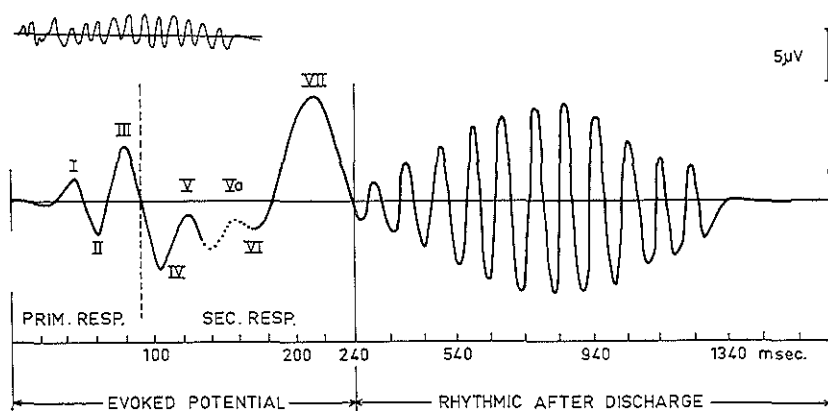
Fig. 2

Schematic representation of a VER recorded from O_z–P_z in the standardized EEG locations. Note the change in time scale at 240 msec (the scheme for the evoked potential with the real ratio of both constituents is reproduced on the left at the top of the figure). Negativity at electrode O_z results in upward deflection.

The many investigators who have devoted themselves to the study of VER have used different experimental set-ups and parameters. Views on the location

5
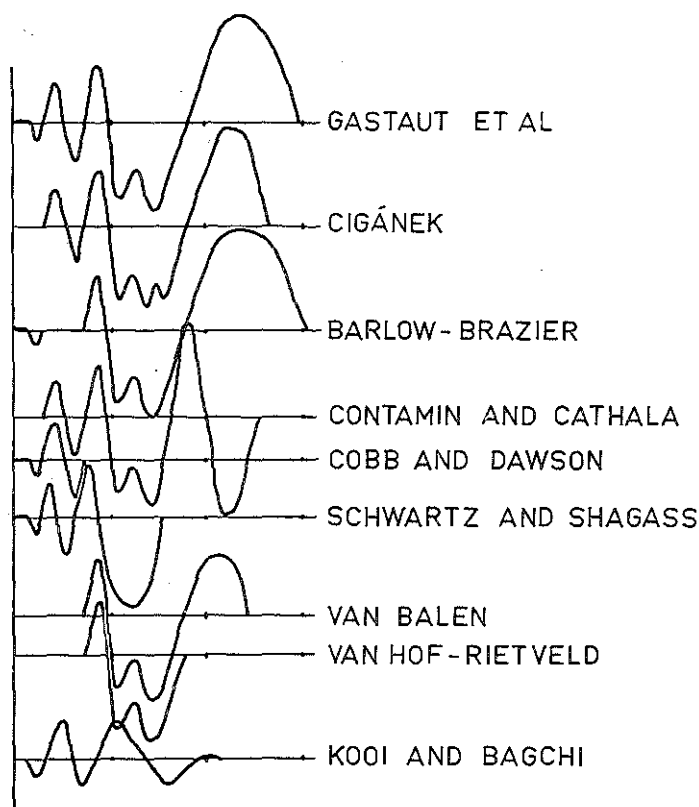
Fig. 3

Schematic comparison of mean VERs obtained by different investigators. (GASTAUT & RÉGIS, 1965).

where the scalp electrodes have to be placed likewise differed. It is therefore all the more surprising that GASTAUT & RÉGIS (1965) were able to publish a survey which demonstrated how great the similarity can be in the configuration of the VER as recorded by various authors (see Fig. 3). PERRY & CHILDERS (1969) maintained that it is indeed possible to trace certain wave complexes, but that failure to find them does not warrant the conclusion that an inadequate investigation has been made. They pointed out that the shape of the curve is jointly determined by a large number of variables, including:

I. Variables related to the test arrangement:

a. Colour, intensity, dimensions, frequency and duration of the stimulus;

6

b. Related to this: the possible use of background illumination in order to give the stimulated retinal area and the surrounding retina a certain state of adaptation. In this case the extent of the adaptive field is of importance.

c. The shape of the stimulus: flash, triangle, square, etc., or a light spot or a certain picture.

d. Stimulation of one eye or of both eyes simultaneously.

e. Placement of the scalp electrodes.

II. Variables related to the individual tested:

a. Age and sex.

b. Pupil diameter.

c. Habituation to the stimulus.

d. Alertness/attention during the test.

A few of these variables merit separate discussion in view of their importance in this study.

Studying the configuration of VER, the investigators mentioned earlier have always used a light source which stimulated the largest possible retinal area. Some have made use of a field of adaptation light with, superposed on it, a small repetitive stimulus. The field of adaptation light served to eliminate stray light effects of the stimulus. Using such a set-up COPENHAVER & PERRY "scanned" the retina in an effort to establish whether stimulation of different retinal areas

Fig. 4

Magnitude of VER for stimulation of the horizontal and vertical meridians. Each point is a mean total area of six VER plotted as a ratio to the mean foveal response. Experimental conditions: 2.5° white spot in a 60° surround, presented 128 times at 3.8 cps. Bipolar electrodes were 2 inches apart and oriented vertically on the midline with the lower electrode over the inion.

would lead to VERs of different configuration and/or amplitude. They confirmed that the VER is largely determined by the central fovea, as VAN HOF had demonstrated earlier (1960).
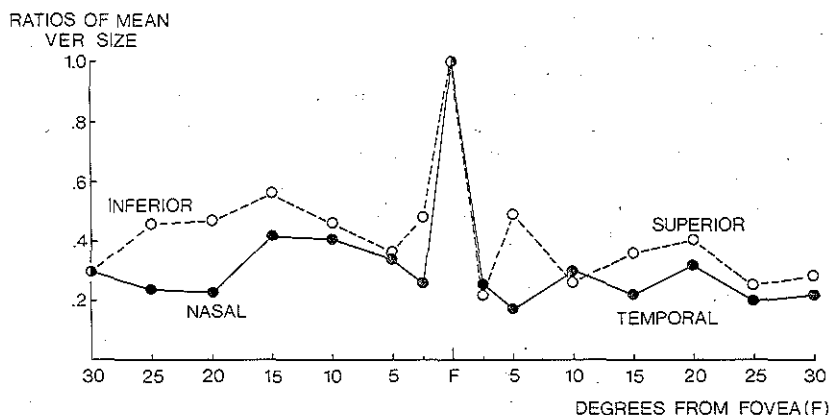
Many authors have studied the influence of attention on the amplitude of the cortical response (we have already mentioned VAN BALEN'S findings in this respect). Several investigators concluded from their experiments that the VER increases in amplitude if the subject focuses attention on the stimulus, e.g. by counting the flashes. VAN HOF c.s. (1966) observed this phenomenon in only a small percentage of the individuals they examined. We quote VAN HOF:

"This discrepancy may be due to variations in the experimental procedures". (VAN HOF et al. carried out an experiment to demonstrate more clearly the uneven contribution of different retinal areas; they presented flickering rings and discs to the subject.) "The subject was sitting in front of a screen into which translucent Plexiglass targets could be fitted. This screen was intermittently illuminated from behind by means of a sector disc rotating in the beam of a projector. The fixation point (30 cm in front of the nasion) was a black dot in the centre of the discs or a transparent small hole (visual angle 0.06°) in the centre of the rings. The visual angles of the discs were 2.15°, 3.85°, 6.80°, 12.14° and 21.30°. The visual angle of the outer diameter of the rings was always 21.30°, the inner diameter being 2.15°, 3.85°, 6.80° and 12.14°. The flash frequency was 3/sec, with a flash duration of 45 msec and a brightness of 0.2 stilb in all cases. The EEG was recorded from scalp electrodes, one being located on the midline over the occipital area (2 cm above the inion) and the other over the mastoid. The stimulation consisted of a series of about 150 flashes with each disc and ring offered in a random sequence, each of the nine targets being presented three times during the experiment. The average response to 100 flashes with each target was determined and the three curves were then averaged. Initially it was found with this method that the small hole in the centre of the rings did not itself elicit a response; when offering this hole alone, the average curve to 300 flashes was found to be a straight line. The average evoked potentials are presented with the appropriate disc or ring." (see fig. 5). "The illustration shows that the peak-to-peak amplitude increases when the surface area of the target increases. However, the 3.85° disc causes a larger amplitude than the 21.30–12.14° ring (area ratio 1:21.25) and the 6.80° disc a larger one than the 21.30–6.80° ring (ratio 1:9.00). From this it is evident that the contribution per retinal area unit decreases strongly when the eccentricity increases."

VAN HOF concluded from his experiments that the smaller the surface area of the target, the more susceptible the amplitude of the VER to a slight improvement in fixation, such as may be achieved by greater attention on the part of a subject who is asked to count the stimuli. In addition VAN HOF demonstrated that the VER increases in amplitude with an increase of the stimulus diameter, provided the latter does not exceed 12.14° (in his experiments). As we saw, VAN HOF used no field of adaptation light and an influence of stray light therefore remains a possibility. VAN LITH & HENKES (1970) carried out a similar exper-

8
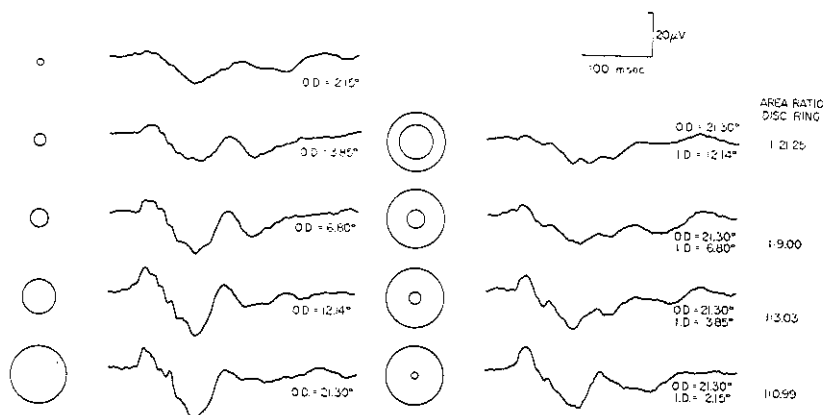
Fig. 5

VER with disc stimuli and ring stimuli of different sizes, (VAN HOF, 1966).

iment, but used a field of adaptation light of sufficient luminance to eliminate stray light responses (their experimental set-up was the same as the one described in detail in this study; see CHAPTER IV). Van LITH & HENKES confirmed the finding of VAN HOF that the VER amplitude increases when the stimulus diameter increases from 1° to 12°. With a stimulus diameter exceeding 12°, the VER shows no significant increase in amplitude (see Fig. 6).
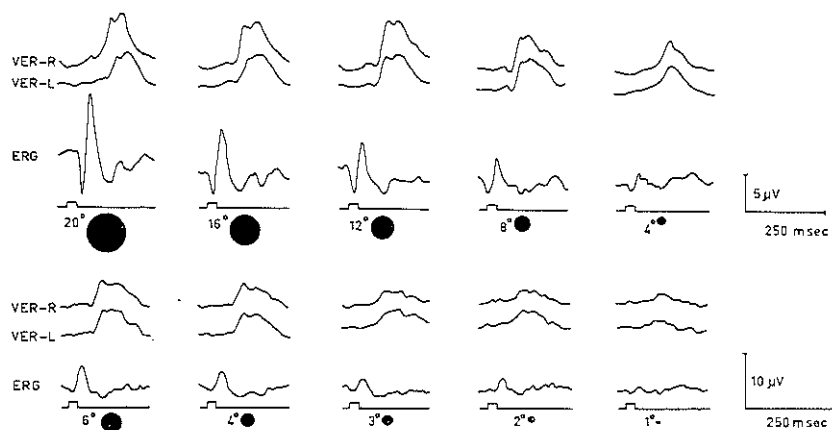
Fig. 6

ERG and VER with disc stimuli of different sizes, (VAN LITH & HENKES, 1970).

9

THE ERG AFTER LOCAL REPETITIVE STIMULATION OF THE RETINA

The recording of a local ERG response first became possible in the early Sixties. The impossibility of recording such an ERG prior to that time was clearly shown by ASHER (1951) and, independently, BOYNTON & RIGGS (1951). They demonstrated that, with a photic stimulus applied to or beside the disc, an ERG of identical shape and size could be obtained. BOYNTON & RIGGS explained this by stating that such an ERG is elicited by:
a. entoptic scatter;
b. light which is reflected by the disc.

Reduction of the luminance of the photic stimulus to eliminate the influence of stray light so reduces the height of the response that it cannot be measured with the aid of amplifiers of the type in use prior to 1960. Even the response of the central fovea proved to be too small for recording, although its local cell density is high. (On the other hand the position of the fovea in relation to the recording corneal electrode is unfavourable due to the great distance). If, for example, we wish to measure exclusively the amplitude of the photopic response of the central fovea, what is the height of the response to be expected?

ØSTERBERG (1935) computed the total number of cones of the retina as 6.3 to 6.8 million. POLYAK (1941) reported that the central fovea comprises 100.000–115.000 cones, i.e. about 2% of the total number of retinal cones. The foveal diameter corresponds to about 5° in the visual field. In the test arrangement we used, photopic full field stimulation results in a photopic ERG with an amplitude of about 100 μV. In that case, the central foveal response to be expected does not exceed a few microvolts. A response in this order of magnitude was far beyond the measuring range of the conventional amplifier, with which in actual practice no signals smaller than 20 μV could be isolated from the ever-present noise.

To achieve the recording of a purely local ERG response, it was necessary to improve the signal-to-noise ratio. HENKES, VAN DER TWEEL & DENIER VAN DER GON (1956,) used a selective amplifier, to be tuned to pre-selected stimulus frequencies. In this way they were able to detect, amidst the noise, responses to flicker stimuli which had a lower amplitude than responses recordable with the aid of the conventional amplifier. HENKES & VAN BALEN (1960) were among

the first to record a very small response in cases of retinal degeneration in which only a small central visual field of 5–10° remained. With the amplifier techniques commonly used until then, no ERG could be recorded in these cases. HENKES & VAN BALEN resorted for this purpose to superposed oscilloscope screen photography and mathematical integration of ERG responses.

Even better facilities became available with the introduction of electronic averaging techniques. With these, the ERG recording technique was so improved that a start could be made with the recording of local ERG responses as well. Obviously, the interest in this respect focused on the ERG of the central fovea, clinically because visual acuity is a function of the central fovea, and electrophysiologically because the fovea with its high neural element density is the most favourable choice for local ERG recording.

ARMINGTON et al. (1961) were the first to record a local ERG with the aid of an early computer technique. They used a field of adaptation light, above which they stimulated the central fovea with a 3° stimulus. They obtained an ERG response of less than 10 μV, which consisted of a negative a-wave and two positive waves. The a-wave and the second positive wave showed a scotopic spectral sensitivity, and can therefore be attributed to the rod system. The first positive wave had a mixed photo-scotopic spectral sensitivity, and was therefore no pure response of the cone system. Nevertheless they found that the first positive wave was higher upon stimulation of the central fovea than upon stimulation of a peripheral retinal area. In this way ARMINGTON et al. demonstrated the recordability of a response which was more or less specific of the central fovea. In their experiments, the activity of the rod system was not yet totally suppressed.

BRINDLEY & WESTHEIMER (1965) focused their attention on elimination of the effects of stray light by varying the background illumination. Their findings showed that the latter should not be less than about one-tenth of the luminance of the stimulus. Like ARMINGTON et al. they found a lower response upon stimulation of the peripheral than upon stimulation of the central retina. They used a relatively large stimulus of 30° square.

AIBA, ALPERN & MAASEIDVAAG (1967) used in their studies a 40° field of blue adaptation light. Its luminance on the retina amounted to 2.0×10^4 scotopic td. This was above the rod saturation level as determined by AGUILAR & STILES (1954). Nevertheless they determined a spectral sensitivity curve for their responses which showed a supranormal value in blue, which may indicate insufficient suppression of scotopic retinal activity. They gave no definite explanation of this fact (see page 60 of their publication). In their experiments, the ratio between the luminance of the adaptation light and that of the test light

was in agreement with that found by BRINDLEY & WESTHEIMER: 1:10. They found no response when the disc itself was stimulated with a field of 2° diameter.

In 1966 ARDEN & BANKES, and in 1968 BANKES published data on a method of recording an ERG from the central fovea. This method provided the basis for the methods further developed by VAN LITH & HENKES, which have finally resulted in a valid technique of investigation for clinical use. Like AIBA et al., ARDEN & BANKES used a 2° stimulus and a bluish-green background illumination. The luminance of the latter was such that stimulation of the disc produced no response. However, it is not certain that absence of a response upon stimulation of the disc is a valid criterion for determination of the luminance of the adaptation light in order to eliminate stray light responses. Data collected by ØSTERBERG (1935) show that the peripapillary retina comprises much fewer cones than the perifoveal area. The absence of stray light responses upon stimulation of the disc, therefore, does not necessarily mean that stray light responses will remain absent upon stimulation of the central fovea. A stimulus of only 2°, applied to the optic disc of 5°, as AIBA et al. and ARDEN & BANKES did, is even less capable of giving this guarantee (the only argument which can be offered in this respect is that the fovea will reflect less light than the disc).

BEINHOCKER et al. (1966) likewise recorded a local ERG, employing their method of electroperimetry. They used a field of adaptation light (consisting of the illuminated inside of a perimeter) and above it stimulated various areas of the retina with stimuli which ranged in diameter from 0.5° subtended visual angle at the fovea to 10° subtended visual angle at the 90° temporal position. In their experiments, the ratio in luminance between adaptation light and stimulus light was so chosen for all stimuli that a mass retinal discharge as a result of stray light was prevented.

RECORDING OF ERG AND VER (methods and equipment used)

I. *General considerations on the recording of the FERG together with the VER*

For the recording of a local ERG from the central fovea together with the VER an adaptive field was used with in the centre a white disc on which the stimulus beam was projected. The ratio between the luminance of the adaptation light and that of the stimulus was so chosen as to achieve the following two goals:

    1. Avoidance of stray light responses.

    2. Elimination of admixture of rod activity. This was initially done in order to avoid a possibly unclear mixed rod and cone response; but there were additional reasons:

a. the recording of a pure cone response from the central fovea is most useful in comparison with an examination of visual acuity and visual fields;
b. electrophysiologically, the VER is largely determined by the cones, and in particular by those of the central fovea;
c. we intended to compare the syndroms studied in terms of the correlation between ERG and VER. This correlation has been clearly established only for the foveal cone system.

Notes on 2b and 2c

MONNIER (1952), ARMINGTON (1964, 1966), DEVOE et al. (1968) and RIPPS & VAUGHAN (1969) concluded from their experiments that the VER results chiefly from stimulation of the cone system. That the VER is so little dependent on the rod system may be explained by the fact that the rods always converge via the bipolar cells on the ganglion cells. This results in a relatively small projection of the rod system in the optic cortex. Moreover, GOURAS & LINK (1966) believed that the cone signal possibly blocks the rod signal at a level beyond the layer of bipolar cells.

The VER is not only determined by the cone system, but especially by the cones of the fovea (e.g. VAN HOF 1960, COPENHAVER & PERRY 1964). This is attributed to the fact that the projection of the cones of the central fovea is localized on the outside of the calcarine sulcus. A potential evoked at this place will be most "accessible" to electrodes placed on the scalp over the occipital lobes. VAN LITH & HENKES (1970) specified two other reasons why the VER is

largely determined by the central retina:

1. The convergence of several cones on a single ganglion cell, too, can be of influence on the rapid dimunition of the amplitude of the VER with increasingly eccentric stimulation. This explanation was based on the work of TEN DOESCHATE (1946), who compared the dimunition of visual acuity with the centrifugal dimunition of the retinal cone density (he derived data on the cone density in various parts of the retina from the work of ØSTERBERG, 1935). TEN DOESCHATE calculated that, within a pericentral retinal zone of 10° each cone synapses with one ganglion cell; from 10° to 20° eccentrically, three cones converge on one ganglion cell.

2. As already mentioned before, ARMINGTON (1961), BRINDLEY (1965) and AIBA (1967) found that the ERG elicited by eccentric stimulation was smaller than the ERG of the fovea itself. VAN LITH & HENKES compared quantitatively ERG and VER with the number of cones. They found that, up to a given limit (about 6° eccentrically), both the local ERG and the VER show a relation to the number of cones stimulated (from the centre of the retina to the periphery, the number of cones per sq mm rapidly diminishes: ØSTERBERG's data (1935) show that 1° from the centre of the fovea the number of cones per sq mm is only one-third of that at the centre of the central fovea). VAN LITH & HENKES made these experiments, on the analogy of those of VAN HOF, with disc and ring stimuli of varying diameter. A field of adaptation light (see also the description of our method of investigation in CHAPTER IV) enabled them to record a purely local photopic response from the central fovea and the perifoveal retina.

Finally it should be mentioned that further reduction, that is convergence so far as the peripheral rod and cone system is concerned, takes place in the lateral geniculate body. This reduction does not affect the foveal cone system.

II. *General considerations on the recording of ERG and VER after full field stimulation*

Full field stimulation was applied in the light adapted (1) and in the dark adapted (2) state.

1. In the recording of the ERG and VER after full field stimulation in light adapted state, too, the ratio in luminance between adaptation light and stimulus light was such that a photopic ERG response was obtained. Using this condition it is certain that the recorded VER resulted from stimulation of the photopic system. This seemed the logical next step after recording the VER which is evoked by stimulation of the central fovea.

If recording of the FERG and the "foveal" VER should fail to produce

14

interpretable results, an examination of the ERG and VER with full field stimulation in light adapted state would make it nevertheless possible to collect data on transmission in the maculopapillary fibre bundle. Because in full field stimulation under photopic conditions, the central fovea still is most important in eliciting the VER.

2. When by the recording of FERG and "foveal" VER a transmission disorder in the maculopapillary fibre bundle could be demonstrated, it was a great consideration to establish whether in such cases it would be possible at all to record a VER. In that case it no longer seemed of importance to stimulate exclusively the photopic system.

The stimulus

I. *Local (foveal) stimulation*

The light source of the stimulus was a Xenon lamp (type Osram XBO 150 W) provided with an XV 150-lf-2b-L Ernst Leitz powersupply. The light was collimated into a parallel beam with the aid of an optical bench, and projected upon circular white discs, placed in the centre of the adaptive field. The maximal illumination of the white discs (8° disc) amounted to 6.000 lumen/sq m. For local stimulation this light flux was reduced to 600 lumen/sq m by means of a neutral density filter, giving the white discs a luminance of 2,5 log asb.

The choice of white light for the stimulus was determined by our wish to stimulate, as far as possible, the cones of all systems (red-, green- and blue-sensitive cones). That in particular the blue-sensitive cones were adapted by the background illumination, however, was apparent from the fact that the white stimulus light was subjectively perceived as reddish. In each standardized test three stimulus fields were used successively, which, at a distance of 30 cm, covered 8°, 5° and 3° of the visual field.

The stimulus frequency was 4/sec. Investigations by MONNIER (1952) and CIGANEK (1958, 1961) showed that the VER could be recorded in its totality if the interval between the stimuli was at least 250 msec, i.e. a maximal stimulus frequency of 4/sec. CIGANEK (1958) moreover, indicated that the waves he called IV, V and VI disappeared at a frequency of 5 cps.

The stimulus duration was 20 msec. When the stimulus is superposed on an adaptation light, which is meant to suppress the rod activity, it is advisable to use a stimulus duration under 100 msec. This as well contributes to the prevention of rod contamination in the response, as the rods are less sensitive to stimuli of short duration.

15

Stimuli of the above mentioned frequency and duration were obtained by means of an electromagnetic shutter (type DODT & JESSEN, 1961), placed in the optical pathway of the stimulus light.

II. *Full field stimulation*

In these examinations, the same light source was used for the stimulus, but the set-up was modified. Instead of the white discs a mirror, covering about 15° of the subject's visual field, was placed in the centre of the adaptive field. This mirror reflected the light beam to a diffuser, viz. a thin sheet of white paper, placed just in front of the subject's eye. Obtaining a light spot of 5 cm diameter on the white paper, the latter served as a source of diffuse stimulation, subtending a visual angle of 100°. For the total retinal stimulation, the light flux was reduced from 6.000 lumen/sq m to 60 lumen/sq m, giving the thin white paper a luminance of 1.0 log asb, measured at the site of the subject's eye.

The stimulus frequency, as in local stimulation, was 4/sec; the stimulus duration was 20 msec.

The adaptive field

I. *Local (foveal) stimulation*

The adaptive field was supplied by six fluorescent tubes (Philips no. 33), in front of which a milky glass diffuser and a blue cinemoid filter no. 20 were placed. The luminance of the adaptation light, measured at the plane of the cornea, was 3,3 log lumen/sq m without, and 2,3 log lumen/sq m with the blue cinemoid filter. At a distance of 30 cm from the subject, the adaptive field covered 90° of the visual field. It was interrupted only by the white stimulus discs, placed in the centre of the adaptive field.

VAN LITH & HENKES (1967) demonstrated that with this set-up stray light responses are eliminated. The deviation, which VAN LITH & HENKES (1967) found in the spectral sensitivity curve, viz. a too high blue sensitivity, indicated that some rod activity still had to be present. However, this proved to exert no significant influence on the results when using a white stimulus light, as demonstrated by the good agreement between amplitude of FERG and cone density.

II. *Full field stimulation*

For this purpose we used the same adaptive field as for the recording of FERG and "foveal" VER. Because the test eye was screened by the thin white paper,

16

the luminance of the adaptation light, with the blue cinemoid filter, diminished from 2,3 log lumen/sq m to about 2,0 log lumen/sq m, measured at the plane of the cornea. As the luminance of the stimulus light too was reduced by the white paper, the ratio between adaptation light and stimulus light remained about the same, as compared with local stimulation.

Technical data on the recording equipment

For the recording of ERG and VER a Van Gogh encephalograph as well as a Grass polygraph were used. For the Van Gogh encephalograph type EEG 4, the time constant was set at 1 sec; the filters at 75 cps. For the Grass polygraph Seven, with seven P5A pre-amplifiers, the time constant was set at 0.5 sec and the filters at 500 cps. Both apparatuses were calibrated so that 50 μV at the input gave 1 V at the output.

For recording of the ERG after local (foveal) stimulation, 500 responses were averaged by means of a CAT Mnemotron 400C; after full field stimulation in light adapted state, 250 responses were averaged and after full field stimulation in dark adapted state only 25–35 responses. For recording of the VER always 500 responses were averaged. The counts were made with the aid of a pre-set counter.

The analysis time of the CAT was 250 msec. The resolving power initially was 1/50, but in 1970 this was changed to 1/100. This change did not influence the general configuration of the curve. Synchronization between shutter (DODT & JESSEN) and CAT was achieved with the aid of a type S4H Grass stimulator. A delay of 20 msec was chosen, so that each count by the CAT was started 20 msec before presentation of the stimulus.

The recordings were reproduced on an X-Y plotter, connected with the CAT.

The subject during examination

The subject was placed in supine position with the head slightly raised and supported by a pillow. The adaptive field with the white discs for local stimulation in its centre was so placed that the subject was able to fix the stimulus by looking straight ahead. The centre of the white discs was perforated, and a red fixation light was placed behind the pin-point aperture to help the subject in fixation. When using full field stimulation the subject was asked to "look at the light" with the test eye, which was screened by the thin white paper. In this situation the subject was not aided by a steady fixation point.

All examinations were done in mydriasis unless this was contraindicated.

Mydriasis was applied to ensure optimal standardization of the test. The two eyes were always examined separately. When one eye was being examined, the other eye was covered with a lightproof bandage. The test eye carried a clear contact lens electrode as developed by HENKES. Methyl cellulose was used as conduction fluid. A reference electrode and an earth electrode were placed on the subject's ears.

The subject was generally not wearing his/her glasses during the examination. A study of normal test subjects (see Chapter VI) showed that this exerted but little influence on the amplitude of the local ERG response.

Monitoring during recording was effected with the aid of a Tele-equipment Oscilloscope type S 51, which records the rest potential as reflected in the potential difference between corneal electrode and ear electrode. Ocular movements manifest themselves as large potential alterations between the two electrodes.

For recording of the VER, three scalp electrodes were used, which were placed as follows:
electrode 1: on the inion;
electrode 2: 2 cm above the inion and 2 cm to the right of the cranial midline;
electrode 3: 2 cm above the inion and 2 cm to the left of the cranial midline.

This placement was determined on account of the following considerations:

1. By measuring the potential variation between electrodes placed close together at the site of the projection of the area striata, one records a response which is more or less specific for the visual cortex.

2. It seemed safe to place the electrodes as far as possible from the area where the auditory cortex is localized (in view of the "clicking" sounds procuced by the shutter).

3. SCHREINEMACHERS (1967) in his study also used the above described places. He demonstrated in a few test subjects that, if the retina of, for instance, the right eye is being stimulated in an area nasal to the fovea, a potential can be recorded in the left hemicortex, whereas the right hemicortex shows no activity. Stimulating an area temporal to the fovea, one finds that the right hemicortex in particular shows activity. This finding could be of importance in, for example, examination of patients with homonymous hemianopia.

Two general remarks on the recording of ERG and VER after local stimulation of the retina

1. The subject's ability to maintain fixation of the stimulus was essential to the success of this examination. Yet the reason for the examination in the majority of patients was an often severely diminished visual acuity. Moreover, tenseness

18

on the part of the patient during examination could have an unfavourable effect on his ability to fix the stimulus. Another factor unfavourable to calm fixation was the necessity of applying the contact lens to the test eye. The examination of patients with low visual acuity, however, proved that fixation of the stimulus was generally achieved surprisingly well, provided the dimunition of visual acuity had not occurred long before the time of examination.

2. The examination was feasible only for patients with unclouded refracting media.

CASE MATERIAL AND PROTOCOL OF EXAMINATION

The majority of the patients we examined, had reported for treatment at the Eye Hospital, Rotterdam (The Netherlands). The Departments of Neurology and Neurosurgery of the Dijkzigt Hospital, Medical Faculty, Rotterdam, gave their cooperation for the examination of patients with intracranial disorders. By courtesy of Dr. A. H. C. van Senus we were enabled to examine patients suffering from hereditary optic atrophy of Leber.

The following is a survey of the affections considered in this study, with for each affection the number of patients examined.

Affection	Number of patients
1. Optic neuritis	44
2. Hereditary optic atrophy of Leber	14
3. Traumatic optic atrophy	12
4. Other affections of the optic nerve and retina (glaucoma, juxtapapillary chorioretinitis, iatrogenic opticopathy)	19
5. Intracranial conditions influencing the normal function of the visual system	29

Protocol of examination

The complete examination carried out in the context of our study, encompassed the following activities:

1. Determination of visual acuity with, if necessary, correction by means of test glasses;

2. Determination of visual acuity with correction, if necessary, and with red filter;

3. Slit-lamp biomicroscopy of the refracting media;

4. Determination of intraocular pressure with the applanation tonometer in patients over age 45;

5. Funduscopy in mydriasis;

6. Examination of the visual fields with the GOLDMANN perimeter;

7. Examination (in selected cases) of the central visual field by the method of BJERRUM;

8. Examination of colour discrimination, using the Hardy, Rand, Rittler test, the 15HUE test and the anomaloscope (Raleigh equation) for each eye separately;

9. Electro-ophthalmological examination, always consisting of the recording of ERG and VER after stimulation of the central fovea.

For each eye we recorded the response to 500 flashes of the 8° stimulus then that to 500 flashes of the 5° stimulus, and finally the response to 500 flashes of the 3° stimulus. Actual practice revealed that it was useful to repeat the first 8° recording because the patient, then familiar with what was being required, not infrequently achieved better fixation.

The responses were recorded on four channels, viz.:

Channel IV	: recording of the FERG
Channels I, II, III	: recording of the VER
Channel I	: inion electrode – electrode over right occipital cortex: 1–2 lead
Channel II	: inion electrode – electrode over left occipital cortex: 1–3 lead
Channel III	: electrode over right occipital cortex – electrode over left occipital cortex: 2–3 lead.

On the basis of the simultaneously recorded ocular movements (see page 18), the curves were marked:
1. optimal fixation;
2. satisfactory fixation;
3. insufficient fixation.

If possible the examination was then continued by the recording of ERG and VER after full field stimulation in light adapted and in dark adapted state. Sometimes, however, the total duration of the examination was too long for the patient: in some of these cases one of the two examinations could be completed, while in other cases both had to be omitted.

In a number of cases a general photopic and scotopic ERG was recorded by the method used as routine in the Rotterdam Eye Hospital. In some patients the light peak-dark trough ratio in the electro-oculogram was recorded as well.

1. The ERG is recorded with the aid of a xenon flash in a lamphouse with a parabolic mirror. A milky glass diffuser is always placed in front of the lamphouse and – if necessary – neutral and colour filters can be used as well. The scotopic ERG is recorded from the dark adapted retina with the aid of blue flashes (cinemoid filter no. 20) given in a frequency of 1/sec with three luminance steps, 1.0 log unit different from each

other; the highest luminance was obtained with 0.01 Joule. The photopic ERG is recorded from the light adapted retina with the aid of red flashes (cinemoid filter no. 6), given in a flash frequency of 4/sec and a luminance obtained with 0.1 Joule. Light adaptation is achieved with a lamphouse containing six fluorescent tubes (Philips no. 33), which subtends a visual angle of 90°. A milky glass diffuser and a blue filter (cinemoid no. 20) are placed in front of the lamphouse.

2. The light peak/dark trough ratio in the EOG is determined according to the method of ARDEN (1962).

Evaluation of ERG and VER after stimulation of the central fovea

In cases of an affection of the visual pathways with diminished visual acuity, the ability of fixation is reduced. It seemed reasonable, as a consequence, to assume that the function of the central fovea was intact if a "normal" response was obtained in one of the recordings (8°, 5°, 3°). The criteria to be met by a response in order to be considered normal are discussed in Chapter VI (on findings in normal subjects).

The VER elicited by stimulation of one eye was compared, where possible, exclusively with that elicited by stimulation of the other eye. The following criteria of evaluation were used:
1. well developed $(+)$
2. discernible $(\pm)$
3. absent $(-)$

The choice of these criteria is elucidated in Chapter VI.

Evaluation of ERG and VER after full field stimulation of the retina

The ERG was again evaluated on the basis of the criteria established in Chapter VI. For the VER the same qualifications were used as for those recorded after local stimulation of the retina.

22

ERG AND VER AFTER FOVEAL AND FULL FIELD STIMULATION IN NORMAL SUBJECTS

The electro-ophthalmological method of investigation was used in an examination of a number of test subjects in order to establish criteria for an evaluation of findings in patients. One of the prerequisites was that, like the patient, the test subject should not be familiar with the nature of the examination.

All test subjects were able to declare that they were in good health. General ophthalmological examination, which routinely preceded the electro-ophthalmological examination, never disclosed any abnormalities other than some minor anomalies of refraction in a few cases.

A. *ERG and VER after local (foveal) stimulation*

It proved impossible in actual practice to examine an identical number of individuals in the various age groups. We did get the cooperation of a number of undergraduates (age 20–25). The group of test subjects also included patients with an unilateral eye affection such as a traumatic lesion or cataract; these patients had consented to submit to electro-ophthalmological examination of the unaffected eye.

Graph I presents the age distribution of 43 test subjects, in whom we examined a total of 66 eyes.
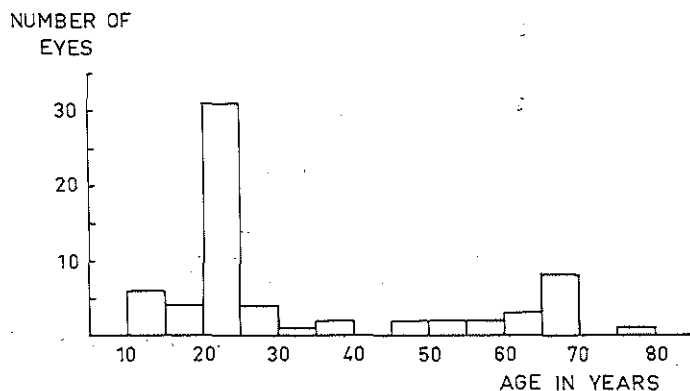
Graph. I
Age distribution of 43 test subjects, in whom 66 eyes were examined.

1. *The FERG*

As criteria for evaluation of the FERG we may consider:

a. The amplitude of the photopic b-wave.

b. The amplitude of the a-wave.

a. Amplitude of the photopic b-wave of the FERG* after stimulation with field
size 8°, 5° and 3°

The results of this study are shown in graphs II, III and IV.
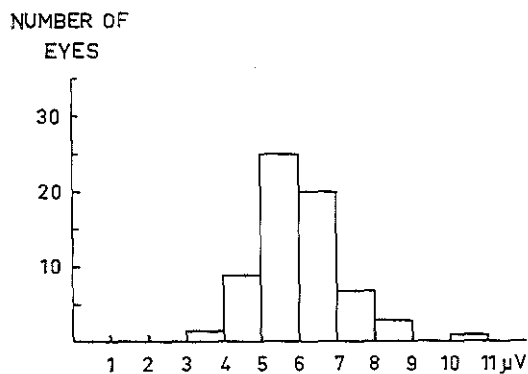
Graph. II

Amplitude of the photopic b-wave of FERG with a stimulus of 8° subtended visual
angle in normal subjects.
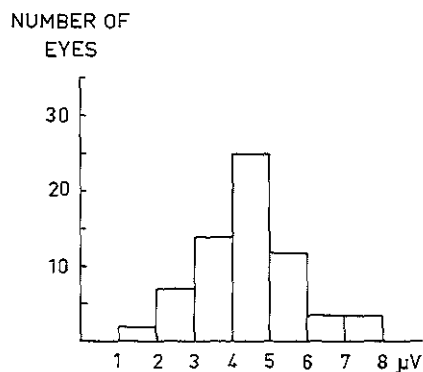
Graph. III

Amplitude of the photopic b-wave of FERG with a stimulus of 5° subtended visual
angle in normal subjects.

---

* This was measured from the trough of the a-wave.
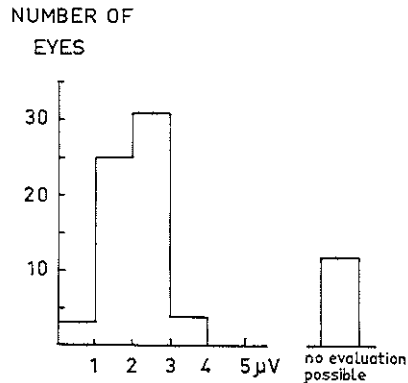
Graph. IV

Amplitude of the photopic b-wave of FERG with a stimulus of 3° subtended visual angle in normal subjects.

In an effort to establish whether the age of the test subject might influence the amplitude of the photopic b-wave, we divided our test subjects into two groups: a large group of 30 younger individuals (age 10–40), in whom 48 eyes were examined, and a smaller group of 13 older individuals (age 45–80), in whom 18 eyes were examined.

The mean amplitude of the photopic b-wave was:

	8°	5°	3°
Younger group	6.25 μV	4.46 μV	2.69 μV
Older group	5.92 μV	4.02 μV	2.70 μV

The intergroup differences were so small that it was considered sufficient to establish normal values applicable to the entire age group 10–80.

Plotted in graphs, our data proved to approximate the shape of a gaussian curve, and we therefore decided – for practical use – to distinguish:

normal value = mean value $\pm$ 1 × standard deviation
borderline value = any value between the mean value $\pm$ 1 × standard deviation, and the mean value $\pm$ 2 × standard deviation
subnormal or supranormal value = any value outside the above mentioned limits

	8°	5°	3°
Mean amplitude of the photopic b-wave (all test subjects)	6.16 μV	4.34 μV	2.69 μV
Standard deviation	1.10 μV	1.29 μV	0.74 μV

We now propose the following ratings:

Photopic b-wave of FERG after stimulation with field size 8°:
5.1 μV – 7.2 μV: normal value
4 μV – 5.1 μV ⎫
7.2 μV – 8.3 μV ⎭ borderline values

Photopic b-wave of FERG after stimulation with field size 5°:
3.0 μV – 5.6 μV: normal value
1.7 μV – 3.0 μV ⎫
5.6 μV – 6.9 μV ⎭ borderline values

Photopic b-wave of FERG after stimulation with field size 3°:
1.9 μV – 3.4 μV: normal value
1.2 μV – 1.9 μV ⎫
3.4 μV – 4.2 μV ⎭ borderline values

Discussion

The photopic b-wave is a reflection of retinal activity at the level of the layer of bipolar cells of the central fovea (cf. DOWLING 1970). In this part of the retina, the photopic system has by far the highest cone density (ØSTERBERG 1935). VAN LITH & HENKES (1967) have demonstrated that, in our test arrangement for the recording of a local photopic ERG, the response elicited by stimulation of the central fovea is higher than that elicited by stimulation of any other part of the retina. A subnormal photopic b-wave of the FERG therefore indicates:
1. insufficiently centric fixation of the stimulus, or
2. the presence of abnormalities at the level of the bipolar cell layer in the area of the central fovea.
   In patients with an extraocular affection of the visual pathway, the retina is

26

generally intact (as far as is known) up to the level of the ganglion cells. In our study, the recording of a normal photopic b-wave therefore proves that the simultaneously recorded VER was elicited by stimulation of the central fovea.

The influence of anomalies of refraction on the amplitude of the FERG was generally negligible. This was demonstrated by the findings obtained in a few (trained) test subjects (with corrections of S-8 and S + 3,5 = C + 1.75 × 90°). There was no significant difference in amplitude between photopic b-waves recorded with and those recorded without correction. Nevertheless, for greater certainty, subjects with a correction exceeding 6 dioptres were asked to wear their glasses during the examination.

b. Amplitude of the a-wave of the FERG after stimulation with field size 8° and 5°

Graphs V and VI show amplitudes of the a-wave after stimulation with field size 8° and 5°, as recorded in normal subjects. The a-wave after stimulation with field size 3° was usually so small that accurate measurement of its amplitude was impossible.

NUMBER OF
EYES
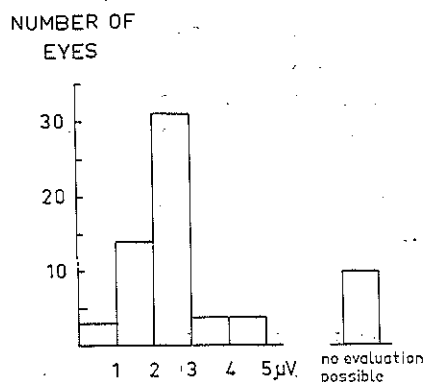
Graph. V

Amplitude of the a-wave of FERG with a stimulus of 8° subtended visual angle in normal subjects.

The a-wave of the FERG after stimulation of the retina by means of a stimulus field of 8° diameter, varies in amplitude between 0 and 5 μV, with a maximum representation between 2 μV and 3 μV. For a field of 5° diameter we found an a-wave with an amplitude of 1–3 μV (range: 0–4 μV).

The a-wave reflects the activity of the photoreceptors after photic stimulation (BROWN 1968; PENN & HAGINS 1969; DOWLING 1970).

27

NUMBER OF
EYES
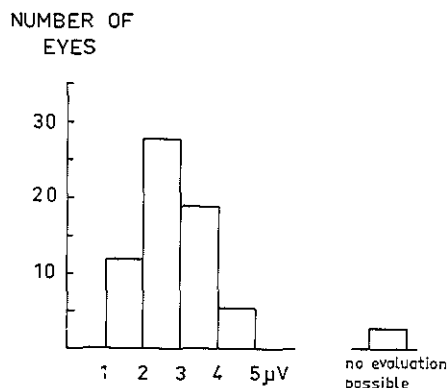
Graph. VI

Amplitude of the a-wave of FERG with a stimulus of 5° subtended visual angle in normal subjects.

VAN LITH (1970), using the same test arrangement as that applied by us, found a higher amplitude of the a-wave in the local ERG after eccentric stimulation than after stimulation of the central fovea (VAN LITH stimulated the retina up to about 16° eccentric from the foveola). A similar observation was reported as early as 1967 by AIBA, ALPERN & MAASEIDVAAG.

Disorders of retinal circulation are known to enlarge the a-wave, at least in the total ERG, by virtue of elimination of the influence of the b-wave complex (see also JACOBSON: Clinical Electroretinography 1961).

In our study, we found that the FERG showed an average ratio of 2.9:1 between the amplitude of the photopic b-wave and that of the a-wave after stimulation with field size 8°. After stimulation with field size 5° this ratio averaged 2.5 : 1.

If in examination of patients a ratio of less than 2.5 : 1 were found, then this might be ascribed to two different causes: 1. enlargement of the a-wave per sé; 2. enlargement of the a-wave by reduction of the photopic b-wave (as observed in disorders of retinal circulation).

In view of these considerations, the a-wave must be regarded as a less reliable criterion for evaluation of the FERG.

In this study, therefore, the FERG will be evaluated exclusively on the basis of the amplitude of the photopic b-wave.

2. *The VER after local (foveal) stimulation*

In our evaluation of these VERs, we focused on the following questions:

28

a. Do VERs recorded from different test subjects show a disparity of configuration and/or amplitude?
b. Is the VER recorded after stimulation of one eye different in configuration and/or amplitude from that recorded after stimulation of the other eye in the same test subject?

Figure 7, collates the VERs recorded after local (foveal) stimulation with field size 8° from each of the two eyes in six test subjects. These VERs, each made up of three leads, were so selected from the material that the greatest possible differences were apparent.

Studying these VERs, it seems impossible to establish a sequence of positive and negative peaks which can be traced in all corresponding leads (i.e. either in the 1–2 leads, or in the 1–3 leads, or in the 2–3 leads).

Nevertheless, the recordings of the VER after foveal stimulation in test subjects do warrant an important conclusion: in all test subjects the VERs after local (foveal) stimulation were well developed or at least discernible. In no case was the local VER of a test subject absent. (This also implies that, in normal individuals, it never happened that two or more electrodes were localized in an equipotential field during recording. For in that case the recording would have had to be rated as "VER absent".)

In all cases, the similarity in amplitude and configuration between the VER recorded after stimulation of one eye and that recorded after stimulation of the other eye in the same test subject, was so marked that the VERs were rated the same: either both well developed or both discernible.

In our discussion of patients it will be shown that the local VER from one eye was sometimes rated e.g. well developed, whereas the corresponding VER from the other eye was rated discernible. In these cases, we believe, there was a difference in the VERs obtained after stimulation of each of the two eyes, which can be ascribed to a difference in conduction between the two optic nerves (provided that the simultaneously recorded FERGs from both eyes were identical).

Some test subjects were unable to maintain adequate fixation of the stimulus. This resulted in a FERG rated subnormal or borderline value. If the FERG was subnormal, then the simultaneously recorded VER was rated discernible. If the FERG was of borderline value, then the VER was well developed.

FIGURE 7

VERs AFTER FOVEAL STIMULATION (8° SUBTENDED VISUAL ANGLE)

30
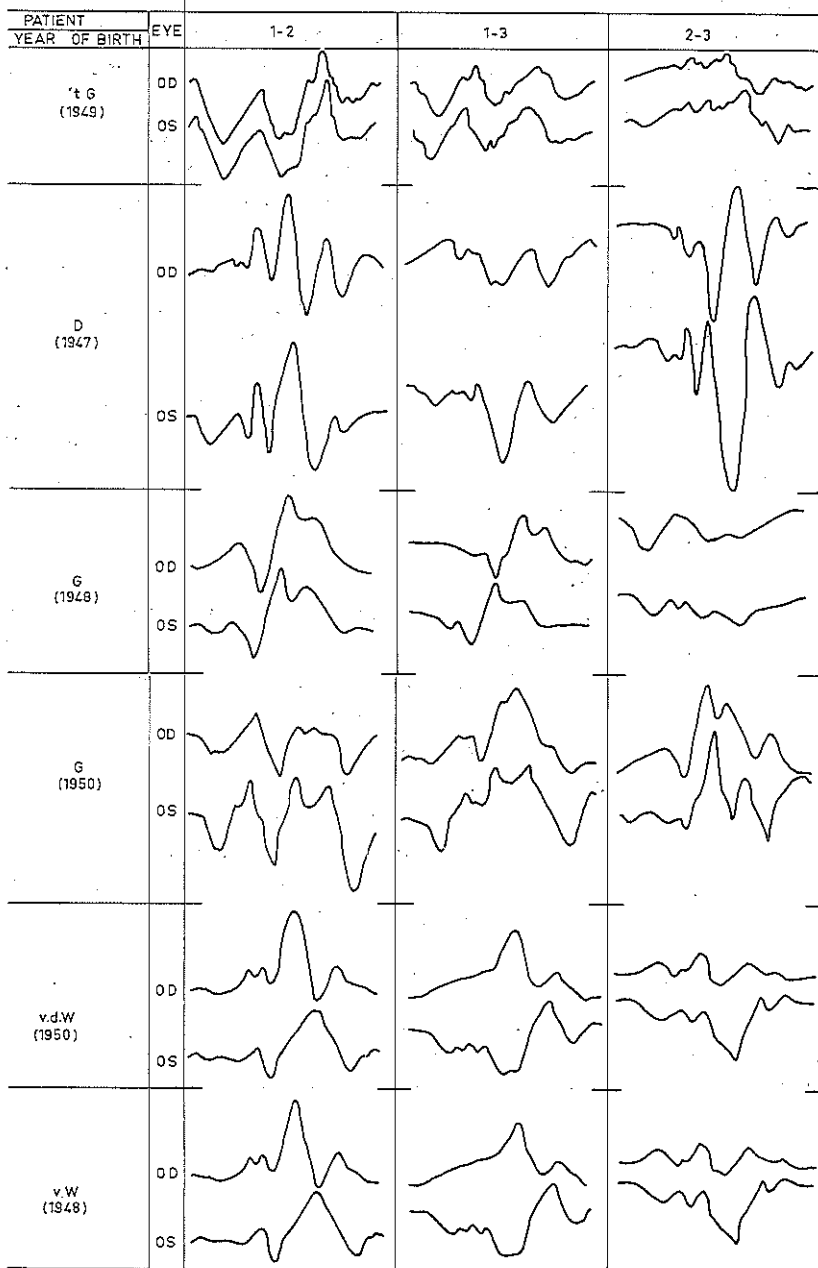
B. *ERG and VER after full field stimulation in light adapted
and in dark adapted state*

Due to circumstances, this part of the study was carried out in other test sub-
jects than those mentioned above.

Graph VII shows the age distribution in this second group of 20 test subjects,
in all of whom both eyes were examined.
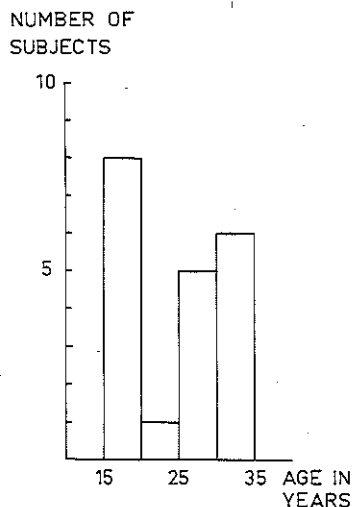
Graph. VII

Age distribution in the second group of 20 test subjects, in all of whom both eyes were
examined.

3. *The ERG after full field stimulation in light adapted and in dark adapted state*

These ERGs too, were evaluated on the basis of the amplitude of the b-wave.
Graphs VIII and IX present the results obtained.

For the ERG after full field stimulation in light adapted and in dark adapted
state, normal values were established by determination of 1) the mean amplitude
of the b-wave, and 2) the standard deviation. (The results, plotted in a graph,
constitute no perfect gaussian curve but approximate it sufficiently to warrant
evaluation of normal values in this manner for routine clinical use.)

31

NUMBER
OF EYES
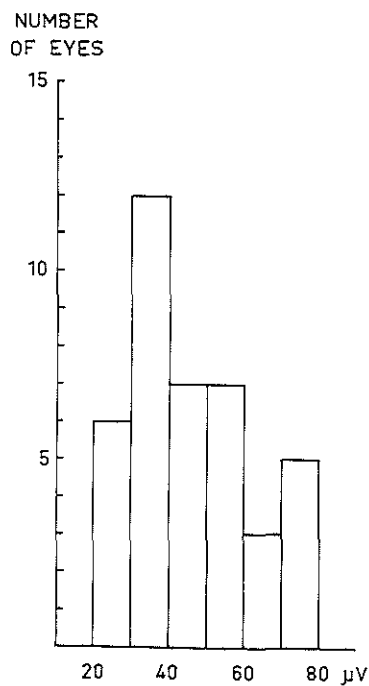
Graph. VIII.

Amplitude of the photopic b-wave of the ERG after full field stimulation in light adapted state.

NUMBER
OF EYES
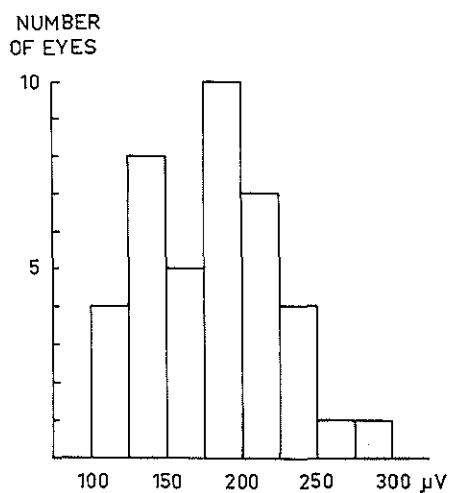
Graph. IX

Amplitude of the b-wave of the ERG after full field stimulation in dark adapted state.

The ERG after full field stimulation in light adapted state:

Mean amplitude of (photopic) b-wave: 44.9 μV.
Standard deviation   : 14.9 μV.

30 μV – 60 μV: normal value
15 μV – 30 μV ⎫
60 μV – 75 μV ⎬ borderline values

The ERG after full field stimulation in dark adapted state:

Mean amplitude of scoto-photopic response: 179 μV.
Standard deviation   : 43 μV.

136 μV – 222 μV: normal value
 93 μV – 136 μV ⎫
222 μV – 265 μV ⎬ borderline values

It has been pointed out that, in the test arrangement for recording of the ERG after full field stimulation, the eye was screened by a sheet of white paper. This made it impossible to verify whether the subject was properly looking at the stimulus light. The subject often found it difficult to know where he/she had to look, because a fixation point was absent. These circumstances may have contributed to the fact that fairly high values were found for the standard deviation.

4. *The VER after full field stimulation in light adapted and in dark adapted state*

Figure 8 and 9 collate the VERs most widely different in configuration and amplitude from six test subjects.

These curves warrant the deduction that, after full field stimulation as well, there was a fair similarity in configuration and amplitude between the VERs recorded after stimulation of each of the two eyes in the same test subject.

The VERs recorded after full field stimulation in light adapted and in dark adapted state can therefore be evaluated in the same way as those recorded after local (foveal) stimulation.

FIGURE 9

VERs AFTER FULL FIELD STIMULATION OF THE RETINA IN DARK ADAPTED STATE

PATIENT / YEAR OF BIRTH	EYE	1-2	1-3	2-3
H (1939)	OD / OS			
M (1936)	OD / OS			
R (1957)	OD / OS			
M-C (1937)	OD / OS			
B (1951)	OD / OS			
B (1948)	OD / OS			
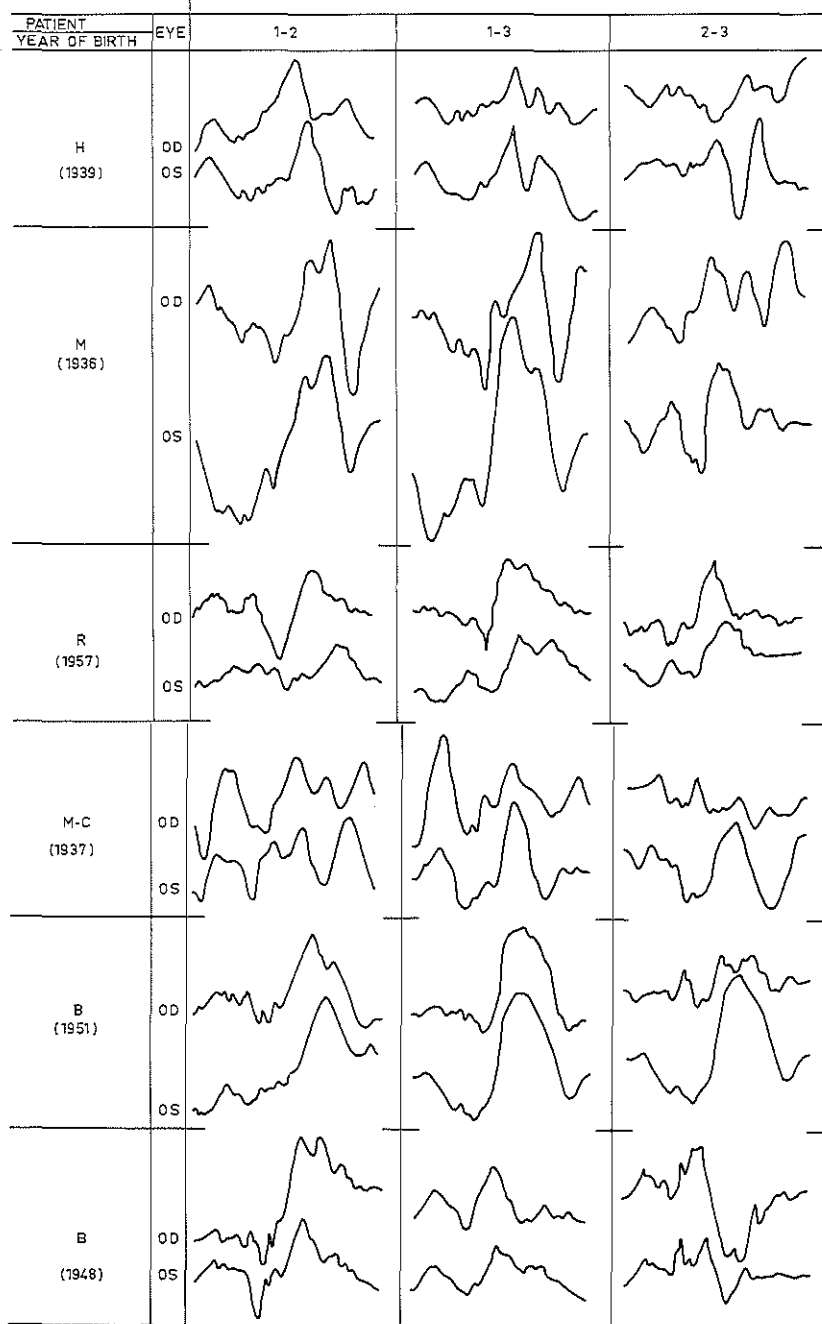
OPTIC NEURITIS

Optic neuritis is an affection characterized by the following phenomena:

1. Acute diminution of visual acuity, usually unilateral but sometimes bilateral. Another possibility is that visual acuity diminishes first in one eye, and subsequently in the other.

2. A sensation of pain in and behind the eyeball, particularly at abduction, or when looking up, and in response to external pressure on the eye.

3. A peculiar pupillary reaction in which, although both direct and consensual reactions are present, the contraction is not maintained under bright illumination so that the pupil slowly dilates again while the light is kept upon the eye.

4. No objectively demonstrable abnormalities of refracting media and fundus that might be related to the acute diminution of visual acuity.

5. Visual field studies disclose a central scotoma which can show inter-individual variations in intensity and extent.

In some reports, hyperaemia of the disc is listed among the manifestations of optic neuritis. This hyperaemia should be regarded as indicating that the process extends to the disc. In these cases, therefore, the designation "papillitis" seems more appropriate. The further course in these cases may be characterized by occurrence of haemorrhages and oedema in and around the disc. The term "papillitis" is sometimes used in distinction from the term "retrobulbar neuritis", which implies a localization of the process elsewhere in the optic nerve. In this context it is to be noted that, in its bilateral form, the process can also be localized in the optic chiasm.

The central scotoma in the visual field suggests that in most cases the process is confined, at least initially, to the maculopapillary fibre bundle of the optic nerve.

An investigation into the aetiology of optic neuritis reveals that the process can be caused by a wide variety of affections. It also discloses that not all of these cases involve a true inflammatory process, as the term "optic neuritis" would seem to imply (see vascular origin, page 37). Finally, it is evident that in many cases the aetiology of the neuritis cannot be established with certainty at the time of its onset.

A primary inflammatory process of the optic nerve is generally regarded as exceedingly rare.

VAN DER HOEVE (1922, 1925) believed that an inflammatory process in the paranasal sinuses is a common aetiological factor. The close anatomical relationship between the posterior sphenoidal and ethmoidal sinuses on the one hand, and the optic canal on the other, in his opinion permit a transmission of an inflammatory process to the optic nerve.

WHITE (1928) and WILMER (1930) assumed that the cause might be "focal sepsis".

ADIE (1930) focused attention on multiple sclerosis; and many publications indicate that multiple sclerosis is indeed among the principal causes. Multiple sclerosis was reported as a cause of optic neuritis by:

BENEDICT (1933)   : in 68.8% of 225 cases
CARROLL (1952)   : in 32 % of 240 cases
SUGAWARA (1958)   : in 28.6% of 225 cases
OTRADOVEC & VOTOCKOVÁ (1962): in 25.1% of 270 cases.

GORNIG & BISCHOF (1969) studied the age distribution of 401 cases of optic neuritis and found that multiple sclerosis is present in particular in patients who develop optic neuritis between age 20 and age 40. In this age group there is a female predominance.

In order to establish whether a case involves multiple sclerosis, a sufficient follow-up period is of paramount importance. Only too often, optic neuritis is observed as a solitary symptom, present years before additional symptoms develop which clinch an ultimate diagnosis of multiple sclerosis. OTRADOVEC & VOTOCKOVÁ found a correlation between cases in which multiple sclerosis was diagnosed with certainty and the increase in the number of years during which the patients had been followed up.

SUGAWARA, GORNIG & BISCHOF reported, finally, that in age group 20–40 the process relatively often takes the course of a retrobulbar neuritis.

A vascular origin of optic neuritis merits most careful consideration in cases which become manifest after age 50 (GORNIG & BISCHOF 1969). In the age group over 50 there is a male predominance, as noted by PIETRUSCHKA (1964) and GORNIG & BISCHOF (1969). The same authors mentioned that in patients over 50 the process not uncommonly takes the course of a papillitis.

Prior to World War II, GASTEIGER wrote in "Gegenwarts Probleme der Augenheilkunde" (1937) that arteriosclerosis was receiving insufficient attention as a possible cause of optic neuritis. A survey of the pertinent literature shows that a vascular origin is more frequently assumed in more recent publications:

CIBIS (1939)   : in 1.1% of 189 cases
DREYER (1947)   : in 2.6% of cases studied

OTRADOVEC & VOTOCKOVÁ (1962): in   8.7% of 270 cases
JACOBSEN (1964)   : in 22.1% of cases studied
PIETRUSCHKA (1962)   : in 38.4% of 164 cases
GORNIG & BISCHOF (1969)   : in 20.2% of 401 cases.

PIETRUSCHKA was among the few authors who elucidated their exact meaning in assuming a vascular history in cases of optic neuritis. In a series of 63 patients (45 male and 18 female), he found temporal arteritis as a cause in 5; a pseudo-Foster Kennedy syndrome existed in 8 cases, and in 1 case an intracranial aneurysm was the cause of a homolateral retrobulbar neuritis (this was established when rupture of the aneurysm led to the patient's acute death). In the majority of cases, however, we are confronted with tentative diagnoses based on signs of general arteriosclerosis found by representatives of various disciplines. Carotid angiography takes a prominent position in these investigations. In the context of differential diagnosis, mention should be made also of diabetic opticopathy, although the above mentioned author does not explicitly state this.

Other, less common causes of optic neuritis are:

1. intoxications:

a. alcohol and/or tobacco;

b. therapeutic agents such as streptomycin, ethambutol, chloramphenicol, isoniazid, iod-chlorhydroxychinolin, etc.;

c. industrial products such as organic arsenic compounds, lead, carbon monoxide, trichlorethylene, thallium, aniline, dinitrobenzene, chlordinitrobenzene, trinitrotoluene;

2. hereditary diseases, of which hereditary optic atrophy of Leber is one of the most prominent;

3. inflammatory processes in the vicinity of the optic nerve: uveitis, chorioretinitis, epidemic meningitis, meningitis secondary to otitis media, intraorbital inflammatory processes;

4. diseases accompanied by demyelination of nerve fibres: acute disseminated encephalitis, optic neuromyelitis of Devic, Schilder's disease;

5. infectious encephalitis;

6. systemic diseases:
   diabetes, lymphogranulomatoses, collagen diseases;

7. tuberculosis, syphilis and mycoses.
   (data derived in part from Duke Elder 1971)

Optic neuritis is rare in young people. KENNEDY & CARROLL (1960) described 41 cases, some of which were found to be related to malnutrition or diabetes; in a few cases, measles had preceded the process. In 30 cases the aetiology remained obscure.

MEADOWS (1969) described 44 cases, 9 of which were unilateral while 35 were bilateral. He never observed unilateral optic neuritis prior to age 10 (the nine unilateral cases were in patients aged 10–16). A choked disc was found in 3 of the 4 cases observed in the acute stage. Five patients were not seen until later in life, when neurological symptoms had become manifest which suggested the possibility of multiple sclerosis. The history of these patients included a period of unilateral diminution of visual acuity which had occurred at about age 15. MEADOWS consequently assumed that unilateral optic neuritis during puberty can be an early manifestation of multiple sclerosis. His 35 cases of bilateral optic neuritis showed no other neurological changes; not even during the follow-up period. In none of these cases could the aetiology be established.

Hereditary optic atrophy of Leber not uncommonly has its onset in early childhood or puberty. VAN SENUS (1963) found that the onset of symptoms occurred prior to age 20 in 39.2% of 286 cases (and prior to age 15 in 13.3% of the 286 cases).

Prognosis

The prognosis of optic neuritis is generally described as favourable in all the aforementioned age groups.

I. *Age group under 20*

MEADOWS described the prognosis, particularly in bilateral cases, as fair. HIERONS & LYLE (1959), who studied 13 children with bilateral optic neuritis, reached a similar conclusion. The prognosis of hereditary optic atrophy of Leber will be separately discussed in the relevant section of this study (chapter VIII).

II. *Age group 20–40*

RAWSON et al. (1966) studied 150 fresh cases of optic neuritis and observed recovery to normal visual acuity in 70–80%. In 20–30% of cases a diminution of visual acuity and/or a disturbance of the visual field persisted. SUGAWARA,

too, found that the prognosis is favourable in the majority of cases which become manifest between age 20 and age 30.

III. *Age group over 50*

PIETRUSCHKA described the prognosis in this age group as encouraging. Adequate lasting improvement of visual acuity was achieved in 41.2% of 63 cases; moderate improvement was recorded in 25.4%, and no improvement of visual acuity occurred in 33.4% of cases.

Pathology and pathophysiology of optic neuritis

Our discussion of these subjects focuses mainly on changes which occur in the optic nerve when multiple sclerosis is or subsequently proves to be the cause of the process. This choice has been made because, in our discussion of personal observations, the emphasis will be on results obtained in younger, mostly female patients.

Preceding the discussion we should present some data of a more general nature on the anatomy and physiology of the optic nerve, and in particular of the maculopapillary fibre bundle.

The optic nerve is a central nerve tract which, anatomically, differs from peripheral nerves in that the central extracellular space is much smaller. In fact the outer myelin lamellae can be found fused (PETERS 1960). Moreover, while in the peripheral nerve fibre a single Schwann cell constitutes only that segment of the total myelin sheath that is localized between two nodes of Ranvier, in the central nervous system a single oligodendrocyte can form parts of myelin sheaths of several nerve fibres (BUNGE 1968). In nerve fibres of the central nervous system, the space between two consecutive segments of the myelin sheath is larger than that in the fibres of the peripheral nervous system at the node of Ranvier. The manner in which the myelin lamellae end at the constrictions is likewise believed to be different, (UZMAN & VILLEGAS, 1960, PETERS, 1966). Finally, the fibres of the central nervous system have no enveloping basement membrane – not even at the constrictions of the myelin sheaths.

POLYAK's description of the distribution of nerve fibres in the optic nerve (1957) has so far remained the most widely accepted. POLYAK distinguished two types of fibre: "thin fibres" and "thick fibres". Both types of fibre have a myelin sheath. The so-called maculopapillary fibre bundle consists almost exclusively of "thin fibres".

For the peripheral nervous system it is assumed that thin fibres conduct

more slowly than thick fibres. The conduction velocity is expressed in the Hursch formula, which states that the conduction velocity at 37°C is six times the figure indicating the diameter of the axon in μ. For the central nervous system, however, this is by no means certain. If the thick nerve fibres in the optic nerve should conduct more quickly than the thin fibres, then the conclusion should be that impulses from the peripheral retina attain the cortex earlier than impulses generated by stimulation of the central retina. As early as 1948, CHACKO pointed out that the composition of the myelin sheath, as well, can be of importance for the conduction velocity. A difference in structure between fibres of the central and those of the peripheral nervous system may also result in a difference in conduction velocity.

It has been assumed (although little is actually known about it) that the fibre of the central nervous system, like that of the peripheral nervous system, conducts impulses by a mechanism known as saltatory conduction. This means that the impulse is conducted as a series of depolarizations in the nerve fibre, each subsequent depolarization always occurring at the next interruption of the myelin sheath in the course of the nerve fibre.

Pathology of optic neuritis in multiple sclerosis

Neurologists have come to know multiple sclerosis, not only as a disease with a widely varying symptomatology (to be left undiscussed here) but also as a condition with a very variable clinical course. There are chronic progressive as well as subacute forms, and in some cases the course is acute to apoplectiform.

The central process in the pathology of multiple sclerosis is the disintegration of the myelin sheaths of the nerve fibres. According to WALSH (1957), ANDERSON (1960) and HOGAN & ZIMMERMAN (1962), the changes in the optic nerve can be described as follows. In the early stage of the formation of a "focus" which can be 1 mm to 5 cm in diameter, there is an infiltration of mostly lymphocytes and plasma cells; the infiltrate contains few leucocytes when compared with that of a "real" inflammatory process of the nerve. Inflammatory cells accumulate in particular in the perivascular spaces. The type of infiltration is the same as that seen in experimental allergic encephalitis. All structures of the nerve fibre become oedematous in the area of the developing focus, the oedema also involving the axis cylinders. The process differs from that which occurs in the case of a choked disc due to increased intracranial pressure. This is evident from the immediately disturbed visual functions. BONAMOUR et al. (1968) maintained that this difference results from the influence of a toxic factor:

The presence of the inflammatory process in the optic nerve causes the release of toxins which almost immediately produce a pathological change in the walls of the small vessels supplying blood to the nerve fibres. The released toxins, together with the vascular changes and the resulting oedema, which in turn impedes the blood supply, cause the occurrence of metabolic abnormalities in the nerve fibres. The oxidation-reduction process is disturbed, and accumulation of lactic acid and pyruvic acid occurs.

The principal localization of the process is the maculopapillary fibre bundle, but it is possible that the optic nerve is affected throughout its cross section.

As a result of the process, the myelin sheaths disintegrate, and the material thus released is phagocytized by microglia cells.

The axis cylinders generally remain intact, unless they succumb to excessive pressure as a result of the oedema or to the influence of toxins. ANDERSON believed that the functional recovery which can occur following an attack of optic neuritis, is attributable to the continued intactness of the axis cylinders.

Once the inflammatory reaction abates, the area is infiltrated by astrocytes; this innidiation of astrocytes is the so-called "plaque formation".

WALSH concluded his description of the pathology of optic neuritis with the statement that, in mild cases of papillitis and retrobulbar neuritis, total functional recovery of the optic nerve can occur. A disc which previously showed pathological changes, can regain a normal appearance.

In our opinion, an important question remains unanswered: is it possible that the attack takes its course without real demyelination of the fibres in the area of the focus if:

a. optic neuritis occurs as an isolated early symptom of multiple sclerosis which is not to become manifest until later, and,

b. complete functional recovery occurs (normal visual acuity, normal visual field, no atrophy of the disc).

We intend to revert to this question in the discussion of our personal observations. A second question is whether complete functional recovery of the optic nerve is possible if optic neuritis is accompanied with demyelination. The answer to this question is mainly contained in what we know of the pathophysiology of the demyelinated fibre of the central nervous system. Again with reference to personal observations, this question will be discussed in detail later.

Pathophysiological data on disturbed conduction in the central nervous system

Few pertinent data are available. The most interesting information is probably that obtained from experiments in cats by MCDONALD & SEARS (1969, 1970).

42

After dissecting the spinal cord of the cat at the transition from thoracic to lumbar vertebrae, they injected a minute quantity of diphtheria toxin into the dorsolateral sulcus.

Twelve to twenty-eight days later, they studied the antidromic conduction in the area involved in the injection, i.e. that encompassing the posterior column, the dorsal horn and the dorsal portion of the lateral funiculus.

These electrophysiological experiments were followed by a study of the pathological changes in the above mentioned structures. These changes largely consisted of demyelination of nerve fibres. Most of the axis cylinders were intact in their course through the lesion area. Only a small proportion of the fibres showed so-called Wallerian degeneration (in this type of degeneration, the peripheral parts of the nerve fibre degenerate with their myelin sheaths after transection).

An important feature is that, peripheral to the lesion (peripheral in relation to the cell body), the nerve fibre was intact with the corresponding myelin sheath. The authors believed that demyelination might have resulted from a direct effect of the diphtheria toxin on the oligodendrocyte.

Although the cause of the above mentioned lesion was of course quite different from that in multiple sclerosis, both lesions have the same morphological characteristic: demyelination.

The electrophysiological findings were the following.

1. When a large lesion had been inflicted with the aid of the diphtheria toxin, conduction at the site of the lesion was totally blocked. But conduction from the cell body as far as the lesion, and that from the lesion further peripherally, were normal . This is not the case in a Wallerian degeneration. This is why the authors attached such great importance to a study of antidromic conduction: it enabled them to differentiate between the two disturbances in conduction.

2. In smaller lesions, conduction continued to be possible in some fibres. In that case the conduction at the site of the lesion was characterized by a lower rate of velocity, an increased refractory period and a diminished capacity to conduct trains of impulses of high frequency. The degree of alteration of the conduction differed for different nerve fibres: some conducted quite normally, whereas others showed the above mentioned changes in varying degrees.

This difference in (patho)physiological behaviour is consistent with the electron-microscopic findings indicating that, close together in the lesion area, fibres were encountered in various stages of demyelination as well as remyelination.

Although the authors succeeded in demonstrating experimentally that the conduction of a single fibre was involved, they were unable to identify the same

fibre in the electron-microscopic specimen. Consequently they caution against any attempt to explain the electrophysiological findings merely from the pathological anatomical changes, which have been found.

The authors finally point out that possibly not only demyelination plays a role in disturbances of conduction. Such factors as nodal widening, compression of fibres caused by oedema and the change in the composition of the intercellular fluid may also be causative. Finally, the diphtheria toxin may have a direct effect on the axon.

Of course the results of an experimental demyelination in the spinal cord of the cat cannot as such afford an explanation of the pathophysiological behaviour of processes in the human optic nerve which are (or are believed to be) accompanied with demyelination. Nevertheless we wish to stress one particular point: the probability of a relationship between the degree of demyelination and the degree of disturbance in conduction, and particularly in the conduction velocity. Here we may well have the germ of a solution of the question as to why the terminal state after an attack of optic neuritis can be so widely different (this terminal state can range from permanent loss of function to complete functional recovery). We intend to revert to this question in the discussion of personal observations.

Personal observations

PATIENT I, female, born 19th June 1939

When this patient was first seen at the out-patient clinic of the Rotterdam Eye Hospital, 21 months before she was hospitalized with bilateral optic neuritis, she complained of diplopia. During the preceding period she had felt tingling sensations and tremors throughout the body. Ophthalmological examination revealed paresis of the internal and external rectus muscles ODS; visual acuity of both eyes was 1,0, with correction (S-5.5 and S-5, respectively). The patient was referred to the neurologist, who found her to be suffering from multiple sclerosis.

Later – a few days prior to admission – the patient noticed that her visual acuity had deteriorated, particularly when she was tired. Ophthalmological examination yielded a diagnosis of bilateral optic neuritis.

An internal examination during this patient's stay in hospital disclosed that she had suffered of tuberculosis.

The patient was clinically treated by retrobulbar application of 40 mg triamcinolone acetonide (Kenacort A40) OD, and twice-weekly retrobulbar application of 20 mg dexamethasone 21-phosphate (Decadron) OS. Further

medication included vitamin B¹, vitamin B⁶ and vitamin B¹², initially by intra-muscular injection and subsequently by mouth.

I. *Examination at admission*

Visual acuity	OD 5/300	OS 0,2–0,3
Media	no abnormality	no abnormality
	pupil diameter OD > OS, slow reaction to light	
Fundi	no abnormality	no abnormality

Fig. 10

Patient I, ♀, Age: 30 years
First examination: Fovea-ERG (8°), VER

45

Visual fields (Goldmann)	absolute central scotoma extending 5° from fixation point to all sides, surrounded by relative central scotoma extending 10° in nasal and 20° in temporal direction.	relative central scotoma, extending 10° in temporal and 15° in nasal direction from fixation point. 1–2 and 1–3 isopters absent, 1–4 limited.
Colour discrimination	not examined	not examined
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8° and 5°; simultaneous recording of VER. ERG and VER after full field stimulation in dark adapted state.	

Fig. 11

Patient I, ♀, Age: 30 years
First examination: ERG (30 counts), VER (500 counts)
Full field stimulation in dark adapted state

Description (see also Figure 10 and 11: 8°-recording and recording of ERG and VER after full field stimulation in dark adapted state):

ERG OD after local (foveal) stimulation: 4.2 µV: borderline value.
ERG OS after local (foveal) stimulation: 4.0 µV: borderline value.
VER OD and VER OS after local (foveal) stimulation: absent.

ERG OD after full field stimulation in dark adapted state: 250 μV: borderline value.
ERG OS after full field stimulation in dark adapted state: 220 μV: normal.
VER OD after full field stimulation in dark adapted state: absent.
VER OS after full field stimulation in dark adapted state: discernible.
(The amplitude of the local ERG OD might indicate that, despite the absolute central scotoma, it was chiefly the central fovea that was stimulated. The amplitude of the local ERG OS shows that fixation with the left eye was difficult.)

II. *Examination 16 days after admission*

Visual acuity	OD 1–2/300	OS 0,6; red filter: 0,2
Media	no abnormality	no abnormality
Fundi	no abnormality	no abnormality
Visual fields (Goldmann)	not examined	not examined
Colour discrimination	not examined	not examined
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8° and 5°; simultaneous recording of VER. ERG and VER after full field stimulation in dark adapted state.	

Fig. 12

Patient I, ♀, Age: 30 years
Second examination: Fovea-ERG (8°), VER

Description (see also Figure 12 and 13: 8°-recording and recording of ERG and VER after full field stimulation in dark adapted state):

ERG OD after local (foveal) stimulation: 3.2 μV: subnormal.
ERG OS after local (foveal) stimulation: 4.5 μV: borderline value.
VER OD and VER OS after local (foveal) stimulation: absent.
ERG OD after full field stimulation in dark adapted state: 175 μV: normal.
ERG OS after full field stimulation in dark adapted state: 165 μV: normal.
VER OD after full field stimulation in dark adapted state: discernible.
VER OS after full field stimulation in dark adapted state: discernible.
(Although the amplitude of the photopic b-wave is lower than in the first examination, yet it remains within the normal range.)

The visual acuity of the right eye did not improve in the course of time; the visual acuity of the left eye diminished:
18 days after admission: VOD: 1–2/300 VOS: 0,3, red filter 5/60.
32 days after admission: VOD: 1–2/300 VOS: 1/60.
Atrophy of the optic nerve became visible in both fundi.
In this condition the patient was discharged from hospital.

Fig. 13
Patient I, ♀, Age: 30 years
Second examination: ERG (25 counts) VER (500 counts)
Full field stimulation in dark adapted state

III. *Examination 7 months and 2 weeks after admission*

Visual acuity	OD 1–2/300		OS 1/60
Media	no abnormality		no abnormality
Fundi	atrophy N.II		atrophy N.II
Visual fields	absolute central scotoma		absolute central scotoma
(Goldmann)	extending 10° in all direc-		extending 10° in all direc-
	tions from fixation point.		tions from fixation point,
	1–2 isopter absent. On		and surrounded by a large
	nasal side, large relative		relative scotoma extending
	scotoma extending up to		up to 50° in nasal direc-
	40°.		tion.*

Fig. 14

Patient I, ♀, Age: 30 years
Third examination: Fovea-ERG (8°), VER

---

* Although the visual fields OD and OS were quite equal, we nevertheless (see above) found a slightly better visual acuity OS.

Colour discrimination   failure of examination   failure of examination
Electro-ophthalmology   ERG: local (foveal) stimulation with field size 8° and 5°;
                              simultaneous recording of VER.
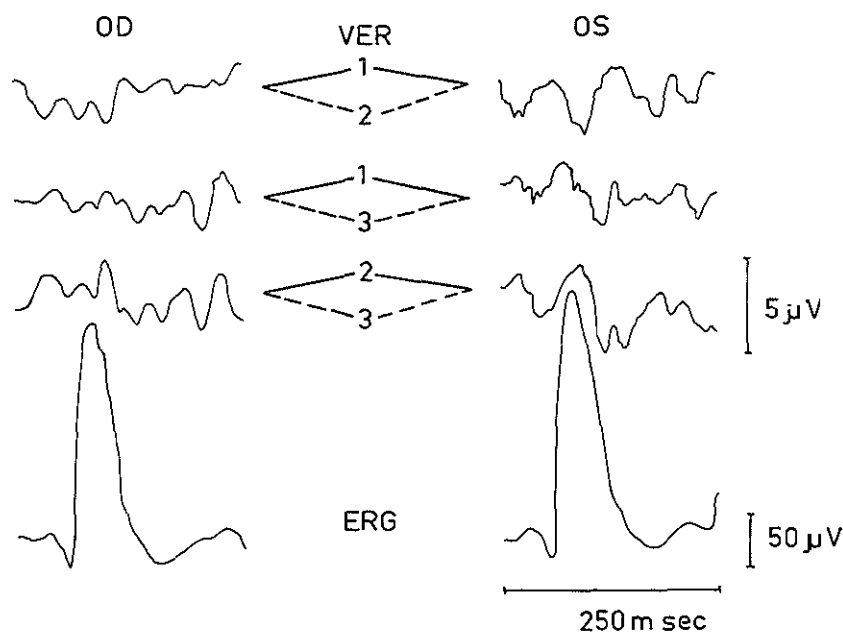   ERG and VER after full field stimulation in dark adapted
                         state.

Description (see also figure 14 and 15: 8°-recording and recording of ERG and VER
       after full field stimulation in dark adapted state):

ERG OD after local (foveal) stimulation: 3.2 μV: subnormal.
ERG OS after local (foveal) stimulation: 2.5 μV: subnormal.
VER OD and VER OS after local (foveal) stimulation: absent.
ERG OD after full field stimulation in dark adapted state: 205 μV: normal.
ERG OS after full field stimulation in dark adapted state: 190 μV: normal.
VER OD and VER OS after full field stimulation in dark adapted state: absent.
(The value of the photopic b-wave of the 8° local ERG shows that fixation of the
stimulus was now impossible for both eyes as a result of the absolute central scotomas
in the visual fields.)
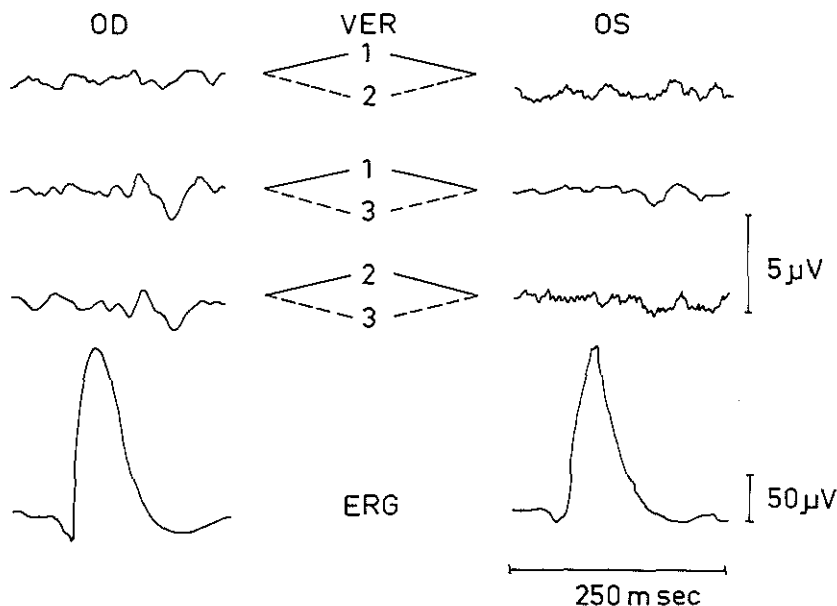
Fig. 15

Patient I, ♀, Age: 30 years
Third examination: ERG (25 counts) VER (500 counts)
Full field stimulation in dark adapted state

50

IV. *Examination 13 months after admission*

The general ophthalmological findings showed that the patient's condition had remained unchanged since examination III.

Electro-ophthalmology ERG: local (foveal) stimulation with field size 8° and 5°; simultaneous recording of VER.

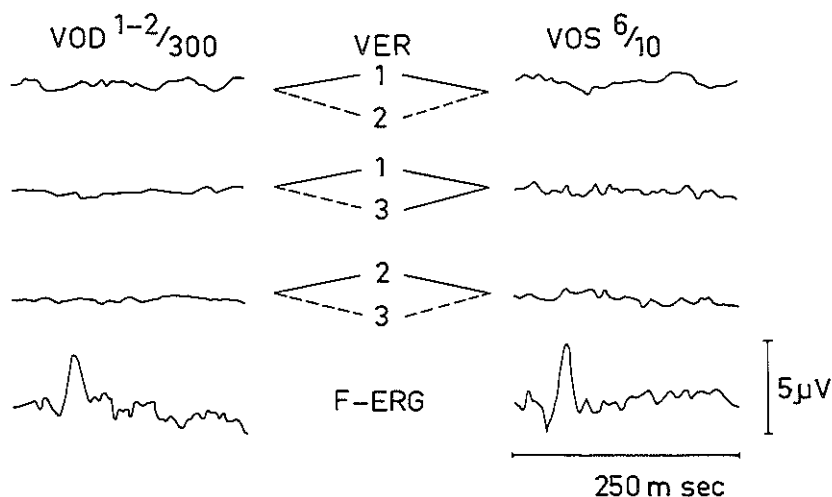ERG and VER after full field stimulation in dark adapted state.

Description (see also figure 16 and 17: 8°-recording and recording of ERG and VER after full field stimulation in dark adapted state):

ERG OD after local (foveal) stimulation: 2.8 μV: subnormal.
ERG OS after local (foveal) stimulation: 2.5 μV: subnormal.
VER OD and VER OS after local (foveal) stimulation: absent.
ERG OD after full field stimulation in dark adapted state: 200 μV: normal.
ERG OS after full field stimulation in dark adapted state: 220 μV: normal.
VER OD and VER OS after full field stimulation in dark adapted state: absent.
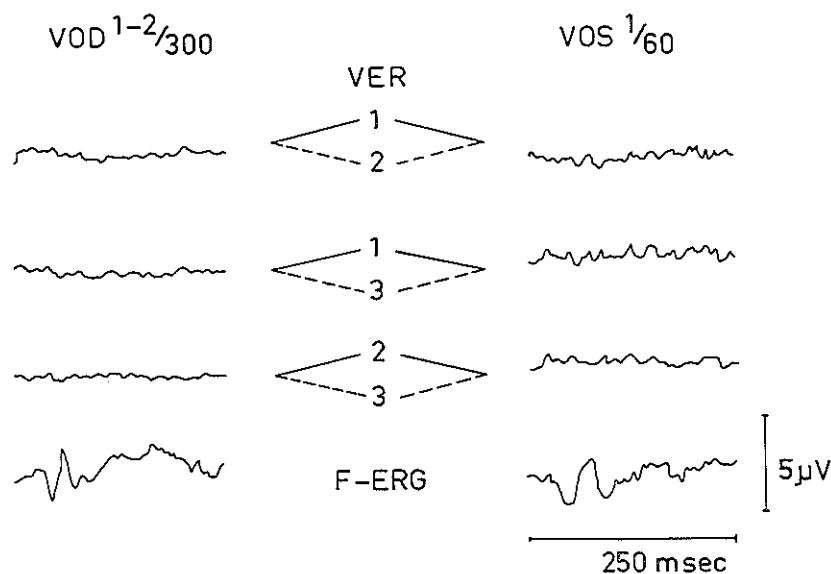
Fig. 16

Patient I, ♀, Age: 31 years
Fourth examination: Fovea-ERG (8°), VER
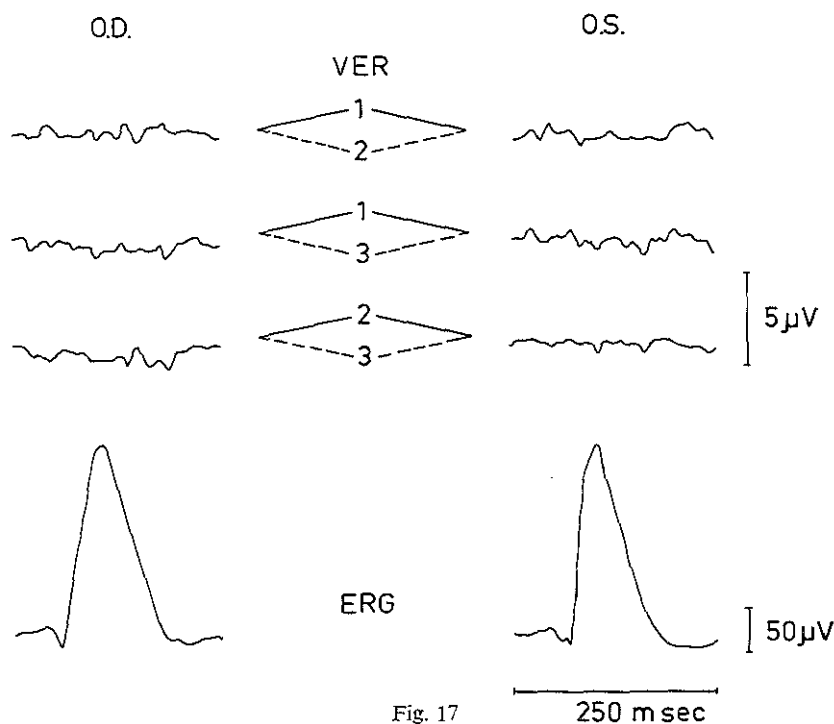
Fig. 17

Patient I, ♀, Age: 31 years
Fourth examination, ERG (25 counts), VER (500 counts)
Full field stimulation in dark adapted state

Some slight improvement in visual acuity occurred 20 months after admission.

V. *Examination 20 months after admission*

Visual acuity	OD 1–2/60	OS 0,2–0,3, red filter: 5/60
Media	no abnormality	no abnormality
Fundi	atrophy N.II	atrophy N.II
Visual fields (Goldmann)	relative central scotoma extending 10° in all direc- tions from fixation point, and surrounded by a large relative scotoma of less intensity.	about the same as OD.
Colour discrimination	HRR: unclassified	HRR: tritanopia? – unclassified
	15HUE: axis most con- sistent with deuteranopia	15HUE: axis most con- sistent with tritanopia
	Anomaloscopic examination unsuccessful.	

52

Electro-ophthalmology   ERG: local (foveal) stimulation with field size 8° and 5°;
                         simultaneous recording of VER.
                         ERG and VER after full field stimulation in dark adapted
                         state.

Description (see also figure 18 and 19: 8°-recording and recording of ERG and VER
            after full field stimulation in dark adapted state):

ERG OD after local (foveal) stimulation: 3.5 μV: subnormal.
ERG OS after local (foveal) stimulation: 3.2 μV: subnormal.
VER OD and VER OS after local (foveal) stimulation: absent.
ERG OD after full field stimulation in dark adapted state: 200 μV: normal.
ERG OS after full field stimulation in dark adapted state: 220 μV: normal.
VER OD and VER OS after full field stimulation in dark adapted state: absent.

VOD $^{1-2}/_{60}$ VOS $^{2-3}/_{10}$

VER

F-ERG

5 μV

250 m sec

Fig. 18

Patient I, ♀, Age: 31 years
Fifth examination: Fovea-ERG (8°), VER

53

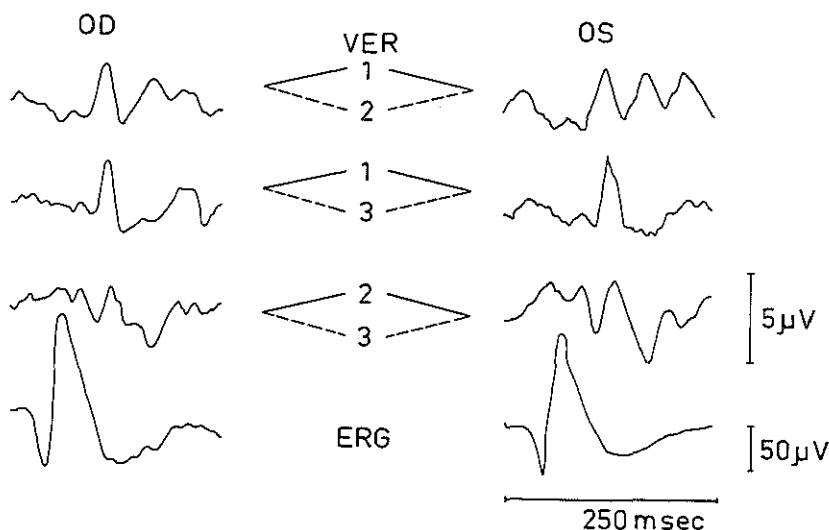O.D.   O.S.

VER

5μV

ERG

50μV

250 m sec

Fig. 19

Patient I, ♀, Age: 31 years
Fifth examination: ERG (25 counts), VER (500 counts)
Full field stimulation in dark adapted state

Summary

Bilateral optic neuritis in multiple sclerosis. No major restoration of visual
acuity. An electro-ophthalmological examination was made five times. No
VERs were recordable after local (foveal) stimulation, either in the acute stage
or in the further course.

After full field stimulation in dark adapted state, the VERs were initially
discernible, but in the last three examinations they were absent.

Discussion of the electro-ophthalmological findings obtained in patient I

1. The FERG

In none of the examinations a normal value of the photopic b-wave was
recorded. We believe that this is due to the diminished visual acuity. It is a
striking fact that stimulation of both foveae was still quite feasible in examination
I, when the diminution of visual acuity was still of recent date. That this could
be fairly achieved with the right eye (visual acuity: 1–2/300, absolute central
scotoma, 8° FERG: borderline value) is actually incomprehensible.

54

We observed in general, that recording of the local ERG and local VER in an eye with diminished visual acuity and consequently impaired fixation, was in fact best possible if the diminution of visual acuity had occurred very recently.

The FERGs in the successive examinations show that the amplitude of the photopic b-wave diminished with (further) diminution of visual acuity (OS) and with the lengthening of the period of diminished visual acuity (OD) (examinations I through IV).

Examination V took place much later, when some slight improvement in the patient's conditon had manifested itself: she could see a little better and was therefore more cheerful and more enterprising than on previous occasions.

Although the FERGs remained subnormal in examination V, yet the recordings showed a slightly higher amplitude of the photopic b-wave than in examination IV.

2. *The VERs after local and full field stimulation of the retina*

In examination I, the local VERs objectively indicated the possibility of a disorder of conduction in the maculopapillary fibre bundles: the VERs after local stimulation of the retina were absent while the FERGs (still) showed a borderline value. At that time the VERs after full field stimulation of the retina did not yet warrant the definite conclusion of a "disorder of conduction": after stimulation of both eyes the VERs, although not very well developed, were in fact discernible in the response.

In examinations III, IV and V, the VERs after full field stimulation of the retina were absent. From these findings alone, a diagnosis of disorder of conduction can be deduced, and recording of local VERs in fact becomes superfluous.

3. *Interpretation of the electro-ophthalmological findings*

Examinations I and II were carried out shortly after optic neuritis had become manifest, that is to say: probably in the inflammatory phase of the demyelinating process. The absence of the VERs after local (foveal) stimulation of both eyes would then indicate blocking of the conduction in the maculopapillary fibre bundles of the optic nerves as a result of oedema in the nerve fibres and release of toxins. Thus the VER after local (foveal) stimulation, was already absent at the time when (in examination II) the visual acuity of the left eye was still 0,6. Two possible explanations present themselves:

a. the fibres of the maculopapillary bundle were already involved in the inflam-

matory process but could still conduct, only their conduction velocity having become unequal (we shall revert to this point in the discussion of patient II);

b. the visual acuity of the left eye of 0,6 was determined by a small number of nerve fibres still intact, in which case only a small part of the projection of the fovea in the optic cortex would depolarize; the resulting potential would be too small to be recorded by the apparatus available to us. If this hypothesis is correct, then there should be a sparing in the central scotoma in the visual field. However, the conventional methods of investigation (in particular: the Goldmann method for quantitative perimetry) are often not sufficiently accurate to demonstrate such a sparing. This will be shown also in the study of patients with hereditary optic atrophy of Leber.

After full field stimulation in dark adapted state, VERs were indeed recordable in the first examinations. We believe that these were determined by the contribution of the peripheral photopic system and of the scotopic system to the generation of the VER.

Examinations III, IV and V were carried out some considerable time after the onset of bilateral optic neuritis. None or only very slight improvement in visual acuity occurred. Atrophy of the optic nerves became visible in the fundi. As before, the VERs after local (foveal) stimulation of the retina were absent. The blocking of the conduction in the fibres of the maculopapillary bundles now is to be ascribed to the process of demyelination and, in some small degree, to Wallerian degeneration of fibres.

The VERs after full field stimulation in dark adapted state were absent in examinations III, IV and V. At the same time, further deterioration of the pericentral visual fields became apparent at repeated examinations. From the fact that the VERs were initially absent only after local stimulation and later after full field stimulation as well, and also from the results of the visual field examinations, we have concluded that the process of demyelination extended in the course of time from the fibres of the maculopapillary bundles to the nerve fibres, which connect the peripheral retina with the optic cortex.

PATIENT II, female, born 26th January 1948

When this patient was first examined in the electro-ophthalmological department of the Rotterdam Eye Hospital, she was recovering from optic neuritis of the left eye. This affection had started 14 days earlier. The visual acuity of the left eye was 5/60 in the acute stage, and at that time the visual field showed a relative central scotoma (extending some 30°). The visual acuity of the right eye was adequate and the visual field was normal.

The patient was in good health, but made mention of a period of paraesthesias and local anaesthesia in the right arm in the past.

General examination disclosed no abnormalities, and no neurological signs.

The optic neuritis was treated by administration of dexamethasone, vitamin B^1, vitamin B^6 and vitamin B^{12} by mouth.

I. *Examination 14 days after onset of optic neuritis OS*

Visual acuity	OD 1.0	OS 0.9–1.0
Media	no abnormality	no abnormality
Fundi	no abnormality	no abnormality
Visual fields	normal	relative paracentral scot-
(Goldmann)		oma (nasal side), extending
		about 5°.

Colour discrimination   not examined

Electro-ophthalmology   ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER.

Description (see also figure 20: 8°-recording):

ERG OD after local (foveal) stimulation: 6.4 μV: normal.
ERG OS after local (foveal) stimulation: 5.9 μV: normal.
VER OD after local (foveal) stimulation: discernible/well developed.
VER OS after local (foveal) stimulation: discernible/well developed.

Four months later the patient was seen again at the out-patient clinic because she believed that visual acuity of the left eye had furter diminished. Examination disclosed that VOS was 0.2. The visual field of the left eye showed a relative central scotoma, extending 10–20°. Ten days later the visual acuity of the left eye was 1/60. The relative central scotoma had become an absolute scotoma. Re-hospitalization followed and an electro-ophthalmological examination was made on the day of admission.

II. *Examination 4 months later*

Visual acuity	OD 1.0	OS 1/60
Media	no abnormality	no abnormality
Fundi	no abnormality	atrophy N.II
Visual fields	normal	absolute central scotoma
(Goldmann)		extending up to 10° in all
		directions from fixation
		point, and surrounded by
		relative scotoma extending
		up to 30–35° from fixation
		point.
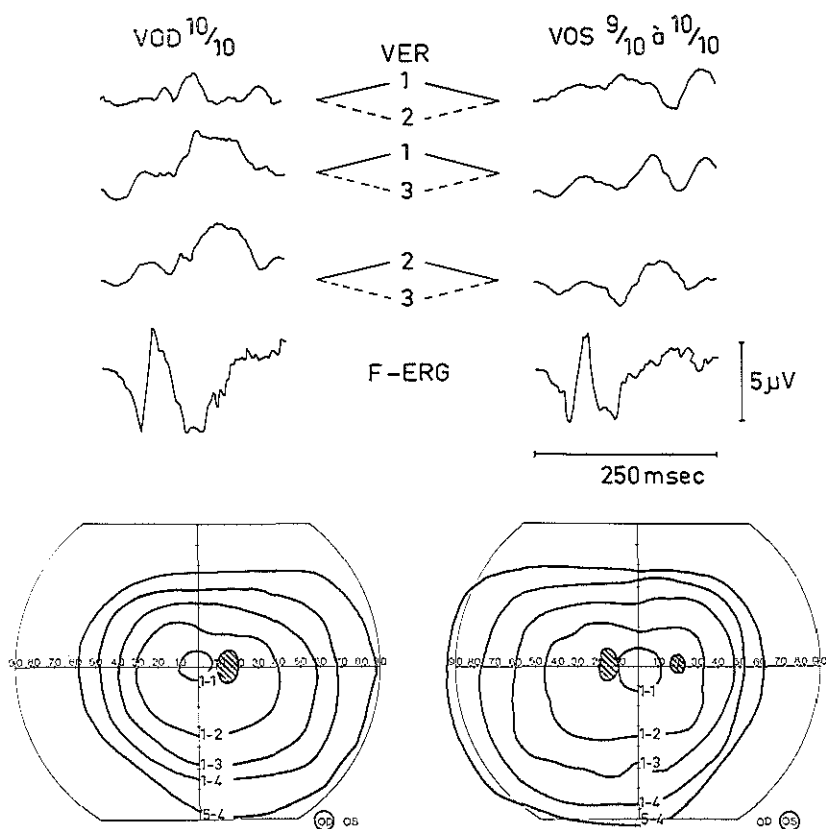
Fig. 20

Patient II, ♀, Age: 22 years
First examination: Fovea-ERG (8°), VER

Colour discrimination	normal	tests precluded by low visual acuity
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER.	
	ERG and VER after full field stimulation in dark adapted state.	

Description (see also figure 21 and 22: 8°-recording and recording of ERG and VER after full field stimulation in dark adapted state):

ERG OD after local (foveal) stimulation: 5 µV(?): normal?

ERG OS after local (foveal) stimulation: 5.9 µV: normal.

VER OD after local (foveal) stimulation: discernible/well developed.

VER OS after local (foveal) stimulation: absent.

ERG OD after full field stimulation in dark adapted state: 187 µV: normal.

ERG OS after full field stimulation in dark adapted state: 188 µV: normal.

VER OD and VER OS after full field stimulation in dark adapted state: discernible.
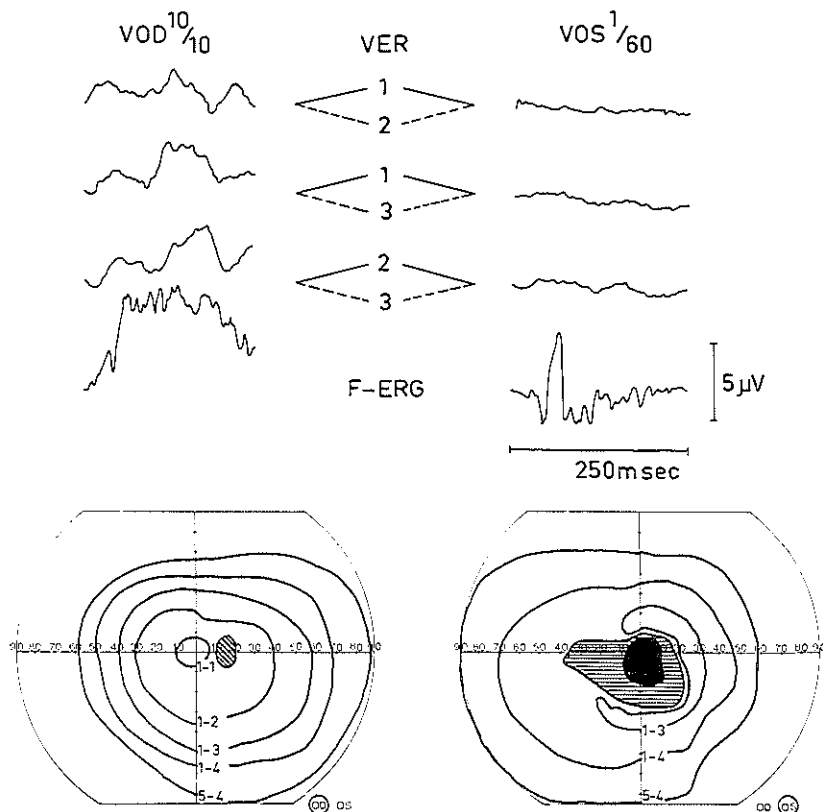
Fig. 21

Patient II. ♀. Age: 22 years
Second examination. Fovea-ERG (8°), VER

59
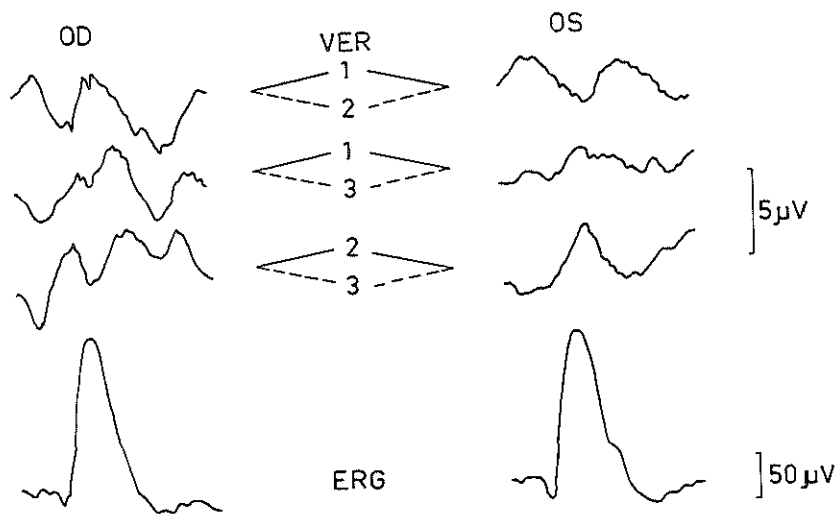
Fig. 22

Patient II, ♀, Age: 22 years
Second examination: ERG (25 counts), VER (500 counts)
Full field stimulation in dark adapted state

III. *Examination 10 days after examination II*

Visual acuity	OD 1,0	OS	0,2 à 0,3
Media	no abnormality		no abnormality
Fundi	no abnormality		atrophy N.II
Visual fields	normal		relative central scotoma
(Goldmann)			extending up to 10° in all directions from fixation point.
Colour discrimination	normal		anomaloscope: unsuccessful. HRR: deuteranopia. 15 HUE: normal in re-test.
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER.		

Description (see also figure 23: 8°-recording):

ERG OD after local (foveal) stimulation: 5.9 µV: normal.
ERG OS after local (foveal) stimulation: 5.9 µV: normal.
VER OD after local (foveal) stimulation: discernible/well developed.
VER OS after local (foveal) stimulation: absent.

60

VOD $^{10}/_{10}$ VER   VOS $^{2}/_{10}$ à $^{3}/_{10}$

F-ERG

5μV

250msec
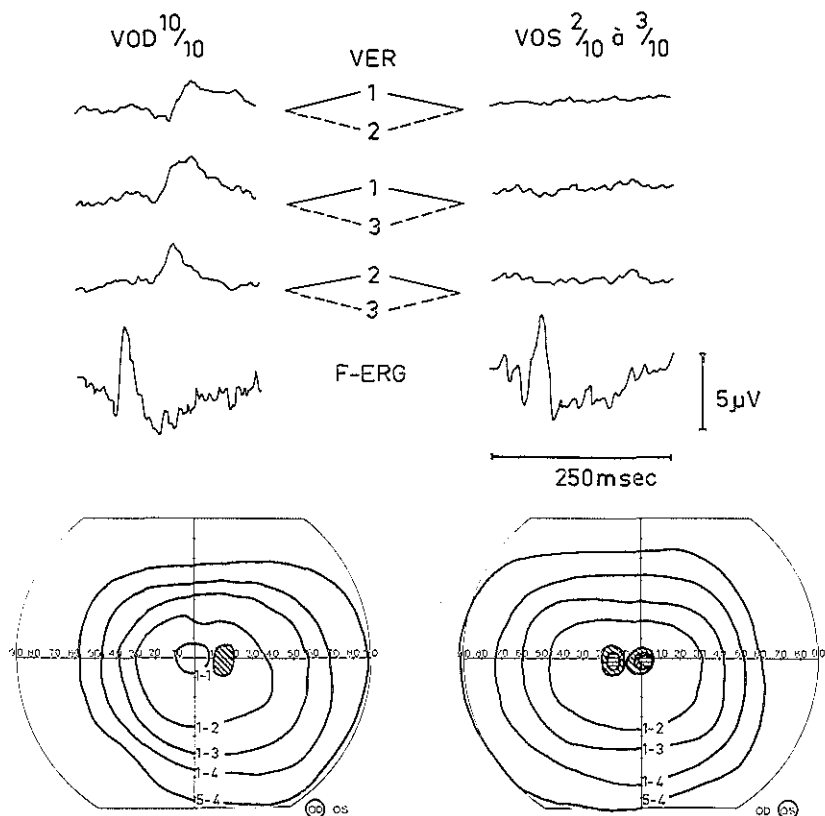
Fig. 23

Patient II, ♀, Age: 22 years
Third examination. Fovea-ERG (8°), VER

IV. *Examination 24 days after examination II*

Visual acuity	OD 1,0	OS 0,6 à 0,7
Media	no abnormality	no abnormality
Fundi	no abnormality	atrophy N.II
Visual fields	ODS unchanged since examination III	
(Goldmann)		
Colour discrimination	normal	normal
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°;	
	simultaneous recording of VER.	

Description (see also figure 24: 8°–recording):

ERG OD after local (foveal) stimulation: 3.4 μV(?): subnormal.
ERG OS after local (foveal) stimulation: 3.4 μV: subnormal.
A difference from previous examinations was the note "insufficient fixation of the stimulus" now added to the curves.
VER OD after local (foveal) stimulation: discernible.
VER OS after local (foveal) stimulation: absent.
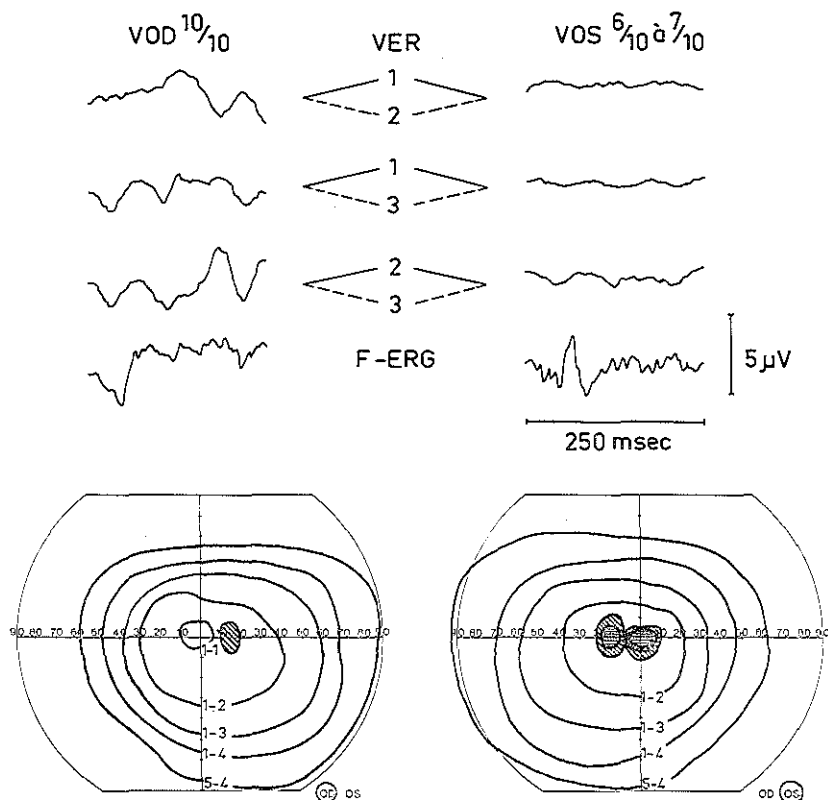
Fig. 24

Patient II, ♀, Age: 22 years
Fourth examination. Fovea-ERG (8°), VER

Summary

Optic neuritis of the left eye. The history encompasses a few symptoms suggestive of multiple sclerosis as aetiological factor. This was not confirmed by neurological findings. The visual acuity of the left eye improved to 1,0. The

62

first electro-ophthalmological examination was made after this restoration of visual acuity.

A return of the neuritis occurred four months later, with the visual acuity of the left eye diminished to 1/60 during the acute stage. A second electro-ophthalmological examination was made. Visual acuity initially improved to 0,2 à 0,3 (examination III), and subsequently to 0,6 à 0,7 (examination IV). A relative central scotoma persisted in the visual field of the left eye.

Discussion of the electro-ophthalmological findings in patient II

1. *The FERG*

In examinations I through III, normal FERGs were recorded of both eyes. In examination II of the left eye this was surprising, because patient had to achieve "fixation" of the stimulus even though at that time there was an absolute central scotoma in the visual field. However, examination II was made shortly after diminution of VOS to 1/60. In examination IV, the FERGs of both eyes were subnormal (even though the right eye had full visual acuity and a normal visual field). The patient had dreaded a repetition of the strenuous examination, and this was probably why she could not achieve calm fixation of the stimulus.

2. *The VER*

In examination I, the VERs after local (foveal) stimulation of both right and left eye were quite equal, although the right eye was entirely normal whereas the left was recovering from optic neuritis.

In examination II, the visual acuity of the left eye showed extreme deterioration due to a recurrence of the optic neuritis. It is therefore not surprising that the VER after local (foveal) stimulation of this eye was absent.

In examinations III and IV the visual acuity of the left eye had improved, and in examination IV it had even attained a value of 0,6 à 0,7. Nevertheless the VER after local (foveal) stimulation did not return in the left eye.

A conspicuous finding in examination IV was that the local VER of the right (intact) eye was not significantly different from that in preceding examinations, in spite of less adequate stimulus fixation (subnormal FERG).

Only in examination II were VERs recorded after full field stimulation of both eyes in dark adapted state. Comparison of the curves does not warrant a definite conclusion on a disorder of conduction in one of the optic nerves. This particular conclusion can be derived only from recordings of the VER after local (foveal) stimulation.

3. *Interpretation of the electro-ophthalmological findings*

During examination I the patient, as we saw, was recovering from optic neuritis of the left eye (first attack). Visual acuity, visual field and local VER of this eye were all virtually normal again. It seems justifiable to conclude that a complete return to normal had occurred. Unfortunately, no electro-ophthalmological examination was made during the acute stage.

Such an examination was made at the recurrence of the optic neuritis of the left eye: the VER after local (foveal) stimulation was absent. The blocking of conduction in this stage of the process must be ascribed to oedema of the fibres of the maculopapillary bundle and release of toxins. That the VER after full field stimulation of the left eye in dark adapted state proved to be recordable, must have been a result of the contribution of the peripheral photopic system and the scotopic system to the generation of the VER.

Although the visual acuity of the left eye improved to 0,6, the VER after foveal stimulation continued to be absent. We believe that this resulted from demyelination of the fibres of the maculopapillary bundle. (Another possible factor of influence may have been Wallerian degeneration of a number of fibres). As a result of the process of demyelination, the conduction velocity of impulses may have changed in each nerve fibre which traverses the focus of demyelination.

As already discussed, it is assumed that conduction in the normal myelinated nerve fibre of the CNS is a saltatory process. The impulse is conducted by way of a series of depolarizations, each subsequent depolarization occurring at the next constriction of the myelin sheath. For it is only at the sites of these constrictions that the outside of the membrane of the axis cylinder is in contact with an adequate electrolyte medium so that a depolarization process can start. Where a myelin sheath is present, this electrolyte medium is absent.

A myelinated nerve fibre conducts impulses much more rapidly than do unmyelinated nerve fibres.

In the naturally unmyelinated nerve fibre, conduction takes place as a continuous wave of depolarization. This is possible because the unmyelinated nerve fibre is completely surrounded by an adequate electrolyte medium.

It has been pointed out that, for example in multiple sclerosis, the axis cylinders often remain intact in the area in which demyelination has occurred. If these demyelinated nerve fibres could still conduct, then it does not seem too far-fetched to assume that the mode of conduction at the site of the focus of demyelination more or less resembles that of the naturally unmyelinated nerve

fibre. This implies that the conduction velocity diminishes at the site of the focus. One of the possible causes of failure of a demyelinated fibre to conduct impulses, although the axis cylinder is still intact, may be the absence of an adequate electrolyte medium on the outside of the membrane of the axis cylinder. After demyelination, therefore, the conduction and particularly the conduction time of the nerve fibre may become dependent on: 1) the length of the demyelinated segment, and 2) the surrounding electrolyte medium. The former can be influenced by the process of remyelination.

Based on these views it is conceivable that the conduction time of the still conducting nerve fibres in the maculopapillary bundle of our patient's eye, varies. As a result, the impulses conducted along different nerve fibres do not all simultaneously attain the optic cortex. The process of depolarization in the optic cortex therefore starts only gradually. The potential thus produced, moreover, can never be so high as that which occurs when the entire projection area of the fovea in the optic cortex depolarizes simultaneously. Consequently it is possible that, during the time that our apparatus is "searching" for the cortical response (250 msec), there is a potential of insufficient height to be identified amidst the random activity.

Apart from this hypothesis, a second possibility is to be considered: the still fair visual acuity was dependent on a relatively small number of nerve fibres still entirely intact. These together polarize so small an area of the optic cortex that the potential which arises escapes recording.

Finally, a combination of these two hypotheses is possible. In reliance upon the results of the visual field study, the absence of the VER after foveal stimulation is probably best explained in this way, for the central scotoma is made up of three relative scotomas of varying intensity (see also figure 24).

PATIENT III, female, born 10th March 1947

This patient was hospitalized with optic neuritis after a period of a few weeks during which visual acuity of the left eye had diminished, while ocular movements were painful. The patient was otherwise in good health; she had no history of serious illness but an abortion had occurred about a year before admission.

General examination failed to reveal any possible causes of the neuritis.

Therapy consisted of oral dexamethasone medication and administration of vitamin B^1, vitamin B^6 and vitamin B^{12}, initially by intramuscular injection and subsequently by mouth.

65

Findings at admission

Visual acuity	OD 1.0	OS 1/300, light projection: faulty
Media	no abnormality	no abnormality
Fundi	no abnormality	optic disc oedematous on its temporal side
Visual fields (Goldmann)	normal	peripheral visual field remnant in both upper quadrants (see figure 25)
Colour discrimination	normal	Examination unsuccessful due to insufficient visual acuity.
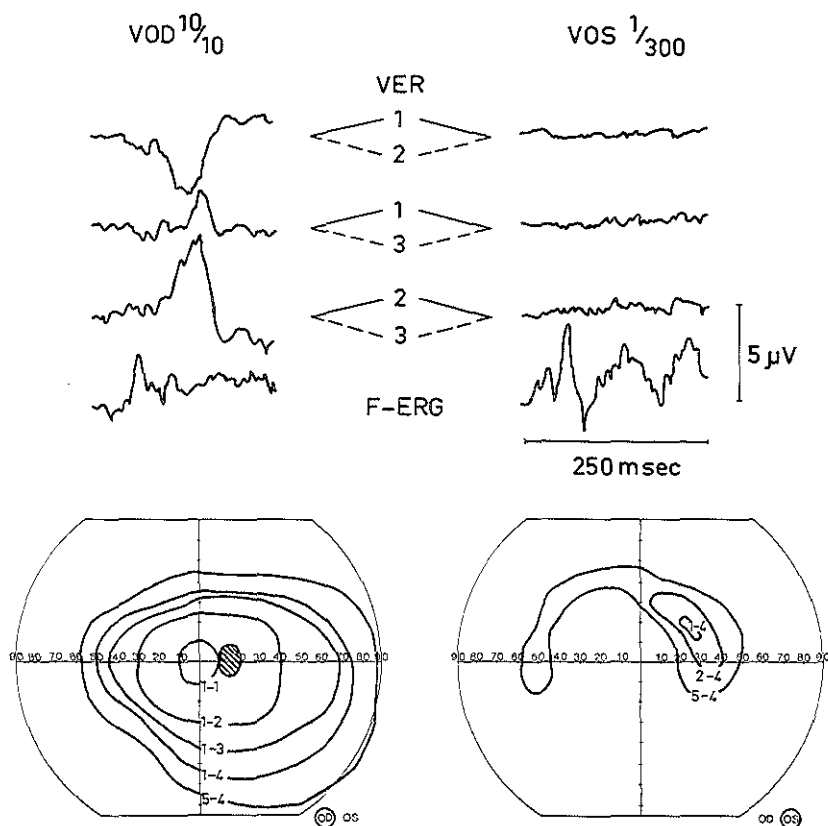
Fig. 25

Patient III, ♀, Age: 23 years
First examination: Fovea-ERG (8°), VER

I. *Examination 4 days after admission*

Visual acuity was still unchanged since admission: VOD 1.0; VOS 1/300.

Electro-ophthalmology   ERG: local (foveal) stimulation with field size 8°; simultaneous recording of VER (after which the examination was discontinued at the patient's request).

Description (see also figure 25: 8°-recording):

ERG OD after local (foveal) stimulation: 2.9 µV: subnormal.
ERG OS after local (foveal) stimulation: 4.1 µV: borderline value.
VER OD after local (foveal) stimulation: well developed.
VER OS after local (foveal) stimulation: absent.

II. *Examination 14 days after admission*

Visual acuity	OD 1.0	OS 0.2
Media	no abnormality	no abnormality
Fundi	no abnormality	no abnormality
Visual fields (Goldmann)	normal	relative central scotoma of varying intensity extending 10° in nasal and about 30° in all other directions from fixation point.
Colour discrimination	normal	examination unsuccessful
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8° and 5°; simultaneous recording of VER (patient was told that only a repetition of examination I was to take place).	

Description (see also figure 26: 8°-recording):

ERG OD after local (foveal) stimulation: 9.3 µV: supranormal.
ERG OS after local (foveal) stimulation: 7.8 µV: borderline value.
VER OD after local (foveal) stimulation: well developed.
VER OS after local (foveal) stimulation: discernible.

VOS was 1.0 from 6 weeks after admission on.

III. *Examination 5 months after admission*

Visual acuity	OD 1.0, with red filter 1.0	OS 1.0, with red filter 0.9
Media	no abnormality	no abnormality
Fundi	no abnormality	no abnormality
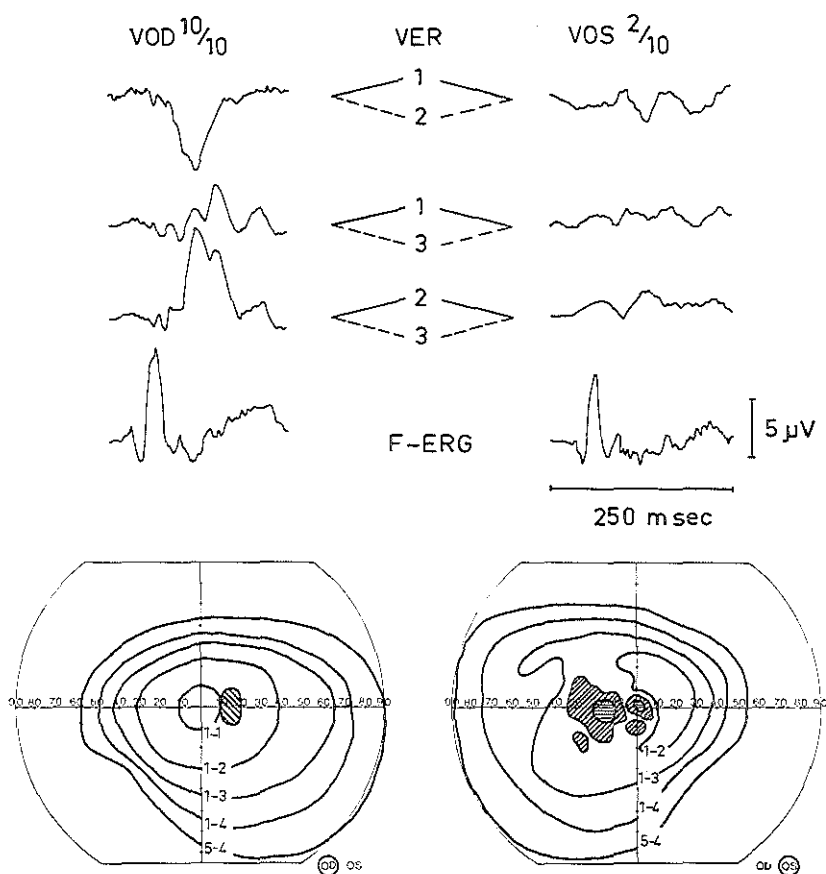
Fig. 26

Patient III, ♀, Age: 23 years
Second examination. Fovea-ERG (8°), VER

Visual fields (Goldmann)	normal	normal
Colour discrimination	normal	normal
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8° and 5°; simultaneous recording of VER. ERG and VER after full field stimulation in dark adapted state.	

Fig. 27

Patient III, ♀, Age: 24 years
Third examination. Fovea-ERG (8°), VER

Description (see also figuur 27 and 28: 8°-recording and recording of ERG and VER
after full field stimulation in dark adapted state):

ERG OD after local (foveal) stimulation: 9.6 μV: supranormal.
ERG OS after local (foveal) stimulation: 8.0 μV: borderline value.
VER OD after local (foveal) stimulation: absent/discernible.
VER OS after local (foveal) stimulation: absent/discernible.
ERG OD after full field stimulation in dark adapted state: 135 μV: normal.
ERG OS after full field stimulation in dark adapted state: 115 μV: borderline value.
VER OD after full field stimulation in dark adapted state: discernible.
VER OS after full field stimulation in dark adapted state: discernible?/absent.
(Note: the 2–3 lead was not recorded).

69

VER

5 μV

ERG

50 μV

250 msec
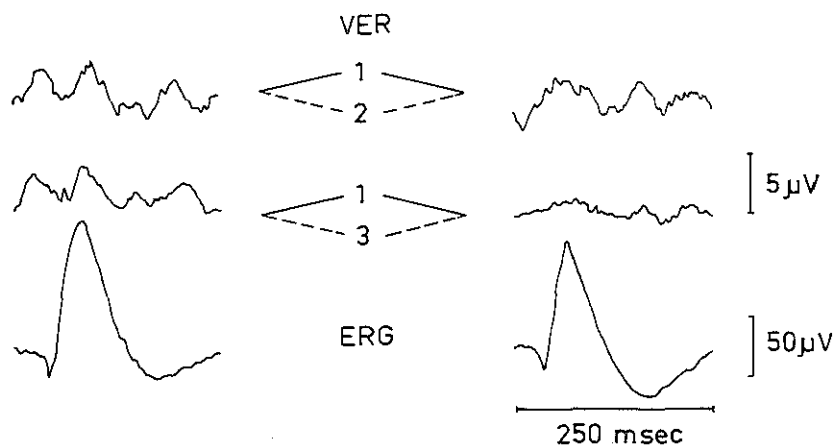
Fig. 28

Patient III, ♀, Age: 24 years
Third examination: ERG (50 counts), VER (500 counts)
Full field stimulation in dark adapted state

Summary

Optic neuritis of the left eye. In the acute stage, VOS was 1/300. The first electro-ophthalmological examination was made 4 days after admission, when the visual acuity had not yet improved. The second was made 14 days after admission, when the visual acuity had improved to 0.2. The visual acuity of the left eye subsequently improved to 1.0, the visual field returning to normal. The third electro-ophthalmological examination was made 5 months after admission. The patient was entirely free from symptoms at that time.

Discussion of the electro-ophthalmological findings in patient III

1. *The FERG*

In examination I, the FERG of the right (intact) eye was subnormal. We ascribe this to the fact that the patient was very tense during this examination. This makes it all the more conspicuous that the FERG of the left eye had a higher amplitude (borderline value), which would indicate better fixation, while at that moment only a peripheral remnant remained of the visual field. Again it is to be noted that the examination was done shortly after diminution of the visual acuity of the left eye.

In examinations II and III, supranormal FERGs were recorded from both eyes. At any rate, these prove that patient could achieve adequate fixation of the stimulus in these examinations.

2. *The VER*

Examination I shows that poor fixation of the stimulus with the right eye was not very detrimental to the generation of the VER: the VER after local (foveal) stimulation of this eye was rated well developed. Although the FERG of the left eye has a higher amplitude, the VER after local (foveal) stimulation was absent.

In examination II the visual acuity of the left eye had improved to 0.2. The VER after local (foveal) stimulation was discernible again.

Examination III (4 months and 2 weeks after examination II) was disappointing. Whereas the VERs after local (foveal) stimulation of the right eye were always well developed in examinations I and II, this was suddenly no longer the case in examination III. The VERs after local (foveal) stimulation of both right and left eye were no longer readily discernible. The poor reproducibility of the VERs in general was thus quite apparent in this case. It is difficult to conclude from the responses that conduction was good and of the same type in both optic nerves.

3. *Interpretation of the electro-ophthalmological findings*

The absence of the VER after local (foveal) stimulation in the acute stage of the optic neuritis of the left eye (examination I) may be explained, we believe, in the same way as in the corresponding examinations in patients I and II.

The cardinal finding was obtained in examination II: the VER after local (foveal) stimulation of the left eye was discernible again when the visual acuity had improved to 0.2.

At that time, apparently, the maculopapillary bundle already encompassed again a sufficient number of nerve fibres with the same conduction time to produce a depolarization in the optic cortex, the potential of which was just sufficient to permit recording. This implies the promise, so to speak, that the optic nerve of the left eye will fully recover. The clinical course (visual field, visual acuity) would subsequently confirm this. It is therefore disappointing that this recovery was not unequivocally and objectively demonstrated by the VER after local (foveal) stimulation of the left eye in examination III. The VER recorded after full field stimulation in dark adapted state as well, was of too poor quality to give conclusive information on the recovery of the optic nerve of the left eye.

PATIENT IV, female, born 28th June 1948

This patient was hospitalized with optic neuritis of the left eye three days after having noticed diminution of the visual acuity of this eye. Eight weeks earlier this patient had given birth to a child whom she was breast-feeding until she had to discontinue this at her admission to hospital. The patient was in good general health, and had no history of serious illness.

An investigation into the possible aetiology of the optic neuritis yielded no conclusive findings. Therapy consisted of oral medication with dexamethasone, vitamin B^1, vitamin B^6 and vitamin B^{12}.

I. *Examination 1 day after admission*

Visual acuity	OD 1.0	OS 1/60, light projection positive
Media	no abnormality	no abnormality
Fundi	no abnormality	no abnormality
Visual fields (Goldmann)	normal	peripheral remnant inferior and temporal to the centre
Colour discrimination	normal	examination unsuccessful
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°: simultaneous recording of VER.	

Description (see also figure 29: 5°-recording):

ERG OD after local (foveal) stimulation: 3.7 μV: normal.
ERG OS after local (foveal) stimulation: 3.5 μV: normal.
VER OD after local (foveal) stimulation: well developed.
VER OS after local (foveal) stimulation: absent.

The patient achieved "fixation" of the stimulus with the left eye by keeping her index finger immediately below the stimulus surface and mentally aiming just above this finger.
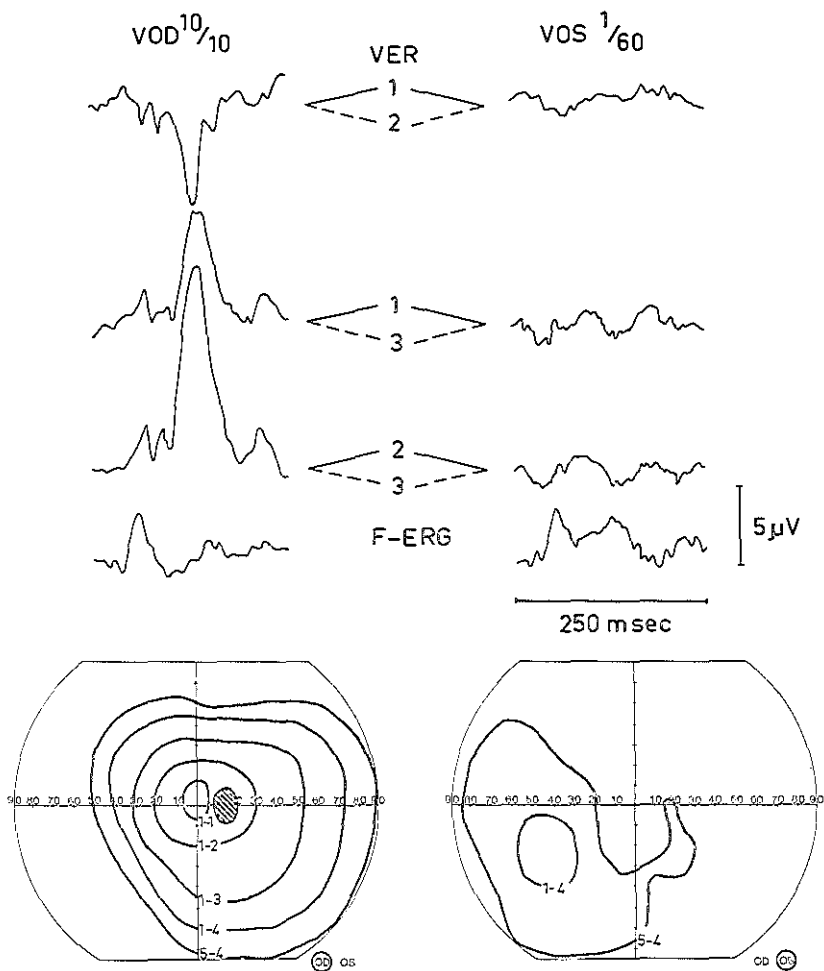
Fig. 29

Patient IV, ♀, Age: 21 years
First examination. Fovea-ERG (5°), VER

II. *Examination 14 days after admission*

Visual acuity	OD 1.0	OS 0.1
Media	no abnormality	no abnormality
Fundi	no abnormality	no abnormality
Visual fields (Goldmann)	normal	relative central scotoma of varying intensity extending about 10–20° in all directions from fixation point; 1–2 isopter limited.
Colour discrimination	normal	examination unsuccessful
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER.	
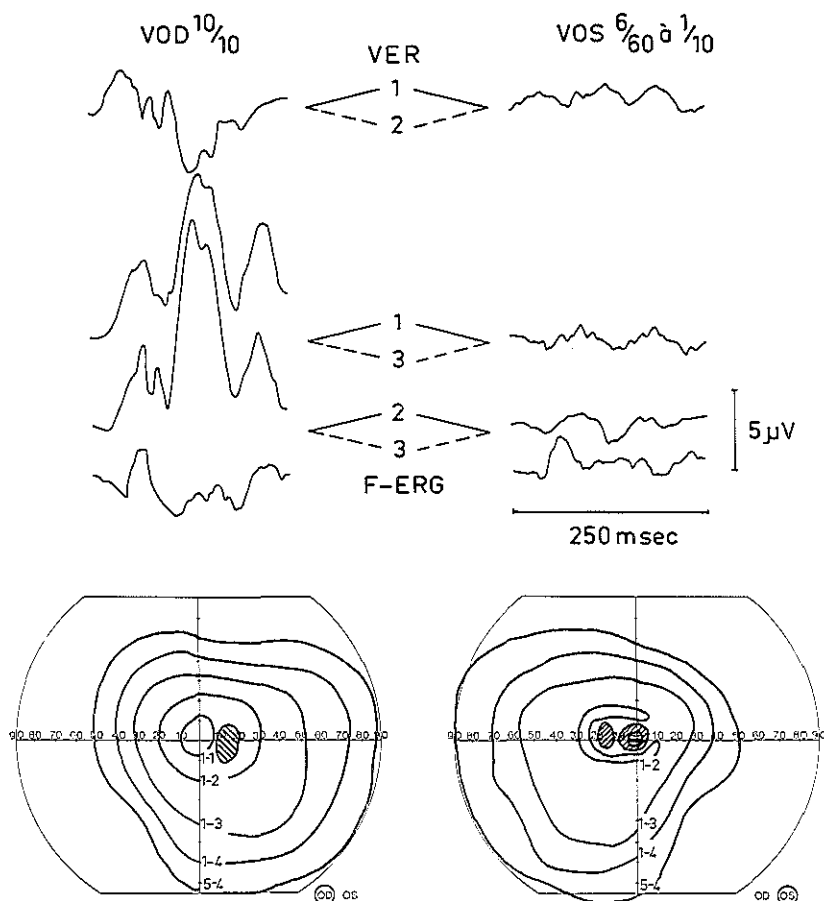
Fig. 30

Patient IV, ♀, Age: 21 years
Second examination. Fovea-ERG (5°), VER

Description (see also figure 30: 5°–recording):

ERG OD after local (foveal) stimulation: 3.2 μV: normal.
ERG OS after local (foveal) stimulation: 2.9 μV: borderline value.
VER OD after local (foveal) stimulation: well developed.
VER OS after local (foveal) stimulation: absent.

III. *Examination 28 days after admission*

Visual acuity	OD 1.0	OS 0.9, with red filter 0.8
Media	no abnormality	no abnormality
Fundi	no abnormality	no abnormality
Visual fields (Goldmann)	normal	slightly diminished central sensitivity (1–1 isopter absent); two small para-central scotomas temporal and superior to fixation point.
Colour discrimination	normal	anomaloscope: normal HRR: normal 15HUE: 1st test trit-anopia: re-test: no distinct axis.
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER.	

Description (see also figure 31: 5°–recording):

ERG OD after local (foveal) stimulation: 3.5 μV: normal
ERG OS after local (foveal) stimulation: ?
VER OD after local (foveal) stimulation: well developed
VER OS after local (foveal) stimulation: discernible.

(The response of the FERG OS was such as to warrant no evaluation beyond the observation that there was a response).

75

VOD $^{10}/_{10}$ VOS $^{9}/_{10}$

VER

1
2

1
3

2
3

F-ERG

5 µV

250 msec

Fig. 31

Patient IV, ♀, Age: 21 years
Third examination. Fovea-ERG (5°), VER

IV. *Examination 4 months after admission*

Visual acuity	OD 1.0	OS 1.0, with red filter 0.7–0.8
Media	no abnormality	no abnormality
Fundi	no abnormality	no abnormality
Visual fields (Goldmann)	normal	normal
Colour discrimination	normal	normal
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER.	

76

Description (see also figure 32: <u>5°</u>–recording):

ERG OD after local (foveal) stimulation: 3.2 μV: normal.
ERG OS after local (foveal) stimulation: 2.9 μV: borderline value.
VER OD after local (foveal) stimulation: well developed.
VER OS after local (foveal) stimulation: well developed.
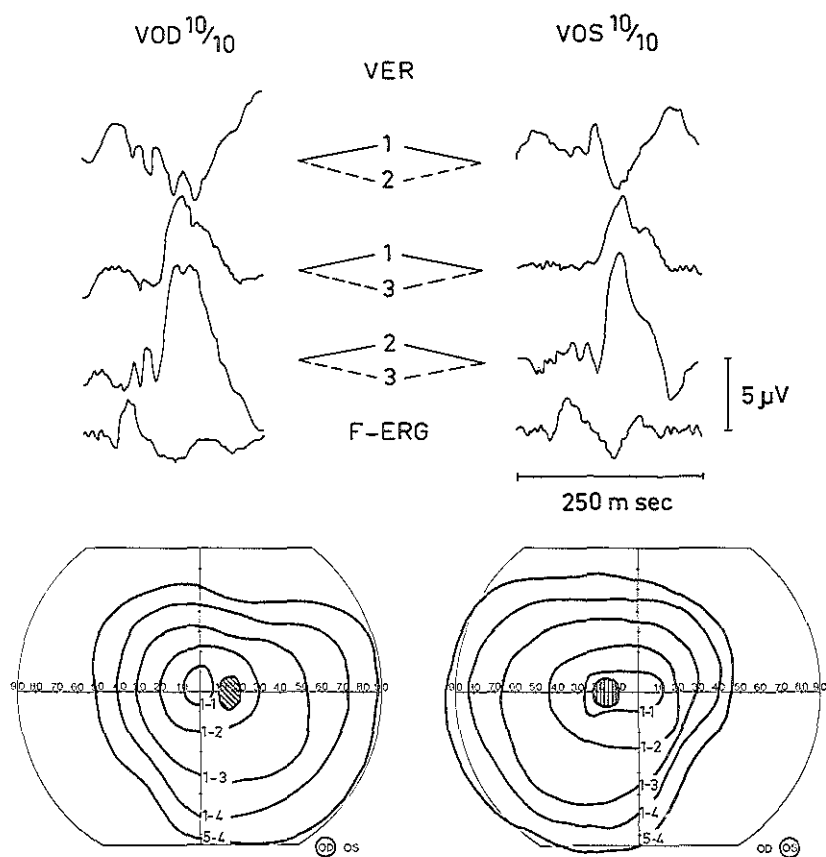
Fig. 32

Patient IV, ♀, Age: 21 years
Fourth examination, Fovea-ERG (5°), VER

Summary

Optic neuritis of the left eye. In the acute stage, when examination I was made, VOS was 1/60, and only a peripheral remnant had remained of the visual field. At the time of examination II, VOS had improved to 0.1; at the time of examination III, visual acuity was 0.9. Examination IV took place some considerable time later, when patient had completely recovered from the optic neuritis (VOS 1.0; visual field normal).

Discussion of the electro-ophthalmological findings in patient IV

1. *The FERG*

The FERGs of both eyes were rated "borderline value" or normal in all examinations, with the exception of the FERG of the left eye in examination III, which escapes an evaluation. Only for this examination we are not certain whether the simultaneously recorded VER was in fact elicited by stimulation of mainly the central fovea.

2. *The VER after local (foveal) stimulation*

In examination I, the VER after local stimulation of the left eye was rated absent. Although the curve was not quite flat, the difference in amplitude from the VER after local (foveal) stimulation of the right eye was so marked that we believe this evaluation to be correct.

Examination II showed that the VER after local (foveal) stimulation had not yet returned when VOS was 0.1.

In examination III, visual acuity of the left eye had improved to 0.9, and the visual field was virtually normal again. The VER after local (foveal) stimulation of the left eye was discernible again; comparison showed that the corresponding VER of the right eye had a substantially higher amplitude. It was not until later, when visual acuity and visual field of the left eye were entirely normal again, that we succeeded in recording the VERs after local (foveal) stimulation of both right and left eye which were virtually identical in amplitude and configuration.

3. *Interpretation of the electro-ophthalmological findings*

The absence of VER after local (foveal) stimulation of the left eye in the acute stage of the optic neuritis of this eye, should be ascribed to blocking of the conduction in the fibres of the maculopapillary bundle. Again, we assume that this blocking results from oedema of the nerve fibres and the release of toxic products from a pathological metabolism as a result of the inflammatory process.

It is generally assumed that this acute stage of optic neuritis is followed by demyelination, at least if multiple sclerosis is the verified aetiological factor (this aetiology was not ascertained in our patient, but her age and sex at least warrant a suspicion of multiple sclerosis). Restoration of visual acuity is believed to result from conduction in the now locally demyelinated nerve fibres (e.g. ANDERSON 1960).

In the case of this particular patient we regard the above-mentioned view as questionable. Examinations III and IV showed that, with the restoration of visual acuity of the left eye, the VER after local (foveal) stimulation returned. Ultimately (examination IV), no longer any difference could be demonstrated between the responses after stimulation of the right eye (the optic nerve of which had never been affected as far as we know) and those after stimulation of the left eye. We believe that this is possible only if the condition of the left optic nerve is virtually the same as that of the right optic nerve. And this is true only if: 1. no or hardly any demyelination of nerve fibres has occurred, or if: 2. a process of remyelination has completely restored the nerve fibres which had been affected by demyelination.

The findings obtained in examination of the remaining patients with optic neuritis are summarized in Survey I on page 154

HEREDITARY OPTIC ATROPHY OF LEBER

In 1871 LEBER described a form of bilateral optic neuritis followed by partial, sometimes total atrophy of the optic nerve. Leber concluded from his studies that he was dealing with a hereditary condition.

The affection shows a male predominance, although women may also be affected. It has an acute onset, usually between age 14 and age 30 (VAN SENUS 1963); the patient notices unilateral or bilateral diminution of the visual acuity. If the onset is unilateral, then the other eye is affected after an interval of usually a few weeks to months. Examination of the visual fields reveals a relative or absolute central scotoma, the peripheral visual field in most cases being normal. The fundoscopic features initially resemble those of optic neuritis or papillitis. These manifestations are followed by atrophy of the optic disc, particularly of its temporal half. Nystagmus is observed in some cases.

The majority of the investigators who examined patients with optic atrophy of LEBER, made mention of a disturbance in colour discrimination. In many cases, colour discrimination improved when the visual acuity improved after the acute stage of the affection. Observations reported differ widely concerning the manner in which colour discrimination is disturbed in the acute stage as well as concerning the manner in which improvement of colour discrimination can become apparent. In his (large) group of patients, VAN SENUS found no fixed pattern in the disturbance of colour discrimination. One of the reasons for this negative finding was that the available methods of investigation (HRR, Ishihara, Nagel anomaloscope) are unsuited for the examination of patients with, often, poor visual acuity and a disturbed central visual field.

Besides ophthalmological changes, neurological disturbances are sometimes observed, e.g. epileptiform symptoms, ataxia, abnormal reflexes, spasticity, rigidity, tremor, dysarthria and hyperhidrosis of the limbs (e.g. DE WEERDT 1969; WALLACE 1970).

WALLACE (1970) described an Australian family in which the disease was remarkably often associated with an encephalopathy, which sometimes led to a fatal issue.

TOVE SEEDORF (1968) reported on a family in whose last generation a case of haemophilia had occurred besides optic atrophy of LEBER. Generally, however, no systemic or endocrinological abnormalities have been found which could be related to the disease.

VAN SENUS found that in 25% of his cases the visual acuity in at least one eye improved to 0.4 (in the acute stage the visual acuity had diminished in most cases to 1/300 or 1/10). VAN SENUS wrote: 'Of the 83 patients who could give information about the time of improvement (of the visual acuity), the majority, 54, had noticed no improvement within 2 years and none (of them) within 2 months'. Nevertheless, VAN SENUS believed, the improved vision did differ from what is normal in that the maximum attainable visual acuity could only be achieved after prolonged looking and with considerable difficulty; he described this as 'delayed vision'.

Moreover, the symptomatology of the disease – and therefore its prognosis – would seem to differ in different families. On the one hand, BRUNETTE & BERNIER (1967) described a family of French Canadian origin in which over 10% of the members affected by the disease, recovered normal visual acuity. In most of these cases the visual fields also returned to normal. On the other hand, there is the family described by WALLACE, in which a severe encephalopathy occurred besides bilateral optic atrophy. The visual acuity of patients in this family usually showed no or hardly any improvement.

Mode of transmission

The familial occurrence of the disease undoubtedly warrants the conclusion that a hereditary condition is involved. An outstanding feature is that the disease can apparently only be transmitted by females. The mode of transmission is still a topic of discussion. So far, it has not been possible to establish a hereditary pattern consistent with the distribution of the disease in all the known families.

The principal theories on the hereditary transmission of the disease are the following:

1. Transmission by genes of the X-chromosome. This possibility has been suggested among others by LENZ (1912) and VOGT (1922).

2. Transmission by an autosomal gene, as postulated by LUNDSGAARD (1944).

3. Transmission by the cytoplasm – a theory advanced by IMAI & MORIWAKI (1936).

4. The disease is basically an inborn error of metabolism, characterized by the inability to neutralize and excrete cyanide. Exogenous factors such as a smoking habit and possibly also nutrition play a role in the complex of factors which determines whether the disease will manifest itself (WILSON 1963). The

toxic effect of cyanide is believed to take the form of a disturbed equilibrium between vitamin B_{12_a} and vitamin B_{12_b}: cyanide converts hydroxycobalamin to cyanocobalamin.

5. WALLACE postulated a form of viral transmission. The idea as such is not new, but WALLACE postulated in addition that resistance to 'infection' by an agent responsible for optic atrophy of LEBER, can be inherited via several genes. In this way, the irregular and erratic pattern of hereditary transmission could be explained.

It would seem to us that the polymorphous symptomatology of the disease should also be considered in heredity studies. This polymorphism raises the question whether it is quite certain that a single disease entity is involved.

Pathological anatomical findings

Postmortem studies are scanty. In a patient who died 7 years after the onset of the disease, VOGT & SCHÖNENBERGER (1923) found demyelination of a large segment of the optic nerve. Not only the maculopapillary fibre bundle was involved but also 'peripheral' fibres, at the level of the disc, on its temporal side. In a large area the axis cylinders had disappeared. The delicate septa, too, had disappeared for the greater part, and those remaining had thickened. In the retina, the ganglion cell layer and the layer of nerve fibres were atrophic. An increase in glia tissue was observed in these atrophic layers. Numerous corpora arenacea were found in the arachnoidea.

KWITTKEN & BAREST (1958) did a postmortem examination on a patient 41 years after onset of the disease. They found atrophy of the ganglion cell layer, in which several ganglion cells showed a pyknotic nucleus. They also observed moderate degeneration in the bipolar cell layer. There was a slightly cupped disc, filled with glial tissue and connective tissue. The optic nerves showed marked atrophy and severe destruction, not only of the myelin sheaths but also of the axons of the maculopapillary fibre bundle.

The postmortem report on an 86-year-old man who had suffered from optic atrophy of LEBER read: in the retina, the ganglion cell layer has virtually disappeared; the nerve fibre layer is too thin. There is a dubious atrophy of the inner molecular layer. There is marked atrophy of the optic nerve: the connective tissue septa seem to dominate the picture due to the reduced volume of the nerve fibre-bundles. The myelin sheaths have largely disappeared. (Data supplied by A. B. DE HAAN, ophthalmologist, Wilhelmina Gasthuis, Amsterdam, on an autopsy done in 1960.)

82

Hereditary optic atrophy of LEBER was included in our study for the following reasons:

1. in order to establish whether the disease is electro-ophthalmologically different from other affections of the optic nerve;

2. optic atrophy, of any aetiology, is usually accompanied by a poor visual acuity; long standing poor visual acuity usually precludes a successful examination by our method; some patients with optic atrophy of LEBER, however, have recovered full visual acuity;

3. we had the opportunity to examine 12 patients with optic atrophy of LEBER, the majority of whom had recovered more or less good visual acuity in at least one eye.

PATIENT I, male, born 1st June 1924.

An acute diminution of visual acuity of the left eye occurred at age 24. 4 Months later visual acuity of the right eye also diminished. Poor visual acuity of both eyes persisted for over a year, whereupon gradual improvement occurred. Ultimately, visual acuity of the right eye had sufficiently recovered to enable the patient to accept a position of responsibility in a public organization.

Examination

Visual acuity	OD	1.1, with red filter 1.0	OS 0.3, with red filter 0.3
Media		no abnormality	no abnormality
Fundi		pale, sharply defined optic disc	same as OD
Intraocular pressure		normal	normal
Visual fields (Goldmann)		relative central scotoma for object 1–3, extending 5° in all directions from fixation point; paracentral relative scotoma for object 1–3, extending 10°; both scotomas are surrounded by a relative scotoma for 1–4, extending 10–25° from centre; periphery normal.	absolute central scotoma extending 10–25° from centre; at its centre, a relative scotoma for object 1–4, extending 5° in all directions; periphery normal.
Central visual fields (Bjerrum)		in a constellation of relative central scotomas, a small area of much higher sensitivity surrounds the fixation point	at the centre, a constellation of merging relative scotomas, with a small paracentral area of higher sensitivity
Colour discrimination		HRR: unclassified 15HUE: failed anomaloscope: deuteranopia	same as OD

Electro-ophthalmology   ERG: local (foveal) stimulation with field size 8°, 5° and 3°;
                         simultaneous recording of VER.
                         ERG and VER after full field stimulation in dark adapted
                         state.
                         Total photopic and scotopic ERG by the standardized
                         procedure of the Rotterdam Eye Hospital.
                         EOG.

Fig. 33

Patient I, male, age 45 years

84
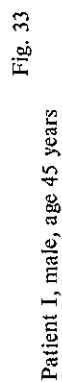
Description (see also figures 33 and 34: 8°-and 5°-recordings and recording of ERG and VER after full field stimulation in dark adapted state):

ERG OD after local (foveal) stimulation field size 8°: 3.8 µV: subnormal.
ERG OD after local (foveal) stimulation field size 5°: 3.8 µV: normal.
ERG OS after local (foveal) stimulation field size 8°: 3.4 µV: subnormal.
ERG OS after local (foveal) stimulation field size 5°: 2.5 µV: borderline value.
VER OD after local (foveal) stimulation field size 8° and 5°: absent.
VER OS after local (foveal) stimulation field size 8° and 5°: absent.
ERG OD after full field stimulation in dark adapted state: 125 µV: borderline value.
ERG OS after full field stimulation in dark adapted state: 185 µV: normal.
VER OD after full field stimulation in dark adapted state: discernible.
VER OS after full field stimulation in dark adapted state: discernible.
Total photopic and scotopic ERG OD and OS: normal.
EOG OD and OS: normal.
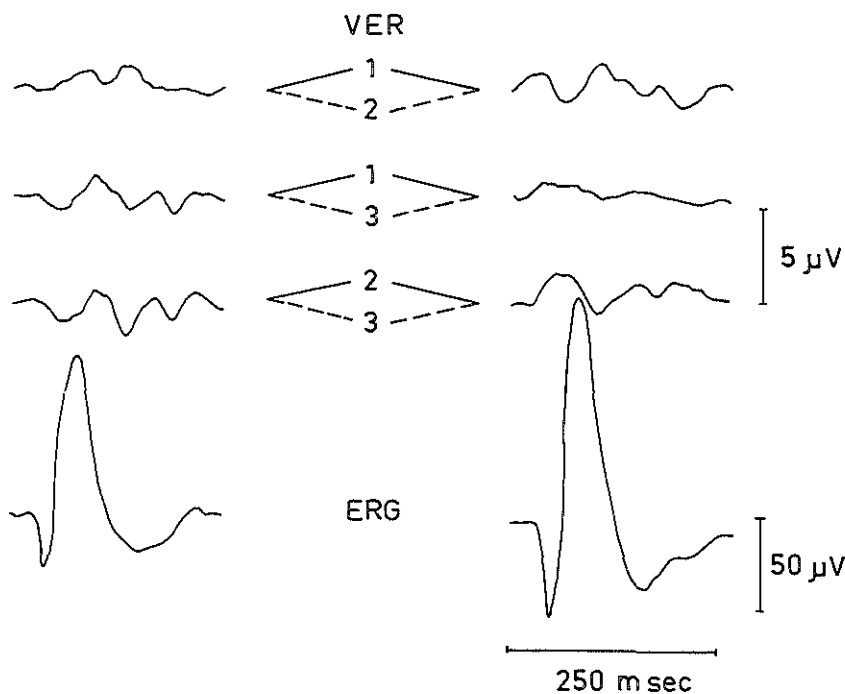
Fig. 34
Patient I, male, age 45 years. ERG (50 counts) and VER (500 counts), full field stimulation in dark adapted state

85

Discussion of the electro-ophthalmological findings obtained in patient 1

1. *The FERG*

The 8°-recordings of the FERGs of both eyes were subnormal, the 5°-recordings being rated normal and borderline value respectively. We contemplated two different explanations for these findings:

a) in the 8°-recording the stimulus was inadequately fixed by the patient; however, the curve was emphatically marked: 'calm fixation';

b) visual field examination according to BJERRUM showed in the centre of the central scotoma a sparing covering much less than 8° of the visual field (as expected, such a small sparing could not be demonstrated by the Goldmann method; static perimetry would certainly have disclosed this sparing). It seems possible that stimulation with field size 5° and 3° exclusively achieved depolarization of central intact bipolar cells, whereas with field size 8°, apart from central intact bipolar cells, also pericentral degenerated bipolar cells were stimulated, thus producing a relatively lower response upon 8° stimulation. On the other hand, the occurrence of (retrograde) degeneration of bipolar cells is not quite certain in the hereditary optic atrophy of LEBER (see pathological anatomical findings).

Degenerative changes in the bipolar cell layer as a result of optic atrophy were observed by FEINSOD, ROWE & AUERBACH (1971). They carried out an electrophysiological examination in 69 cases of optic atrophy of varying aetiology. In 38 cases they found a b-wave of diminished amplitude in the ERG. The b-wave was assessed as to amplitude, configuration and recovery in darkness after light adaptation. The diminished amplitude of the b-wave was explained as follows: in the intact visual system, impulses are conducted via centrifugal fibres in the optic nerve, which inhibit the retinal activity at the level of the bipolar cell layer. The increasing retinal sensitivity during dark adaptation counteracts this effect. If as a result of optic atrophy the function of the above mentioned centrifugal fibres is lost, then this inhibitory effect ceases and a b-wave of increased amplitude can be expected. However, in the event of progressive degeneration the rods and cones as well as the bipolar cells would be involved in the degenerative process, due to their relation with the degenerated centrifugal fibres which terminate in these layers. A subnormal b-wave is to be expected in that case.

2. *The VER after local (foveal) stimulation*

Our discussion focuses mainly on the results obtained after foveal stimulation

of the right eye, because these are the most interesting in view of the good visual acuity (1.0) in this eye.

The recordings of the FERG after stimulation with field size 5° (rated: normal) demonstrate that the absence of the VER after local (foveal) stimulation cannot be ascribed to inadequately centric fixation. Perhaps an explanation is to be found in the following.

As we mentioned, it was demonstrated by VAN HOF (1966) that, if at foveal stimulation a disc stimulus was enlarged from 2.15° to 12.14° subtended visual angle, the peak-to-peak amplitude of the VER increased. VAN LITH (1970) likewise described an increase in the amplitude of the VER after enlargement of the stimulus from 1° to 12° subtended visual angle. The increase in amplitude of the VER might be ascribed to the fact that, with a stimulus diameter increasing to 12° subtended visual angle, an ever-increasing part of the area striata depolarizes. In the patient under discussion the very small sparing in the central scotoma (see visual field examination OD) indicates that only few fibres in the maculopapillary bundle were capable of conducting impulses. That part of the optic cortex which depolarizes as a result of conduction of impulses by these few fibres, is small. It is so small that a VER cannot be recorded, not even with the modern apparatus available.

3. *Interpretation of the electro-ophthalmological findings*

The possible pathophysiological changes in the bipolar cell layer have already been mentioned.

It remains for us to discuss the state of the fibres of the maculopapillary bundle at the time of examination. Many fibres of this bundle will have been affected by Wallerian degeneration. Others may still be conducting even though they have (largely) lost their myelin sheaths. Finally there may still be some (very few) entirely intact fibres. The visual acuity of 1.1 suggests the existence of still intact fibres in the maculopapillary bundle of the right retina. The left eye (visual acuity 0.3) does not differ electro-ophthalmologically from the right. Only on account of the lower visual acuity in the left eye one could conclude that the maculopapillary bundle of this eye contains virtually no more entirely intact fibres.

4. *ERG after full field stimulation in dark adapted state, and total photopic and scotopic ERG*

The results of these examinations could all be regarded as normal. The normal scotopic and photopic b-wave we obtained in this patient, rules out degenera-

tion of the bipolar cell layer in reliance upon the mechanism described by FEINSOD et al. (1971).

5. VER after full field stimulation in dark adapted state

The VERs of both right and left eye were 'discernible' after full field stimulation in dark adapted state. We believe that these recordings represent the contribution of the peripheral retina to the generation of the VER. It is plausible that the nerve fibres which connect the peripheral retina with the optic cortex, were not affected by the pathological process. This assumption is consistent with the results of the visual field examinations.

<div align="center">PATIENT II, male, born 30th April 1941.</div>

Acute diminution of the visual acuity in both eyes occurred early in 1960, and in the subsequent period visual acuity remained so poor that it seemed appropriate to have this patient re-schooled. However, from 1962 onwards the visual acuity of the left eye showed gradual improvement, which in the end enabled the patient to resume his original occupation.

We had the opportunity to examine this patient several times. Examination II took place 6 months and 2 weeks after examination I, the interval between examination I and examination III being 2 years. In the course of these years the patient's condition remained unchanged, and we therefore present only the results of the first examination. Only in electro-ophthalmological respect will the results of examination II be mentioned as well.

Examination

Visual acuity	OD 1/60	OS 1.1, with red filter 1.0
Media	no abnormality ·	no abnormality
Fundi	chalk-white, sharply defined disc	same as OD
Visual fields (Goldmann)	absolute central scotoma extending 20–25° in all directions from fixation point, surrounded by a relative scotoma; 5–4 isopter somewhat limited	absolute central scotoma extending 20–30° in all directions from fixation point central sparing of about 10°, in the exact centre of which object 1-2 is seen; periphery slightly limited, especially on the nasal side. *

---

* Only in this patient the sparing in the absolute central scotoma was found also with the Goldmann method of perimetry.

Central visual fields (Bjerrum)	absolute central scotoma	absolute central scotoma with, in its centre, a minute area of much higher sensitivity
Colour discrimination	examination failed	HRR: unclassified, 15HUE normal (!), anomaloscope: failed
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER	
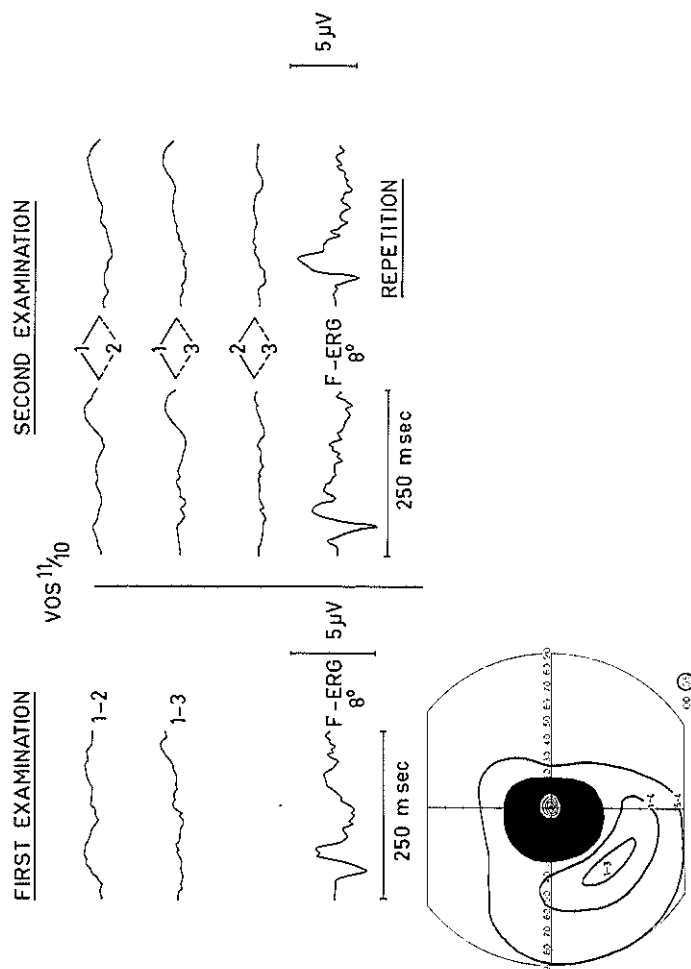
Fig. 35

Patient II, male, age 28 years. Fovea-ERG and VER OS

Description (see also figure 35: 8°-recording OS of examinations I and II, with repeti
 tion in examination II):

Examination I
ERG OS after local (foveal) stimulation: 3.0 μV: subnormal.
VER OS after local (foveal) stimulation: absent.

Examination II
ERG OS after local (foveal) stimulation: 5 μV: normal.
VER OS after local (foveal) stimulation: absent.

Examination II repetition
ERG OS after local (foveal) stimulation: 5 μV: normal.
VER OS after local (foveal) stimulation: absent.

(examination of the right eye was precluded by its long standing poor visual acuity.)

Discussion of the electro-ophthalmological findings in patient II

1. The *FERG*

The above described FERGs of the left eye were compared in an effort to verify
the hypothesis that degenerative changes may occur in the bipolar cell layer of
the central retina in patients with an optic atrophy of LEBER (see discussion
FERG, patient I). The subnormal FERG after stimulation with field size 8°,
as in our patient II (examination I), is a finding we obtained several times in
patients whose visual acuity was good in spite of their optic atrophy of Leber.
Examination II of the same patient revealed a photopic b-wave of normal am-
plitude, but the amplitude of the a-wave (4 μV) was very high in comparison
with the amplitude of the photopic b-wave (however, the a-wave amplitude was
not higher than that found in normal subjects). In order to establish whether
this phenomenon had to be given more attention, recording was repeated imme-
diately: this time the a-wave amplitude was only 1.7 μV, while the photopic
b-wave amplitude was unchanged at 5 μV and therefore considered normal.
Consequently we regard the deep a-wave in the first recording of examination II
as an accidental finding for which we can offer no explanation. The normal
photopic b-wave in examination II is not an accidental finding, because the
result proved to be reproducible. This does not solve the question as to why
a subnormal FERG was recorded in examination I (the note 'calm fixation'
went with this recording also).
 A study of the FERG in patients with LEBER's optic atrophy has therefore not
established with certainty whether degenerative changes occur in the bipolar
cell layer of the central retina.

90

2. *The VER of the left eye after local (foveal) stimulation*

The VER of the left eye was absent despite the adequate visual acuity of this eye. This result differs in no way from that obtained after local (foveal) stimulation of the right eye in patient I, and can therefore be explained in the same way.

3. *Interpretation of the electro-ophthalmological findings*

The pathophysiological considerations based on the FERG recordings have already been mentioned.

The absence of the VER indicates degenerative changes in the maculopapillary fibre bundle of the optic nerve, as we discussed with regard to the examination of patient I. To summarize: few intact fibres conduct impulses from the central retina to the optic cortex (compare: VOD is 1.1). The part of the area striata that depolarizes as a result is so small that a VER cannot be recorded. These fibres are possibly surrounded by mostly demyelinated but still conducting fibres. Outside these fibres there are other fibres which are nearly all affected by Wallerian degeneration (compare the absolute central scotoma in the visual field).

PATIENT III, male, born 27th May 1916.

On a day in 1936, when he was 20 years old, the patient suddenly noticed that he could no longer see. Half an hour later his vision showed some improvement, enabling him to cycle home from his work. Visual acuity remained poor for the next six months until, one night, the patient noticed that he could read the time again. The visual acuity of both eyes subsequently continued to improve slowly.

Of all our patients in this study, this patient had by far the best vision.

Examination

Visual acuity	OD 1.1, with red filter 1.0	OS 1.1, with red filter 1.0
Media	no abnormality	no abnormality
Fundi	disc is whitish-grey and sharply defined	same as OD
Intraocular pressure	normal	normal
Visual fields (Goldmann)	reduced central sensitivity; limitation of the 1–2 isopter, relative paracentral scotoma for 1–3, extending 10°; periphery normal	relative central scotoma for object 1–2, extending 5° in all directions from fixation point; 1–2 isopter limited; periphery normal

Colour discrimination   HRR: deuteranopia   same as OD
                              15HUE: failure
                              anomaloscope: slight
                              deuteranopia

Electro-ophthalmology   ERG: local (foveal) stimulation with field size 8°, 5° and 3°;
simultaneous recording of the VER.
ERG and VER after full field stimulation in dark adapted
state.
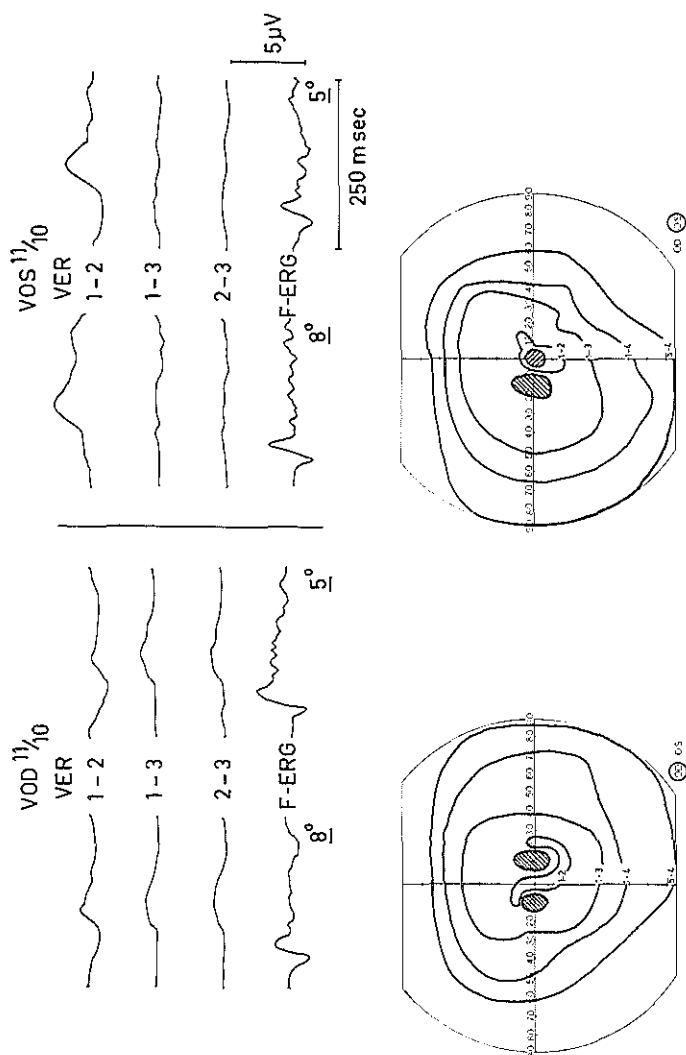
Fig. 36

Patient III, male, age 53 years

VER

5 µV

ERG

50 µV

250 m sec
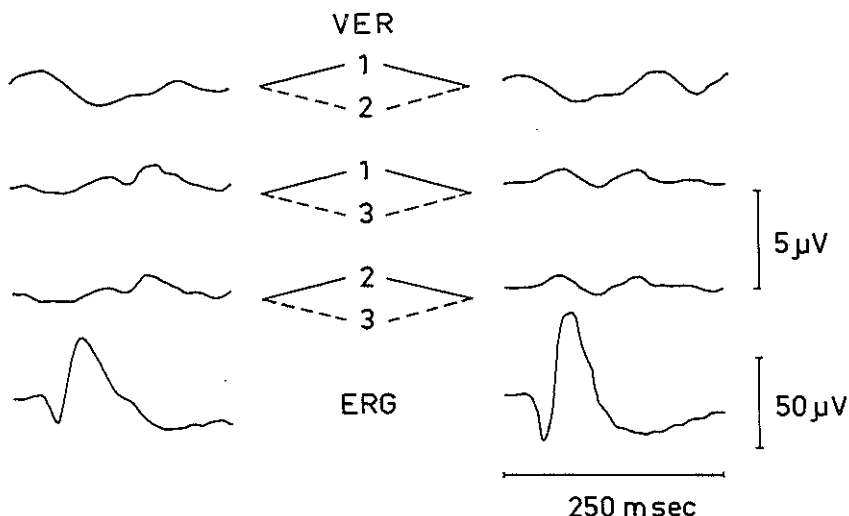
Fig. 37

Patient III, male, age 53 years. ERG (50 counts) and VER (500 counts), full field stimulation in dark adapted state

Description (see also figures 36 and 37: 8°-and 5°-recording and recording ERG and VER after full field stimulation in dark adapted state):

ERG OD after local (foveal) stimulation with field size 8°: 2.5 µV: subnormal.
ERG OD after local (foveal) stimulation with field size 5°: 3.5 µV: normal.
ERG OS after local (foveal) stimulation with field size 8°: 3 µV: subnormal.
ERG OS after local (foveal) stimulation with field size 5°: 2.1 µV: borderline value.
VER OD after local (foveal) stimulation with field size 8°: discernible.
VER OD after local (foveal) stimulation with field size 5°: discernible.
VER OS after local (foveal) stimulation with field size 8° and 5°: discernible/well developed.
ERG ODS after full field stimulation in dark adapted state: subnormal.
VER ODS after full field stimulation in dark adapted state: absent.

Discussion of the electro-ophthalmological findings in patient III

1. *The FERG*

In this examination, too, it was a striking fact that the FERGs of both eyes after stimulation with field size 8° were subnormal, while the 5° FERG of the right eye was normal and the 5° FERG of the left eye of borderline value. If the

subnormal value of the FERGs in the 8°-recording were a result of (retrograde) degeneration of bipolar cells, then the 5° FERG of the right eye would not be expected to show a higher amplitude than the 8° FERG. This strengthens our conviction that the subnormal FERGs must be ascribed to insufficiently centric fixation – in a way which is still obscure to us.

2. *The VER after local (foveal) stimulation*

Patient III was the only one in the group in whom the VER of the left eye after local (foveal) stimulation was fairly clearly present (discernible/well developed), while also the VER of the right eye was discernible.

3. *The ERG after full field stimulation in dark adapted state*

This was subnormal for both eyes, possibly because the patient had averted his eyes from the direction from which the stimulus light came. It has been pointed out that this could not be checked in our set-up.

4. *The VER after full field stimulation in dark adaptated state*

The VER of the left eye was absent after full field stimulation, although local stimulation of this eye had produced a satisfactory response. If in the recording of the VER after full field stimulation the eyes were actually averted from the stimulus light, then it is conceivable that precisely the central retina was not optimally stimulated.

5. *Interpretation of the electro-ophthalmological findings*
   (see also the discussions of patients I and II)

The maculopapillary bundle of the optic nerve of the left eye contains so many fibres with equal velocity of conduction that, after local stimulation, depolarization is simultaneously effected in a sufficiently large part of the area striata to provide a recordable VER.

The relatively little disturbed central visual fields, together with the VERs of both eyes after local stimulation (which were still less well developed than in normal subjects), suggest in addition that many (demyelinated) nerve fibres conduct with unequal velocity.

Degeneration of axis cylinders in the maculopapillary fibre bundle must have been less than in the previously discussed patients.

94

PATIENT IV, male, born 25th January 1928.

This patient was 16 years old when visual acuity of the right eye showed marked diminution within the course of one week. The same happened with the visual acuity of the left eye in the course of the next week.

In 1943, a neurosurgical operation was done; in 1944 this was twice repeated because of complications. The visual acuity improved little in the course of subsequent years.

The patient was otherwise in good health. No neurological abnormalities were found.

Examination

|		
Visual acuity	OD 6/60, with red filter 6/60	OS 0.1, with red filter 0.1
Media	no abnormality	no abnormality
Fundi	optic disc pale and sharply defined, especially on the temporal side	same as OD
Visual fields (Goldmann)	absolute central scotoma extending 5–10° from fixation point, and surrounded by a zone in which object 1–4 is not seen; this zone in turn is surrounded by a band of 2–8° in which object 1–3 is not seen; the periphery is normal	absolute central scotoma extending some 5° from fixation point, and surrounded by a broad zone of reduced sensitivity; indication of quadrant anopsia in upper temporal quadrant
Colour discrimination	HRR: unclassified 15HUE: failure anomaloscope: deuteranopia	same as OD
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER. ERG and VER after full field stimulation in dark adapted state. Total photopic and scotopic ERG. EOG.	

Description (see also figures 38 and 39: 8°-and 5°-recording, and recording of ERG and VER after full field stimulation in dark adapted state):

ERG OD after local (foveal) stimulation with field size 8°: 3.8 μV (?): subnormal.
ERG OD after local (foveal) stimulation with field size 5°: not interpretable.
ERG OS after local (foveal) stimulation with field size 8°: 4.6 μV: borderline value.
ERG OS after local (foveal) stimulation with field size 5°: 3.7μV: normal.

95

VER OD and OS after local (foveal) stimulation with field size 8° and 5°: absent.
ERG OD after full field stimulation in dark adapted state: 225 μV: borderline value.
ERG OS after full field stimulation in dark adapted state: 182 μV: normal.
VER OD and OS after full field stimulation in dark adapted state: discernible.
Total photopic and scotopic ERG: normal.
EOG: normal.
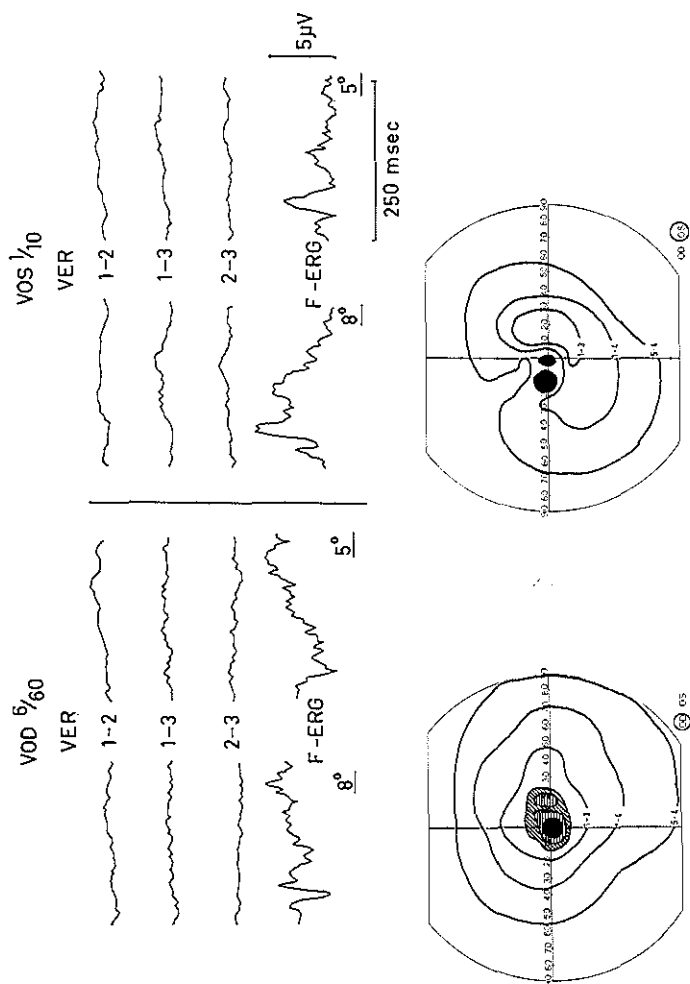
Fig. 38

Patient IV, male, age 41 years
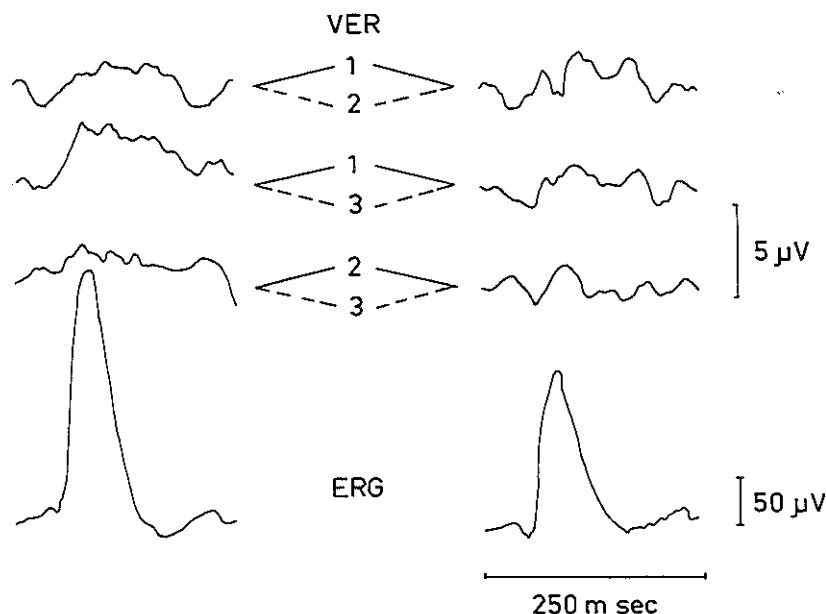
Fig. 39

Patient IV, male, age 41 years. ERG (25 counts) and VER (500 counts), full field stimulation in dark adapted state

Discussion of the electro-ophthalmological findings in patient IV

1. *The FERG*

General ophthalmological examination revealed that the visual acuity of the left and of the right eye were virtually equal. The patient himself regarded the visual acuity of the left eye as much better than that of the right eye. This found expression in the electro-ophthalmological findings: the FERG indicated that patient could not achieve proper fixation of the stimulus with the right eye. The amplitude of the FERG of the left eye (this time also the 8°-recording!) indicates better stimulus fixation.

2. *The VER after local (foveal) stimulation*

As a result of the poor fixation, the VER after local stimulation of the right eye gave no information on conduction in the right optic nerve.

In spite of sufficiently centric fixation, the VER after local (foveal) stimulation of the left eye was absent. This (and the diminished visual acuity of the left eye) is indicative of a disturbance of conduction in the maculo-papillary fibre bundle.

3. *The ERG after full field stimulation in dark adapted state*

The amplitude of the b-wave of the ERG of the right eye was higher than that of the ERG of the left eye; however, both responses corresponded in amplitude to those found in normal subjects.

4. *The VER after full field stimulation in dark adapted state*

With these VERs (rated: discernible), a depolarization in the optic cortex was registered. We believe that this depolarization was caused by impulses conducted by intact nerve fibres which connect the peripheral retina with the optic cortex.

5. *Interpretation of the electro-ophthalmological findings*

In this patient, too, the changes in the maculopapillary fibre bundle must have consisted of demyelination and (Wallerian) degeneration of nerve fibres. In the preceding cases, adequate visual acuity in one or both eyes was attributed to the presence of still intact nerve fibres. In patient IV, visual acuity of both right and left eye was low. In view of this, it is likely that the maculopapillary bundle on both sides entirely lacked intact nerve fibres.

The results of examinations in the remaining patients with hereditary optic atrophy of Leber are summarized in the survey II on page 154.

The results obtained with colour discrimination tests were disappointing. They show that a red-green disorder was indeed always found. In some cases the examination revealed deuteranopia, while protanopia was found in a few other cases. In the majority of patients, however, differentiation was impossible.

TRAUMATIC OPTIC ATROPHY

Not infrequently, a severe head injury (particularly a heavy blow to the forehead or supra-orbital ridge) leads to a lesion of one or both optic nerves. This is believed to be the case in about 1.5% of all head injuries. (TURNER, 1943).

As a rule, the optic nerve on the side of the head injury is damaged; a lesion of the contralateral optic nerve is rare. In some 8% of cases (Turner 1943), both optic nerves are involved in the process.

In severe cases the clinical features are characteristic: nearly always, a period of unconsciousness occurs as an immediate result of the injury. Once the patient regains consciousness, he notices that the visual acuity in one eye (or in both eyes) is greatly diminished or lost entirely. At this stage, fundoscopy discloses no changes. Only the direct pupillary reaction to light is absent.

If the optic nerve is only partly damaged, visual acuity as a rule improves from the 3rd to 4th posttraumatic day on. This improvement usually persists, but in some cases a second deterioration may follow after a few weeks or months. If vision fails to improve within a week of sustaining the injury, then the condition must be regarded as irreversible.

As a result of damage to the optic nerve, a wide variety of changes can occur in the visual field. Most common are changes in the periphery, e.g. concentric limitation of the visual field or hemianopia of the temporal quadrants or lower quadrants. Other patients show central, paracentral, centrocaecal or annular scotomas.

Atrophy of the optic disc usually becomes fundoscopically visible at the end of the 2nd or 3rd posttraumatic week. RODGER (1943) observed atrophy of the disc as early as on the 4th day. In some cases this change does not occur until after a few months, and in less serious cases it may not occur at all.

In serious cases the direct pupillary reaction to light remains absent or delayed. However, the pupils are usually of the same diameter, although traumatic mydriasis, Hutchinson's pupil or a traumatic Argyll Robertson pupil have been described.

Radiological examination can reveal a cranial fracture in many cases – and its absence in almost as many other cases. A fracture of the foramen opticum is rarely observed.

In which way a lesion of the optic nerve occurs as a result of a head injury is still obscure. BERLIN (1879) believed that the optic nerve lesion was always a result of a local fracture. Sufficient confirmation of this hypothesis, however, has not come forth, either from radiological or from postmortem findings.

PRINGLE (1917, 1922) supposed that the disturbed visual acuity resulted from compression of the optic nerve caused by haematomas within the dura mater. Such haematomas do in fact occur, but they seem to be a result rather than the cause of the lesion of the optic nerve.

In all probability, the process is as follows. In the canalis opticus, the optic nerve is directly surrounded by the dura mater; a subarachnoid space is almost entirely absent at this site. When the frontal or frontotemporal aspect of the head collides heavily with a hard surface, torsion and/or hyperextension of the optic nerve can occur. This may have two consequences: 1) rupture of small blood vessels supplying the optic nerve, and 2) diffuse damage to neurons in the optic nerve, leading to loss of many fibres. These changes can be expected to occur in that segment of the optic nerve that is localized in or immediately in front of the canalis opticus, where its mobility is minimal. This might also explain why the (descending) atrophy is usually not fundoscopically visible until after a few weeks.

Personal observations

Only few (about 12) cases of traumatic optic atrophy could be personally examined. In none of these the injury was of recent date. The long standing poor visual acuity often made it impossible to record the ERG and VER after local (foveal) stimulation. For our discussion we selected three patients, one of our objectives being to demonstrate that in cases of dubious diagnosis electro-ophthalmological examination can contribute to its establishment with certainty.

PATIENT I, male, born 9th April 1939.

Sixteen years prior to our examination, this patient sustained fractures of the skull, pelvis and thigh in a motorcycle accident. In hospital, immediately after the accident, it was found that visual acuity of the left eye had diminished. It has not since improved.

100

Examination

Visual acuity	OD 1.1	OS < 1/60
Media	no abnormality	no pupillary reaction to light
Fundi	no abnormality	pale, sharply defined disc
Visual fields (Goldmann)	normal	visual field remnant with absolute central and para-central scotoma
Colour discrimination	normal	not determinable
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°; simultaneous recording of VER	
	ERG and VER after full field stimulation in light and in dark adapted state.	
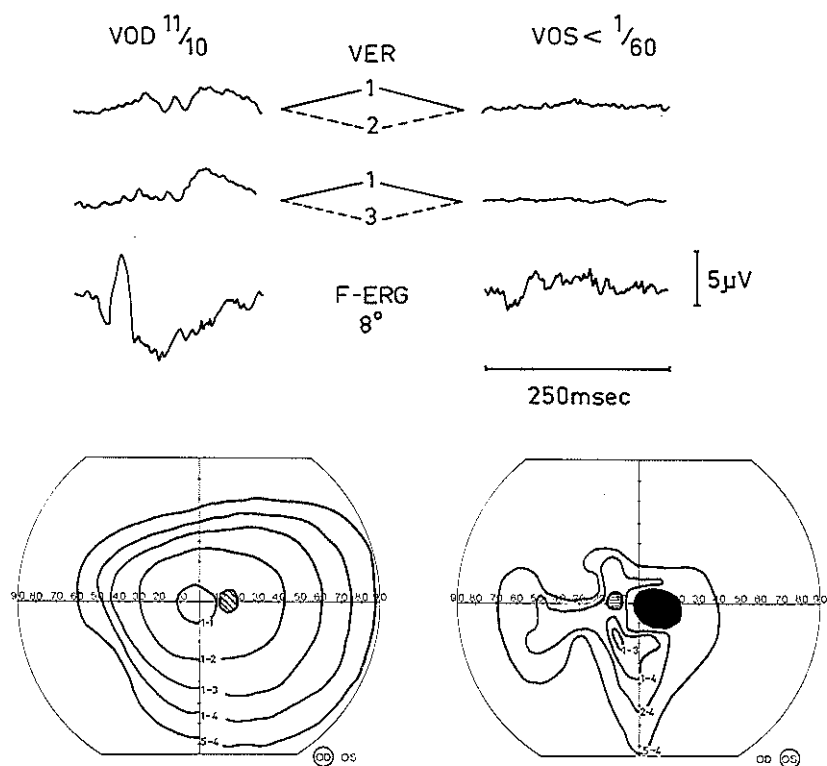
Fig. 40

Patient I, male, age 33 years

101
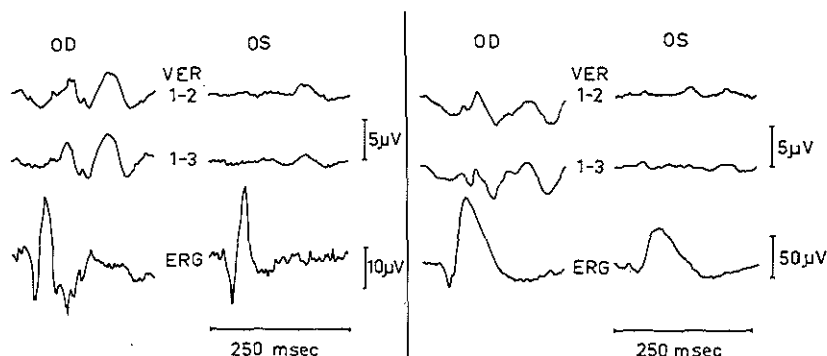
Fig. 41

Patient I, male, age 33 years

left side: full field stimulation in light adapted state: ERG (250 counts) and VER
(500 counts)

right side: full field stimulation in dark adapted state: ERG (50 counts) and VER
(500 counts)

Description (see also figures 40 and 41: 8°-recording and recording of ERG and VER
after full field stimulation in light and in dark adapted state:

ERG OD after local (foveal) stimulation: 6.5 μV: normal.
ERG OS after local (foveal) stimulation: not interpretable.
VER OD after local (foveal) stimulation: discernible.
VER OS after local (foveal) stimulation: absent.
ERG OD after full field stimulation in light adapted state: 25.5 μV: borderline value.
ERG OS after full field stimulation in light adapted state: 28.5 μV: borderline value.
ERG OD after full field stimulation in dark adapted state: 105 μV: borderline value.
ERG OS after full field stimulation in dark adapted state: 55 μV: subnormal.
VER OD after full field stimulation in light and in dark adapted state: well developed.
VER OS after full field stimulation in light and in dark adapted state: absent.

Discussion of the electro-ophthalmological findings in patient I

1. *ERG and VER after local (foveal) stimulation*

In this case our examination primarily focused on the results after stimulation
of the left eye. Undoubtedly as a result of the poor visual acuity and the
resulting inability to fix the stimulus, however, these results are not interpretable.

102

2. *ERG and VER after local (foveal) stimulation*

In light adapted state, the ERGs of both eyes had a borderline value; in dark adapted state, the ERG of the left eye was subnormal. This, too, must have been influenced by the fact that the patient did not know how and where to look with his left eye.

3. *VER after full field stimulation in light and in dark adapted state*

Since the amplitudes of the ERGs after full field stimulation of both eyes were equal, the simultaneously recorded VERs can be optimally interpreted. There was a marked interdifference between these VERs, and this fact objectively demonstrates a disorder of conduction in the left optic nerve. It is true that a similar difference was found between the VERs after full field stimulation in dark adapted state, but the simultaneously recorded ERGs differed so much in amplitude that this part of the examination cannot be reliably interpreted.

4. *Interpretation of the electro-ophthalmological findings*

Also in view of the history, the disorder of conduction in the left optic nerve can only be explained on the basis of large-scale Wallerian degeneration of nerve fibres.

PATIENT II, male, born 20th August 1919.

Six months before we had the opportunity to examine this patient, he had been involved in a moped accident after which he was hospitalized with a haematoma of the left orbit. Visual acuity of the left eye was slightly diminished immediately after the accident. The patient also complained of metamorphopsia of this eye. Visual acuity did not improve in the course of time, and the metamorphopsia failed to disappear.

Examination

Visual acuity	OD 1.1	OS 0.6
Media	no abnormality	no abnormality
Fundi	no abnormality	as compared with OD, 'pale' disc; no distinct optic atrophy
Intraocular pressure	normal	normal

103

|		
Visual fields (Goldmann)	no abnormality	1–1 isopter absent; peripheral visual field limitation in nasal lower quadrant
Colour discrimination	normal	normal
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER	
	ERG and VER after full field stimulation in light and in dark adapted state	

Fig. 42

Patient II, male, age 51 years

Description (see also figures 42 and 43: 8°-recording, and recording of ERG and VER after full field stimulation in dark adapted state)

ERG OD after local (foveal) stimulation: 5.7 µV: normal.
ERG OS after local (foveal) stimulation: 5 µV: normal.
VER OD after local (foveal) stimulation: well developed.
VER OS after local (foveal) stimulation: absent.
ERG OD after full field stimulation in dark adapted state: 130 µV: borderline value.
ERG OS after full field stimulation in dark adatped state: 125 µV: borderline value.
VER OD after full field stimulation in dark adapted state: well developed.
VER OS after full field stimulation in dark adapted state: discernible.

Fig. 43

Patient II, male, age 51 years. ERG (50 counts) and VER (500 counts), full field stimulation in dark adapted state

Discussion of the electro-ophthalmological findings in patient II

1. *The FERG*

The normal amplitudes of the photopic b-wave of both eyes objectively demonstrate that the patient properly fixed the stimulus.

2. *The VER after local (foveal) stimulation*

The marked difference between the VERs after foveal stimulation of both eyes indicates the presence of a disturbance of conduction in the maculopapillary fibre bundle of the left optic nerve.

3. *ERG after full field stimulation in dark adapted state*

Although the recorded amplitudes of the scoto-photopic b-wave were at the lower limit of normal, it may nevertheless be assumed that the largest possible retinal area was fairly well stimulated.

4. *VER after full field stimulation in dark adapted state*

Again a difference between VER of the right eye (well developed) and VER of the left eye (discernible) was found. In view of the absence of the VER after local stimulation of the left eye, we believe that the VER after full field stimulation of this eye represents the cortical activity determined by the peripheral retina.

5. *Interpretation of the electro-ophthalmological findings*

The data available are: VOS 0.6, only slightly reduced central sensitivity in the visual field, and absence of the VER after foveal stimulation. These findings suggest that a great many fibres in the maculopapillary bundle were still conducting, but most of them with an unequal conduction velocity. Similar results were obtained in the examination of patient II in the optic neuritis group (see page 64). In her case, we ascribed the unequal conduction time of the nerve fibres to the process of demyelination (see discussion of the electro-ophthalmological findings). In this case of traumatic lesion of the left optic nerve, too, we are inclined to explain the findings by assuming that demyelination of nerve fibres of the maculopapillary bundle occurred. If this is correct, then all data of the examination are in agreement. The mechanism by which (selective) demyelination of nerve fibres in the maculopapillary bundle was caused, however, remains an open question.

PATIENT III, male, born 10th January 1940.

This young man reported at the out-patient clinic for treatment because he had for some time noticed diminishing visual acuity of both eyes. He had long been a boxer, and had taken heavy blows on the eyes on several occasions. He himself believed that his poor visual acuity was a consequence of his boxing activities, which he had therefore discontinued. He was in good general health. As far as he knew there was no history of serious (eye) diseases in the family.

Examination

Visual acuity	OD 0.4	OS 0.2
Media	no abnormality	no abnormality
Fundi	no abnormality	no abnormality
Visual fields (Goldmann)	normal	1–1 isopter slightly limited; otherwise about normal.*
Colour discrimination	normal	normal

Electro-ophthalmology   ERG: after local (foveal) stimulation with field size 8° and 5°; simultaneous recording of VER.

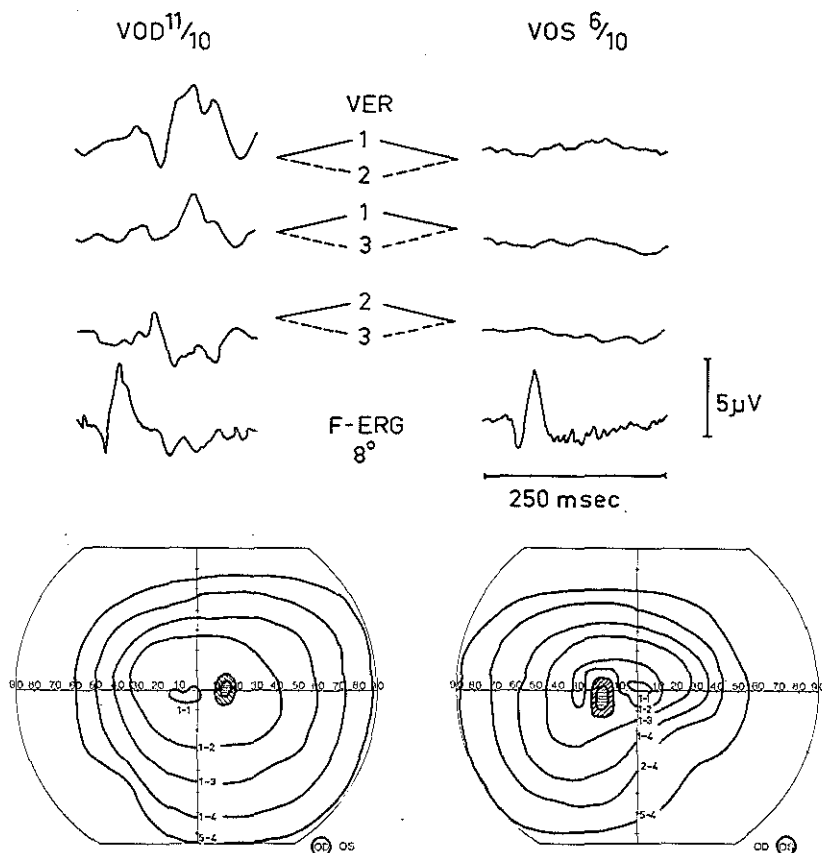ERG and VER after full field stimulation in light and in dark adapted state.

Total scotopic and photopic ERG.

EOG.

Description (see also figures 44 and 45: 8°-recording, and recording of ERG and VER after full field stimulation in light and in dark adapted state):

ERG OD after local (foveal) stimulation: 5.3 μV: normal.
ERG OS after local (foveal) stimulation: 5.6 μV: normal.
VER OD after local (foveal) stimulation: discernible?/absent.
VER OS after local (foveal) stimulation: absent.
ERG OD after full field stimulation in light adapted state: 15 μV: borderline value.
ERG OS after full field stimulation in light adapted state: 15 μV: borderline value.
ERG OD after full field stimulation in dark adapted state: 67 μV: subnormal.
ERG OS after full field stimulation in dark adapted state: 32 μV: subnormal.
VERs ODS after full field stimulation in light adapted state: discernible.
VER OD after full field stimulation in dark adapted state: discernible(?).
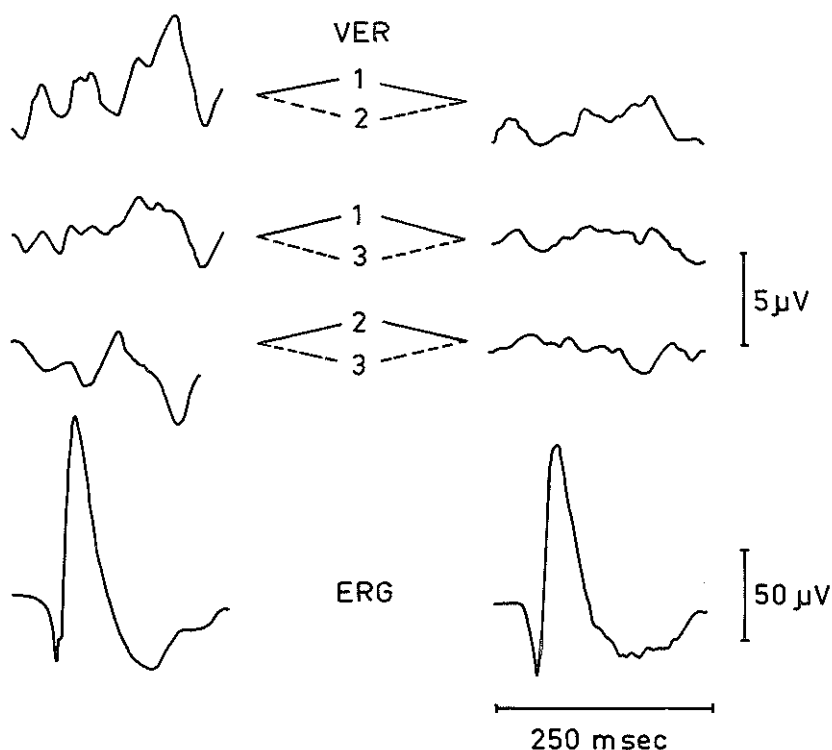VER OS after full field stimulation in dark adapted state: absent.
Total scotopic and photopic ERG OD: normal.
Total scotopic and photopic ERG OS: low normal values.
EOG ODS: normal.

---

* Static perimetry might have disclosed abnormalities.

VOD ⁴/₁₀ VOS ²/₁₀

VER
1
2

1
3

F-ERG
8°

5 μV

250 msec

Fig. 44

Patient III, male, age 31 years

OD OS OD OS
VER VER
1 2 1 2
5μV 5μV
1 3 1 3
ERG ERG 50μV
10μV

250 msec 250 msec
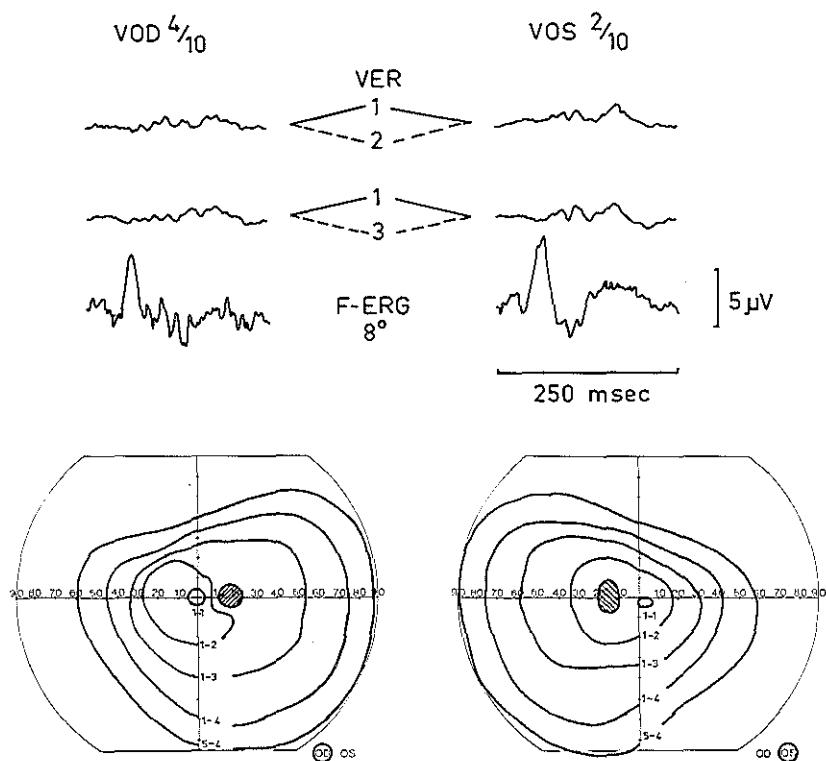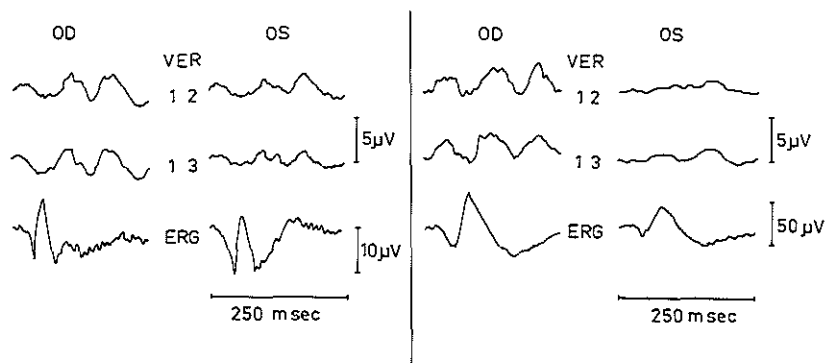
Fig. 45

Patient III, male, age 31 years
left side: full field stimulation in light adapted state: ERG (250 counts) and VER (500 counts)
right side: full field stimulation in dark adapted state: ERG (50 counts) and VER (500 counts)

Discussion of the electro-ophthalmological findings in patient III

1. *The FERG*

The FERGs of both eyes were normal, which shows that the patient properly fixed the stimulus.

2. *The VER after local (foveal) stimulation*

The VERs after local (foveal) stimulation of both eyes were so ill developed that a disturbance of conduction in the maculopapillary fibre bundles must be assumed to exist.

3. *ERG after full field stimulation in light and in dark adapted state*

Only in light adapted state was an interpretable result obtained. In dark adapted state, the amplitude of the scoto-photopic b-wave for both eyes was so low that a retinal disorder might be contemplated. This, however, is refuted by the total photopic and scotopic ERG which, with a better technique of examination, gave normal recorded values.

4. *VER after full field stimulation in light and in dark adapted state*

The VERs after full field stimulation in light adapted state were discernible for both eyes. Since the VERs after local (foveal) stimulation were absent, it can be assumed that the VERs after full field stimulation were determined by the peripheral retina.

The VERs after full field stimulation in dark adapted state could not be evaluated because (in view of the subnormal ERGs) the retina was probably not optimally stimulated (fatigue on the patient's part in the course of the protracted examination may have been a factor of influence in this respect).

5. *Conclusion*

Traumatic optic atrophy is characterized in some cases by a central scotoma in the visual field; in less serious cases, atrophy of the disc does not always become visible at fundoscopy. Our patient, too, showed no fundoscopic changes; nor could a central scotoma be demonstrated in the visual field (at least not by quantitative perimetry). Nevertheless, the results of the electro-ophthalmological examination do indicate the probability of a disturbance of conduction in the maculopapillary fibre bundles of both eyes. This patient may therefore have been right in believing that a causal relationship exists between his boxing and the diminished visual acuity of his eyes.

OTHER AFFECTIONS OF THE OPTIC NERVE AND RETINA

The following conditions will be discussed:
– simple glaucoma; discussion of two patients.
– opticoneuropathy resulting from medication (ethambutol); discussion of one patient.
– juxtapapillary chorioretinitis (JENSEN); discussion of one patient.

SIMPLE GLAUCOMA

In the context of our study we will confine ourselves to the following statement about this condition. Its definition is: 'By simple glaucoma is meant a chronic condition, wherein the ocular tension is raised above a level compatible with the continued health and function of the eye, associated with a gonioscopically open angle and a reduced facility of aqueous outflow. If present over a sufficient period it causes characteristic pathological changes at the optic disc (i.e. cupping of the disc) and in the visual fields' (after DUKE ELDER 1969).

Examination of the visual fields is of paramount importance to establish the diagnosis and as a measure for the progression of the condition. The principal changes occurring are:

1. development of isolated scotomas around the fixation point; after some time these may fuse with each other and with the blind spot to form an arch-shaped scotoma; a lesion of nerve fibre bundles underlies these characteristic changes;

2. a general decrease of sensitivity and limitation of the peripheral field of vision, especially on the nasal side;

3. retention of central vision until a late stage.

The manner in which the (increased) intraocular pressure leads to a disturbance of visual functions has been the subject of numerous publications. In recent years the general opinion has been in favour of the assumption that increased intraocular pressure causes, or is accompanied with, vascular changes in or near the optic disc, leading to a condition of localized ischaemia. Any coinciding vascular sclerosis within the nerve intensifies this damage. The localized ischaemia leads to damage of nerve fibre bundles. The fact that central vision remains intact for a long time implies that the maculopapillary fibre bundle may not be involved in the process until a late stage.

PATIENT I, female, born 12th December 1910.

This patient had consulted her ophthalmologist about reading difficulties. Examination revealed a bilateral increase of intraocular pressure (TOD 28 mm Hg; TOS 23 mm Hg, determined with the applanation tonometer). There was a glaucomatous cupping of the optic discs. Otherwise the patient was in good health. So far as could be established, there was no family history of eye diseases of special significance. Treatment was started on a diagnosis of bilateral simple glaucoma. At the time of the electro-ophthalmological examination, she had been using 4% pilocarpine eye-drops for a week.

Examination

Visual acuity	OD 1.0	OS 1.0
Media	no abnormality	no abnormality
Iridocorneal angle	open, slightly pigmented trabecular system	same as OD
Fundi	temporal mural cupping of optic disc	same as OD
Intraocular pressure	25 mm Hg	17 mm Hg
Visual fields (Goldmann)	severe glaucomatous changes in pericentral visual field, e.g. so-called Bjerrum scotoma; central 1–1 isopter absent; only temporal lower quadrant of peripheral visual field intact	1–1 isopter absent; no other distinct abnormality
Colour discrimination	normal	normal
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER	

Description (see also figure 46: 8°-recording):

ERG OD after local (foveal) stimulation: 5.2 μV: normal.
ERG OS after local (foveal) stimulation: 5.6 μV: normal.
VER OD after local (foveal) stimulation: well developed.
VER OS after local (foveal) stimulation: well developed.

Discussion of the electro-ophthalmological findings in patient I

1. *The FERG*

The recordings show that the patient adequately fixed the stimulus with both eyes.

2. *The VER after local (foveal) stimulation*

The VERs of both eyes were rated well developed. The configuration of the curves of right and left eye is highly similar, but the amplitude is clearly different; specifically, the amplitude of the VER, after stimulation of the right eye, is much lower than that of the VER, after stimulation of the left eye.
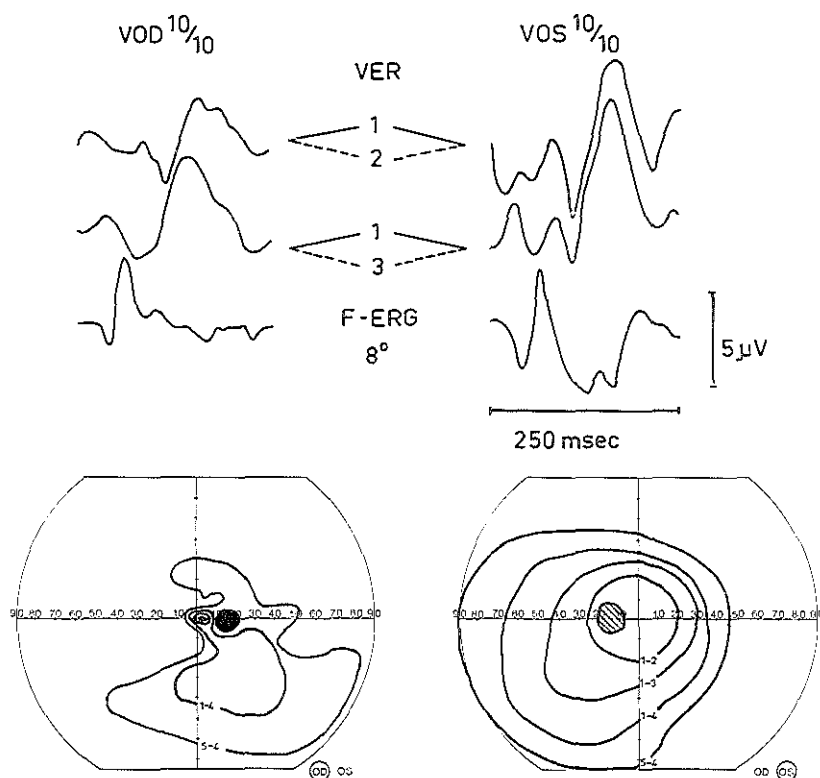
Fig. 46

Patient I, female, age 58 years

3. *Interpretation of the electro-ophthalmological findings*

The general ophthalmological examination shows that the simple glaucoma had taken a much more serious course in the right eye than in the left eye. The central visual field of the right eye is more or less intact over an area of less than 10° subtended visual angle; the central visual field of the left eye is intact over a much larger area. With this the difference in amplitude between the VERs after stimulation of right eye and left eye is in suggestive agreement, (cf. the description of the experiments of VAN HOF (1965) and of VAN LITH (1970) on pages 8 and 9). The difference in amplitude might suggest that in the right maculopapillary bundle a number of fibres are out of function, or that more fibres dropped out than in the left maculopapillary bundle.

Generally speaking, however, it has been impossible in our study to compare the VERs of both eyes of the same patient so accurately that, solely on the basis of a difference in amplitude as found in this case, it can be established with certainty whether a difference in conduction exists between the maculopapillary fibre bundles of the two optic nerves.

PATIENT II, female, born 27th November 1903.

This patient was first seen on account of a sensation of pain 'behind' the right eye, which had been present a few months. Examination disclosed for both eyes diminished visual acuity and increased intraocular pressure (ATOD 43 mm Hg; ATOS 30 mm Hg). Further examination confirmed the diagnosis simple glaucoma. Medication given to regulate the intraocular pressure was successful; the electro-ophthalmological examination was made shortly before the regulating medication was started. According to the patient, she was in good general health. There was no family history of significant eye diseases.

Examination

	OD	OS
Visual acuity	0.3	0.8
Media	no abnormality	no abnormality
Iridocorneal angle	open: no goniosynecchiae	open
Fundi	glaucomatous cupping of optic disc	no distinct glaucomatous cupping of disc
Intraocular pressure	43 mm Hg	30 mm Hg
Visual fields (Goldmann)	relative central and paracentral scotomas of varying intensity, arising from the blind spot and extending 25° from fixation point; periphery normal	no distinct abnormalities

113

Colour discrimination	HRR: normal	normal
	15HUE: failure	
	anomaloscope: failure	
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER	

VOD $\frac{3}{10}$ VOS $\frac{8}{10}$

VER

1
2

1
3

2
3

F-ERG
8°

5µV

250 msec
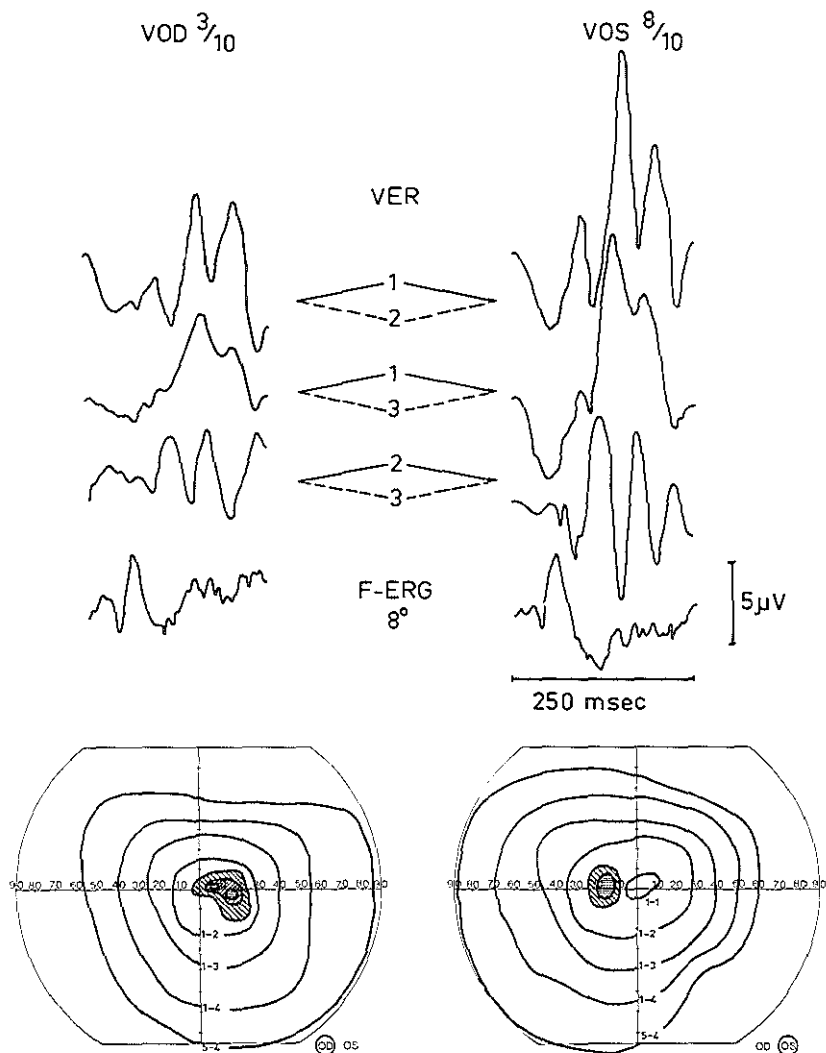
Fig. 47

Patient II, female, age 66 years

114

Description (see also figure 47: 8°-recording):

ERG OD after local (foveal) stimulation: 5 μV: normal.
ERG OS after local (foveal) stimulation: 5 μV: normal.
VER OD after local (foveal) stimulation: well developed.
VER OS after local (foveal) stimulation: well developed.

Discussion of the electro-ophthalmological findings in patient II

1. *The FERG*

Despite the diminished visual acuity (particularly of the right eye), the patient did adequately fix the stimulus with both eyes.

2. *The VER after local (foveal) stimulation*

The amplitude of the VER after stimulation of the right eye differs clearly from that of the VER after stimulation of the left eye; nevertheless, both curves could be rated well developed.

3. *Interpretation of the electro-ophthalmological findings*

Visual acuity and visual field findings indicate the probability of a disturbance of conduction in the maculopapillary fibre bundle–particularly that on the right side. The difference in amplitude between the VERs after stimulation of both right and left eye is consistent with this. However, this difference is not so marked that solely the electro-ophthalmological findings would warrant a conclusion in favour of a disturbance of conduction in, particularly, the right maculopapillary fibre bundle.

OPTICONEUROPATHY RESULTING FROM ETHAMBUTOL MEDICATION

Since CARR & HENKIND's publication (1962) it has been known that ethambutol (2,2'-ethylenediamino-di-1-butanol) can exert a toxic influence on the optic nerve. Ethambutol is used in cases of tuberculosis which show no adequate response to conventional tuberculostatic medications.

The patient to be discussed had been using ethambutol (daily dose 1200 mg) for a year because of miliary and renal tuberculosis. During this period he had noticed gradual diminution of visual acuity in his right (intact) eye; the left eye had been aphakic for years as a result of an injury.

PATIENT III, male, born 14th August 1924.

Examination

Visual acuity	OD 3/60	OS 6/60
Media	no abnormality	aphakia
Fundi	pale optic disc; variable arteriolar luminal width near the disc	same as OD
Intraocular pressure	normal	normal
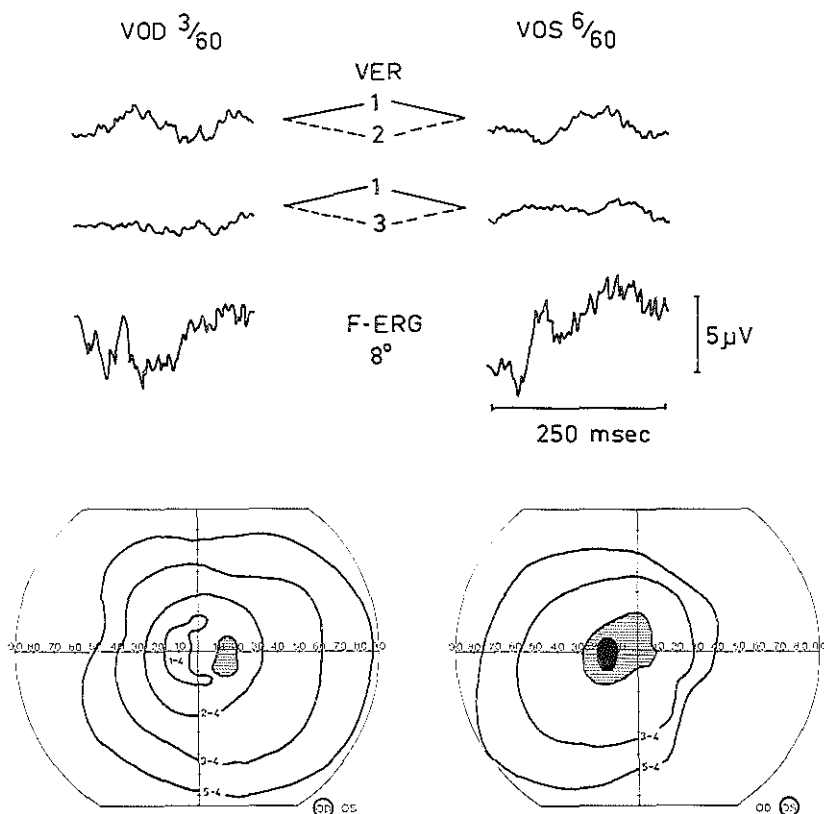
Fig. 48

Patient III, male, age 57 years

Visual fields (Goldmann)	relative central scotoma; decreased general sensitivity in peripheral visual field	same as OD
Colour discrimination	not determinable	not determinable
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER ERG and VER after full field stimulation in light adapted state	

Description (see also figures 48 and 49: 8°-recording and recording of ERG and VER after full field stimulation in light adapted state)

Note: the left (aphakic) eye was electro-ophthalmologically examined while the patient was not wearing correcting glasses.

ERG OD after local (foveal) stimulation: 4.3 μV: borderline value*.
ERG OS after local (foveal) stimulation: 5.8 μV: normal(?)*
VER OD after local (foveal) stimulation: absent/(discernible).
VER OS after local (foveal) stimulation: absent/(discernible).
ERG OD after full field stimulation in light adapted state: 19 μV: borderline value.
ERG OS after full field stimulation in light adapted state: 32 μV: normal.
VER OD after full field stimulation in light adapted state: discernible.
VER OS after full field stimulation in light adapted state: discernible.
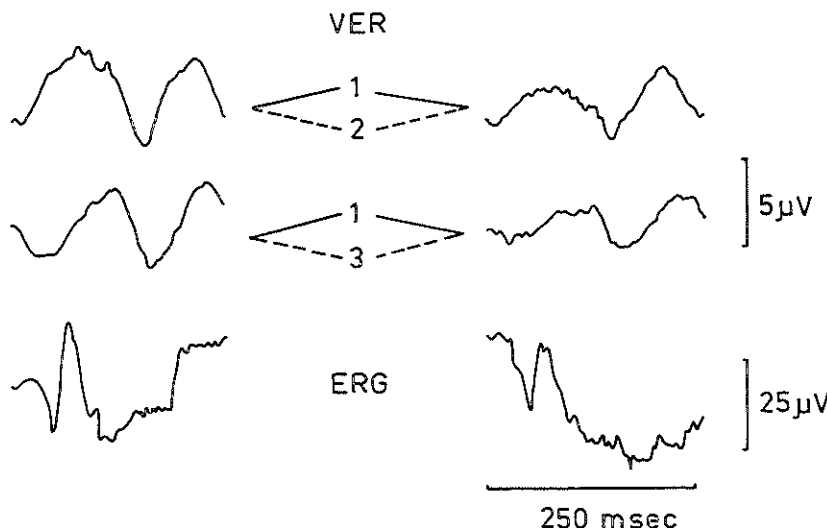
Fig. 49

Patient III, male age 57 years. ERG (70 counts) and VER (500 counts), full field stimulation in light adapted state

---

* Unreliable recording

117

Discussion of the electro-ophthalmological findings in patient III

1. *The FERG*

This patient was very tense during examination. This, together with his poor visual acuity may explain the patient's inability to achieve adequate fixation of the stimulus, as shown by the FERG of his right (intact) eye. The patient was not wearing glasses to correct the aphakia of the left eye during the recordings, and the FERG of the left eye could therefore not be evaluated.

2. *The VER after local (foveal) stimulation*

The VERs after stimulation of both right and left eye were virtually absent. It is difficult to establish whether this was a consequence of poor fixation (OD) or of the presence of a block in the conduction of the maculopapillary fibre bundle. It seems most plausible that both factors played a role.

3. *The ERG after full field stimulation in light adapted state*

The ERG of the right eye was rated as borderline value: full field stimulation was probably just adequate. The ERG of the left eye showed a normal amplitude.

4. *The VER after full field stimulation in light adapted state*

Some cortical activity is recognizable in the responses. Due to difficulties of interpretation of the results after local stimulation of the retina it cannot be established, whether this cortical activity was achieved by stimulation of the peripheral or of the central retina.

JUXTAPAPILLARY CHORIORETINITIS (JENSEN)

PATIENT IV, female, born 12th April 1949.

The patient was first treated for juxtapapillary chorioretinitis of the right eye five years before the electro-ophthalmological examination was carried out. The focus was localized on the nasal side of the disc. Toxoplasmosis reactions were positive. The process was arrested by medication with Tripyron (sulphadiazine, sulphamerazine and sulphadimidine) and Daraprim (pyrimethamine).

At the time of our examination the process was active again, and had extended into a retinal area immediately adjacent to the original focus. The above mentioned medication was re-instituted.

118

Examination

Visual acuity	OD 1.0	OS 1.0
Media	inflammatory cells in vitreous humour	no abnormality
Fundi	chorioretinitis focus on nasal side of disc; pigmentations of original focus visible	no abnormality
Visual fields (Goldmann)	defect of nasal lower quadrant and part of temporal lower quadrant; central visual field intact	normal
Colour discrimination	normal	normal
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER	
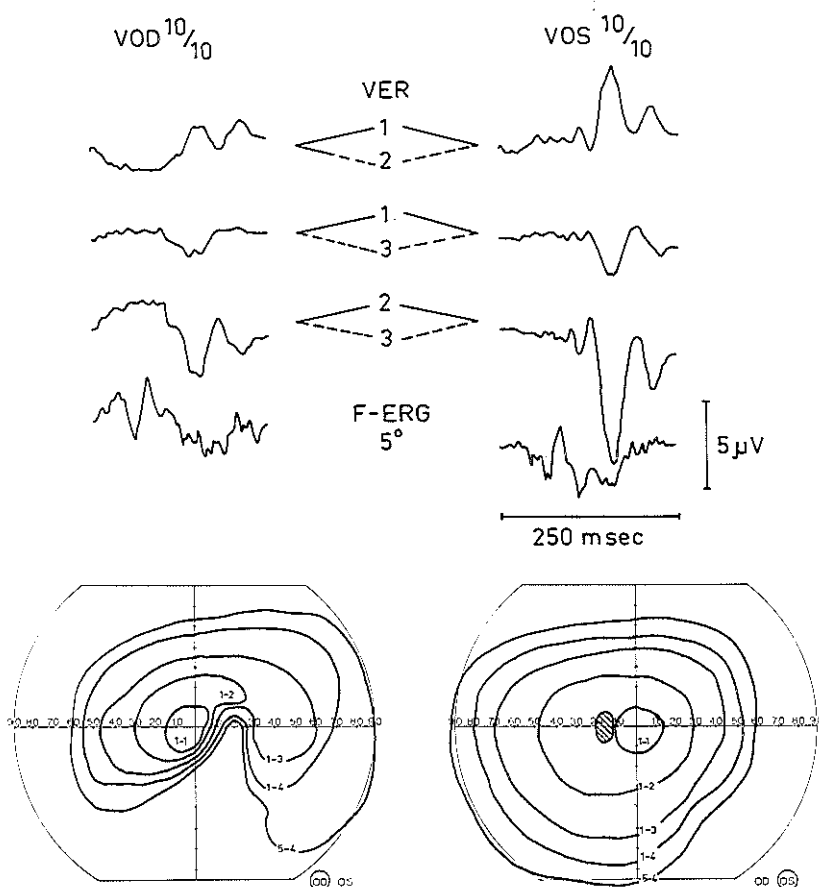
Fig. 50

Patient IV, female, age 21 years

Description (see also figure 50: 5°-recording):

ERG OD after local (foveal) stimulation: 3.6 µV: normal.
ERG OS after local (foveal) stimulation: 3.0 µV: normal.
VER OD after local (foveal) stimulation: discernible/well developed.
VER OS after local (foveal) stimulation: well developed.

Discussion of the electro-ophthalmological findings in patient IV

1. *The FERG*

The normal amplitudes of the photopic b-wave show that the patient did adequately fix the stimulus.

2. *The VER after local (foveal) stimulation*

The curves obtained after stimulation of both right and left eye are of the same configuration. However, the VER of the left eye has a higher amplitude than the VER of the right eye. This would seem to suggest the conduction in the right maculopapillary fibre bundle to be less optimal than that in the left. Nevertheless we believe that the difference between the two curves is not sufficiently marked (particularly since they are of identical configuration) to conclude in favour of a difference in conduction between the two fibre bundles on account of the electro-ophthalmological findings alone.

120

INTRACRANIALLY LOCALIZED CAUSES OF DISTURBED VISION

We examined 29 patients with an intracranial disorder which affected the normal function of the visual system. In terms of the established diagnoses, these patients constitute a heterogeneous group. For greater convenience in discussing their cases, the following subdivision was made.

Group I. Patients in whom an abnormality of the optic nerve and/or optic tract is to be expected in view of the diagnosis:
a. Nine patients with choked discs;
b. Five patients with a tumour arising from the hypophysis.

These patients were examined in an effort to establish whether our electro-ophthalmological method of investigation would enable us to demonstrate objectively a disorder of conduction in the above-mentioned structures of the visual system.

Group II. Patients with homonymous hemianopia:
a. Twelve patients who had sustained a cerebrovascular accident, as a result of which one of the two optic hemicortices no longer functioned;
b. Three patients with a brain tumour which had been surgically removed; homonymous hemianopia was a result of the hemispherectomy.

These patients were examined in order to establish whether, with the placements chosen for the scalp electrodes (see page 18), it would be possible to demonstrate objectively that one of the two hemicortices no longer showed any activity.

Group Ia: Nine patients with choked discs

PATON & HOLMES (1911) defined oedema of the optic disc as 'a passive oedema, due to raised intracranial pressure without primary inflammatory changes and often without disturbance of function'. With this definition they were the first to differentiate between choked disc and optic neuritis (papillitis). However, it is not only increased intracranial pressure that can give rise to papilloedema.

It can be said in general that oedema of the optic disc results when the normal relationship of the circulation on either side of the lamina cribrosa is disturbed.

121

A survey of the causes which can lead to this situation looks as follows:

A. Ocular causes : acutely decreased (e.g. perforation of the eyeball) or acutely increased intraocular pressure (acute glaucoma).*

B. Orbital causes : tumours, abscesses, endocrine exophthalmos.

C. Intracranial causes: 1) increased intracranial pressure due to various causes;
        2) changes in the cerebrospinal fluid;
        3) (indirectly) tumours of the spinal cord;
        4) pseudo-tumour of the brain.

D. Systemic diseases : e.g. vascular hypertension.
  (data derived from DUKE ELDER 1971)

Pathological anatomical changes

Papilloedema is accompanied by an accumulation of fluid in the perivascular spaces and between the nerve fibres; this fluid contains few, if any, inflammatory cells.

Some authors (e.g. DUKE ELDER) hold that also oedema of the nerve fibres themselves occurs at an early stage. There is no agreement on this point. PATON & HOLMES (1911) believed that the nerve fibres themselves were not involved in the process until a late stage. CONE & MCMILLAN (1932) described oedema of the naked nerve fibre as an early phenomenon; this oedema was described as initially not associated with degeneration. BONAMOUR et al. (1968), on the contrary, maintained that the pure forms of choked disc cause little or no oedematous changes of the nerve fibres, at least not in the initial stage. DUKE ELDER (1971) described the changes in the nerve fibres as follows:

'At an early stage the non-medullated fibres upon the disc, particularly those near the margin, swell up and show varicosities wherein the fine neuro-fibrils are seen clearly separated by the oedematous fluid. As the swelling progresses these varicosities multiply and enlarge until the disc is filled with them. After a variable time degenerative changes begin to develop: the neuro-fibrils in the varicosities disappear and fine granules fill the fusiform enlargements. Eventually the granular structure becomes homogeneous, and the enlargements appear to lose connection with the fibres from which they have developed to form cytoid bodies and, as degeneration proceeds, these too suffer lipid degeneration and disappear. Finally, a centripetal Wallerian degeneration develops in the nerve fibres and an axonal chromatolysis in their retinal ganglion cells of origin, while the usual reaction of the neuroglial tissue completes the picture of degeneration – a phagocytosis of the degenerated neural elements by the microglia, and their replacement by a marked proliferation of astrocytes.'

---

* In this case papilloedema can occur as part of a generalized oedema of the eye tissues. This might result from occlusion of the peripapillary blood vessels due to the acutely increased intraocular pressure, giving rise to anoxia. (HAYREH 1969)

The blood vessels of the disc, specifically the veins and capillaries, are dilated; and haemorrhages on the disc are frequently observed.

'The central vein, however, is usually compressed where it leaves the optic nerve and enters the vaginal space. The subarachnoid space of the nerve is greatly distended so that it ends anteriorly at the sclera in a large cul de sac. In the nerve there is invariably much subpial oedema distal to the point of entry of the vessels, a process which usually extends along the septa, while the perivascular lymph sheath of the central vessels may be markedly dilated.' (DUKE ELDER 1971)

If the papilloedema is of long standing and/or of severe type then endothelial proliferation of the small vessels occurs. In the large vessels, thickening of the adventitia can be observed, followed by hyaline degeneration.

The papilloedema can cause the adjacent retina to be lifted so that the connection between retina and pigment epithelium is locally lost (this separation of retina from pigment epithelium explains why an enlarged blind spot is found in examination of the visual field).

Oedema and bleeding occur also in retinal areas adjacent to the disc, and particularly in the layer of nerve fibres. The deeper layers are less vulnerable in this respect. The oedema can extend to the area of the macula lutea. Not infrequently, this process is associated with the formation of delicate plicae in the internal limiting membrane.

If the cause of the choked disc is removed at an early stage, a complete recovery is possible, with no histological changes in the nerve fibres near the disc other than, sometimes, some slight proliferation of glial cells.

Many theories on the pathogenesis of papilloedema have been advanced in the course of the years. A discussion of these theories is not within the scope of our electro-ophthalmological study, and for a review we refer to DUKE ELDER: System of Ophthalmology (Vol. XII Neuro-ophthalmology, 1971). One of the most recent views is presented in E. WEIGELIN's 'Local circulation in papilloedema '(Proceedings of the Second Mackenzie Memorial Symposium, Glasgow 1971, in Press).

Symptomatology and clinical picture

In the early stages of papilloedema, visual functions are little disturbed: visual acuity can be quite normal, but in most cases one finds an enlarged blind spot in the visual field. Visual acuity can diminish if the oedema extends into the macular region, in which case a central scotoma is found in the visual field.

Once atrophy of the nerve fibres has started, progressive concentric limitation of the peripheral visual field occurs in addition to the central changes already mentioned.

Fundoscopy reveals a prominent optic disc. The prominence initially does not exceed about 2 dioptres, but in the course of the process it can increase to an average of 5–7 dioptres or more (DUKE ELDER 1971). The physiological cupping of the disc disappears because it is filled with oedematous tissue and because the lamina cribrosa curves anteriorly (in the direction of the eye cavity). The colour of the disc is abnormally reddish due to dilation of the veins and capillaries. This dilation, which expresses circulatory impairment, can be demonstrated also by fluorescent angiography. The long after-fluorescence also indicates the increased capillary permeability. The outline of the disc is blurred by the oedema; bleeding frequently occurs on and around the disc. Finally, the oedema can extend far beyond the margin of the disc, and in that case delicate stellate or radiating plicae are seen in the macular region.

Personal observations

PATIENT I, female, born 10th July 1946

This patient was hospitalized in the Neurological Department of the Dijkzigt Teaching Hospital on account of headaches, vomiting, visual disturbances and complaints of transient diplopia. She had been in good health until 8 days prior to admission, when the above mentioned symptoms commenced. The patient had sustained a head injury at age 3 and again 7 years prior to admission. Neurological examination yielded a diagnosis of serous meningitis. Fundoscopy disclosed choked discs surrounded by retinal oedema which extended as far as the macular region. Moreover, yellowish exudates were visible in the macular region of both eyes.

Treatment consisted of weekly lumbar punctures, which reduced the intracranial pressure and the papilloedema. The yellowish exudates disappeared almost completely from the macular region of both eyes.

We examined this patient during her third week in hospital (the total stay in hospital was six weeks).

Examination

Visual acuity	OD ranging from 0.5 to 1.0	OS 0.8
Media	no abnormality	no abnormality
Fundi	choked disc, prominence of 3 dioptres; disc surrounded by an area of retinal oedema which encompasses the macula; delicate folds and yellowish exudates in macular region	same as OD

Visual fields	greatly enlarged blind spot;	same as OD
(Goldmann)	otherwise normal visual field*	
Colour discrimination	not examined	not examined
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°;	
	simultaneous recording of VER.	

Description (see also figure 51: 8°-recording):

ERG OD after local (foveal) stimulation: 5.8 μV: normal.
ERG OS after local (foveal) stimulation: 4.9 μV: about normal.
VER OD after local (foveal) stimulation: well developed.
VER OS after local (foveal) stimulation: well developed.

$$VOD\ ^5/_{10} - ^{10}/_{10} \qquad\qquad VOS\ ^8/_{10}$$
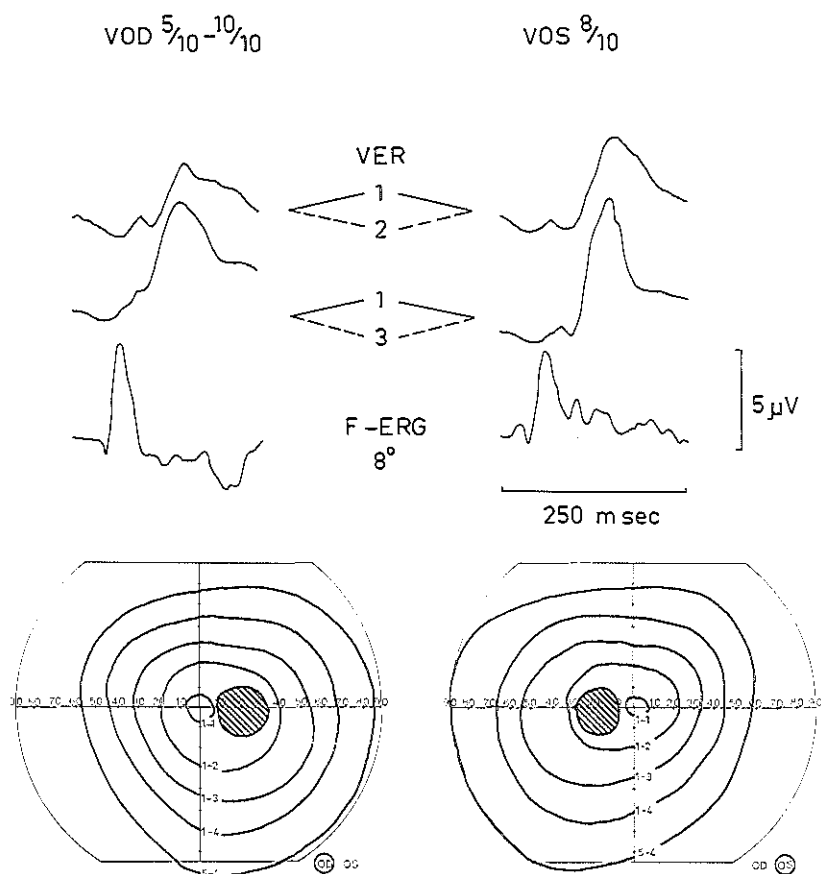
Fig. 51

Patient I, female, age 23 years

---

* In view of the result of the examination of the visual acuity, reduced central sensitivity in the visual field must be assumed; however, this could apparently not be demonstrated with Goldmann's quantitative perimetry.

Discussion of the electro-ophthalmological findings in patient I

The normal FERGs for both eyes objectively show that the simultaneously recorded VERs were obtained by photic stimulation of the central fovea. These were rated 'well developed', indicating that conduction in the maculopapillary fibre bundles was not seriously disturbed. This is consistent with the results of examinations of visual acuity and visual fields. So far as the maculopapillary fibre bundles are concerned, therefore, our findings support the conception of BONAMOUR et al. (1968) that few or no changes occur in the nerve fibres themselves at an early stage of papilloedema.

PATIENT II, male, born 20th May 1924

This patient noticed diminution of visual acuity of both eyes 4 months prior to the electro-ophthalmological examination. At ophthalmological examination, oedema of the optic disc was found in both fundi. An inquiry disclosed that papilloedema in both eyes had been observed as long as three years before the examination under discussion. At that time, neurological examination had failed to disclose any abnormality. Bilateral optic neuritis was considered as possible cause. Neurological examination was repeated when – only much later – visual acuity of both eyes began to deteriorate. This examination established the presence of a tumour in the posterior cranial fossa. Our examination was done before surgical removal of this tumour.

Examination

Visual acuity	OD 0.2		OS 0.2
Media	no abnormality		no abnormality
Fundi	reddish disc, prominence of 4 dioptres; small haemorrhages along the dilated small vessels on the disc; retinal venules show tortuosities and variations of calibre; arterioles very narrow.		prominence of disc 3 dioptres; other fundoscopic features as in OD
Intraocular pressure	normal		normal
Visual fields (Goldmann)	blind spot greatly enlarged; object 1–1 is not perceived; the 1–2 isopter is very limited, as are also the 1–3 and 1–4 isopters; the periphery is normal		blind spot greatly enlarged; object 1–1 is not perceived; the 1–2, 1–3 and 1–4 isopters are limited; the 1–4 isopter suggests a temporal upper quadrant anopsia*
Colour discrimination	not examined		not examined
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER		

---

* Possibly a consequence of the presence of the tumour in the posterior cranial fossa.

Description (see also figure 52: <u>5</u>°-recording):

ERG OD after local (foveal) stimulation: 3.8 μV: normal.
ERG OS after local (foveal) stimulation: 4.0 μV: normal.
VER OD after local (foveal) stimulation: discernible/absent.
VER OS after local (foveal) stimulation: discernible/absent.

Fig. 52

Patient II, male, age 46 years

Discussion of the electro-ophthalmological findings in patient II

1. *The FERG*
The normal FERGs of both eyes prove that patient did properly fix the stimulus. It also lends no support to the assumption that pathological changes occurred in the bipolar cell layer of the central retina as a result of the long standing papilloedema.

2. *The VER after local (foveal) stimulation*
The VERs after local (foveal) stimulation of right and left eye are indicative of the existence of a disorder of conduction in the maculopapillary fibre bundles of both optic nerves.

3. *Interpretation of the electro-ophthalmological findings*
In this case the choked discs had been present a number of years. Diminution of the visual acuity of both eyes had recently occurred. From this recent deterioration of visual acuity as well as from the electro-ophthalmological findings it can be concluded that the optic nerves, more specifically the maculo-papillary fibre bundles, were subject to extensive pathological changes resulting in atrophy of the nerve fibres.

The findings obtained in examination of the remaining patients of group Ia are summarized in the survey III on page 154.

Conclusion

The objective electro-ophthalmological findings confirm that oedema of the optic nerve which occurs in association with increased intracranial pressure, must differ in type from the toxic oedema which occurs in the acute stage of optic neuritis.

At the early stage of papilloedema as a result of increased intracranial pressure, visual acuity is good or fair, the visual fields are virtually normal and the VERs after local stimulation of the retina are well developed. It is only when oedema in the optic nerve gives rise to more extensive pathological changes, as a rule after some considerable time, that visual acuity diminishes and visual fields show abnormalities. In that case the VERs are either absent or merely discernible.

In the case of toxic oedema these changes occur immediately, with as a rule a much more dramatic deterioration of visual acuity, an extensive central scotoma in the visual field and an absent VER. Moreover, this is a unilateral process in the majority of cases.

128

Group Ib: Five patients with a tumour in the region of the sella turcica

A neoplasm arising from the hypophysis can give rise to compression atrophy of the optic nerve or optic tract, or in the optic chiasm, dependent on the localization of the tumour and its volume. Hypophyseal tumours are often characterized by the presence of bitemporal hemianopia. When the compression atrophy involves the fibres of the maculopapillary bundle, diminution of visual acuity can occur.

The patients to be discussed had a chromophobic or eosinophilic adenoma of the hypophysis. Treatment consisted of hypophysectomy with or without postoperative irradiation, or of irradiation only. In only one of these cases did a more or less total bitemporal hemianopia exist. In the remaining four cases it was only in the central visual field that an indication of bitemporal hemianopia was found.

Personal observations

The following two patients were selected for discussion:

PATIENT I, male, born 12th May 1917

A tumour arising from the hypophysis was diagnosed in 1963; the tumour led to hypophyseal insufficiency. In view of its localization, surgical removal of the tumour was considered impossible. Treatment consisted of irradiation and endocrine medication.

Data from an ophthalmological examination in 1963:

Examination

Visual acuity	OD 0.8	OS 5/60 to 0.2
Media	no abnormality	no abnormality
Fundi	no abnormality	no abnormality
Visual fields	temporal hemianopia	visual field remnant; object
(Goldmann)		1–3 just perceived at centre;
		object 1–4 perceived in a
		slightly larger pericentral
		area; some concentric
		limitation of the 5–4 isopter.

Visval acuity of the right eye deteriorated to 6/60 in the course of the years; visual acuity of the left eye remained constant.

Visual acuity	OD 6/60	OS 0.2
Media	no abnormality	no abnormality
Fundi	pale, sharply defined optic disc	same as OD
Intraocular pressure	normal	normal
Visual fields	relative paracentral scotoma in	incomplete temporal
(Goldmann)	temporal lower quadrant, ex-	hemianopia; 1–1 isopter
	tending 10–30° in all directions;	absent; other isopters
	1–1 isopter absent; other isop-	limited
	ters limited	
Colour discrimination	not examined	not examined
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°;	
	simultaneous recording of VER	
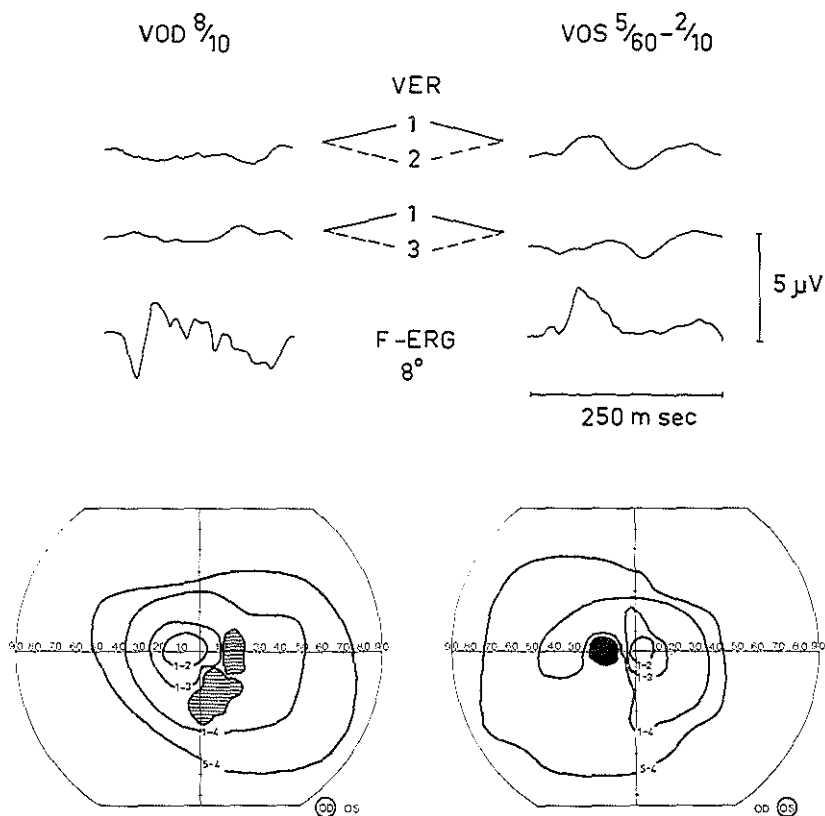
Fig. 53

Patient I, male, age 42 years

Description (see also figure 53: 8°-recording):

ERG OD after local (foveal) stimulation: 3.5 μV(?): subnormal.
ERG OS after local (foveal) stimulation: 2.5 μV(?): subnormal*.
VER OD after local (foveal) stimulation: absent.
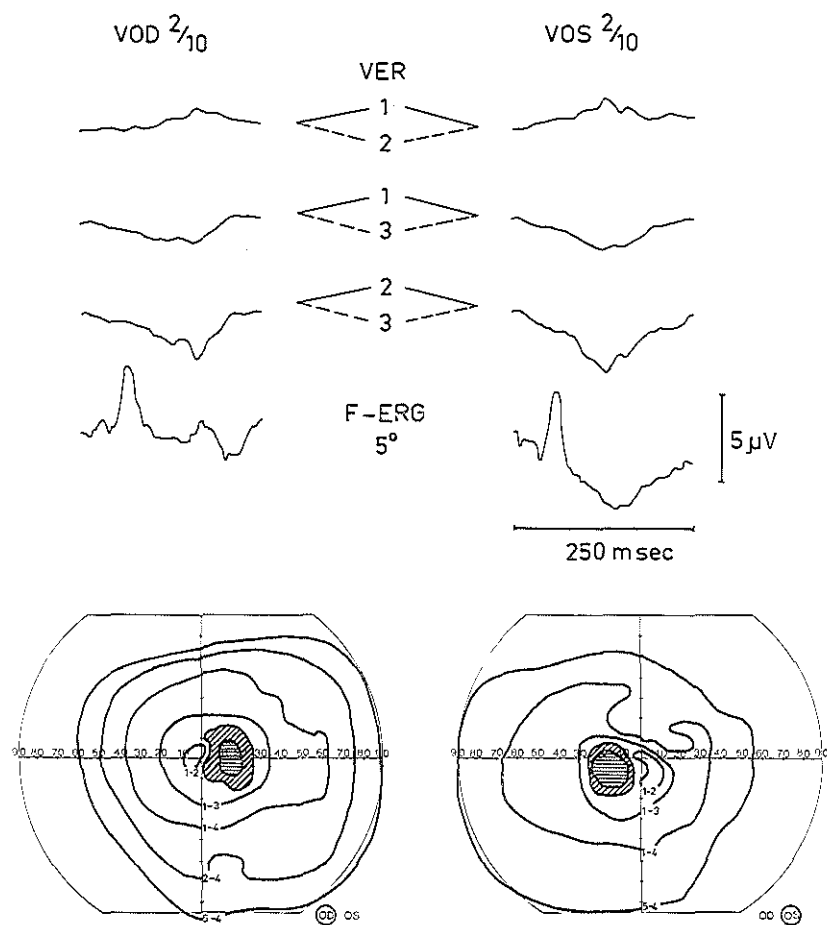VER OS after local (foveal) stimulation: discernible/absent.

Discussion of the electro-ophthalmological findings in patient I

1. *The FERG*

The FERGs of both eyes were subnormal. In view of the long standing dimin-
ished visual acuity of both eyes it seems likely that the low amplitude of the
photopic b-wave should be explained as a result of insufficiently centric fixation
of the stimulus. Moreover, the curves were annotated insufficient fixation'.

2. *The VER after local (foveal) stimulation*

The VERs after local (foveal) stimulation of both eyes were absent. Since the
FERGs of both right and left eye were subnormal, it cannot be established with
certainty whether the absence of the VERs resulted from insufficiently centric
fixation or from disturbed conduction. It was most likely a consequence of both.
Some support for this assumption is found in the examination of normal sub-
jects, which included a few individuals whose fixation was insufficiently steady.
This resulted in a FERG rated as 'borderline value', but in these cases the VER
was well developed.

PATIENT II, male, born 16th August 1921

A hypophyseal tumour was diagnosed some three years before our examina-
tion. Therapy: hypophysectomy followed by irradiation.

A year before our examination, the visual fields showed some relative scoto-
mas temporal to the centre, as the sole indication of pressure exerted on the
optic chiasm by the tumour. The condition subsequently improved, as our
examination showed.

Examination

Visual acuity	OD 1.0	OS 1.0
Media	no abnormality	no abnormality
Fundi	no abnormality	no abnormality
Intraocular pressure	normal	normal
Visual fields (Goldmann)	indication of temporal upper quadrant anopsia	1–1 isopter and 1–2 isopter limited temporal to the centre; periphery normal

---

* It is difficult to evaluate these curves due to the simultaneously recorded activity of
a different (unknown) nature.

Colour discrimination   not examined   not examined
Electro-ophthalmology   ERG: local (foveal) stimulation with field size 8°, 5° and 3°;
                         simultaneous recording of VER

Description (see also figure 54: 8°-recording):

ERG OD after local (foveal) stimulation: 7.0 μV: normal.
ERG OS after local (foveal) stimulation: 6.0 μV(?): normal.
VER OD after local (foveal) stimulation: well developed.
VER OS after local (foveal) stimulation: well developed.
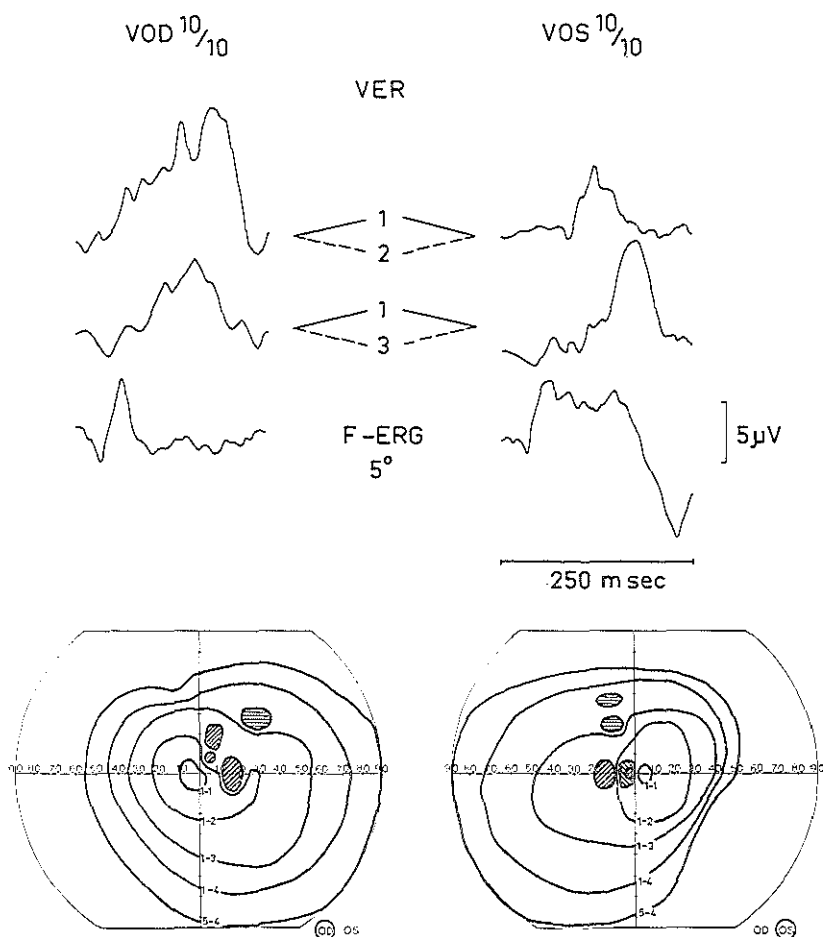
Fig. 54

Patient II, male, age 47 years

Discussion of the electro-ophthalmological findings in patient II

1. *The FERG*

The FERGs of both eyes were normal, which shows that patient achieved adequate fixation of the stimulus. In view of the good visual acuity, this could be expected.

2. *The VER after local (foveal) stimulation*

The VERs after local (foveal) stimulation of both eyes were not identical in amplitude and/or configuration. Careful comparison, however, showed that the differences were not so marked as to necessitate a different rating.

3. *Interpretation of the electro-ophthalmological findings*

The electro-ophthalmological findings warrant the conclusion that the maculopapillary fibre bundles were not significantly affected by compression atrophy as a result of the presence of the hypophyseal tumour. This conclusion is consistent with the results obtained in examining visual acuity and visual fields of both eyes.

Conclusion

If the central retina is intact, then a well developed VER usually implies an intact conduction system up to and including an intact optic cortex. When a hypophyseal tumour exerts pressure on the visual pathway (optic nerve, optic chiasm and/or optic tract), the resulting compression atrophy can also involve the maculopapillary fibre bundle. If this involvement is such that visual acuity and central visual field are seriously disturbed, then the VER is absent after local (foveal) photic stimulation of the eye in question. If the compression atrophy does not, or hardly, involve the maculopapillary fibre bundle, then visual acuity is good, the central visual field is virtually intact and the VER is well developed.

Group IIa: Twelve patients with hemianopia due to a cerebrovascular accident

In the majority of cases in which loss of function of one of the optic hemicortices results from a cerebrovascular accident, an occlusion in the course of the posterior cerebral artery has occurred. The neurological symptoms accom-

panying this situation, depend on the site of occlusion in this artery and on the available possibilities of an immediate collateral circulation.

The neurological symptoms include, besides homonymous hemianopia, such phenomena as hemiplegias, dysphasia and sometimes alexia and agnosia.

A corresponding neurological syndrome rarely results from an occlusion in the basilar artery. Such an occlusion leads to infarction of the area supplied by the posterior cerebral artery.

If homonymous hemianopia occurs without additional neurological symptoms, then a diagnosis of occlusion of the calcarine artery (a branch of the posterior cerebral artery) is to be contemplated.

Personal observations

PATIENT I, male, born 26th December 1896

One year before our examination this patient suddenly developed right-sided homonymous hemianopia without further neurological symptoms. The diagnosis was: occlusion of the left calcarine artery. The patient was known to suffer also from cardiac insufficiency and a thyroid affection.

Examination

|		
Visual acuity	OD 0.8	OS 0.9
Media	no definite abnormality	same as OD
Fundi	signs of vascular sclerosis; no other abnormality	same as OD
Intraocular pressure	normal	normal
Visual fields (Goldmann)	right-sided homonymous hemianopia	same as OD
Colour discrimination	not examined	not examined
Electro-ophthalmology	ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER.	

Description (see also figure 55: 8°-and 5°-recording):

ERG OD after local (foveal) stimulation with field size 8°: 5.2 μV: normal.
ERG OD after local (foveal) stimulation with field size 5°: 5 μV: normal.
ERG OS after local (foveal) stimulation with field size 8°: 3.4 μV: subnormal.
ERG OS after local (foveal) stimulation with field size 5°: 4.1 μV: normal.
VER OD after local (foveal) stimulation with field size 8° and 5°:
             1–2 lead: well developed.
             1–3 lead: well developed/discernible.
VER OS after local (foveal) stimulation with field size 8° and 5°:
             1–2 lead: well developed.
             1–3 lead: well developed/discernible.

134

Fig. 55

Patient, male, age 72 years

The recording after stimulation with field size 8° of the left eye is striking: the FERG is subnormal (result of insufficient fixation of the stimulus); however the VER does not through that differ from, on the one hand the corresponding recording of the other (right) eye, and on the other hand the VER recorded after stimulation with field size 5° of the same (left) eye.

The results obtained in examinations of the remaining patients of group IIa are presented in the survey IV on page 154.

135

Examination of the FERG and the VER in patients with homonymous hemia-
nopia has yielded no results to which practical value can be attached. There
were two reasons for this.

1. In our study, a difference in activity between the two optic hemicortices
might have been recognized only if the 1–2 recording of the VER had differed
in an interpretable manner from the 1–3 recording.

If electrodes 2 and 3 are indeed located on either side over the optic hemicor-
tices, it is fair to assume that the greatest cortical activity in response to photic
stimulation of the eye should develop at these electrodes. In that case the VER
is recordable as a series of potential variations between electrodes 2, 3 and 1,
but it must not be assumed that the inion be inactive in this situation. After all,
the inion (1) is also localized very close to the optic cortex.

The first problem poses itself in this respect: the exact spatial relationships
between electrodes 1, 2 and 3 on the one hand, and the optic cortex on the
other hand, are not known. Although the scalp electrodes are placed in a
standardized way, with the external occipital protuberance as point of reference,
the spatial relationships between the electrodes and the two optic hemicortices
are not thus established. The second problem is that, if one of the optic hemi-
cortices is 'dead', it should be (and is) possible after photic stimulation of the
eye to measure a potential variation between the electrode over the 'dead'
hemicortex, and the inion electrode. The inion electrode could be the 'active'
electrode in this situation, because it is probably localized closest to the site at
which (in the intact optic hemicortex) cortical activity develops. Even this
would be no obstacle if it were certain that in normal subjects the 1–2 and 1–3
recordings of the VER were always identical in configuration and amplitude.
In that case a difference in amplitude and/or configuration between the 1–2
and 1–3 recordings of the VER could be an indication of a pathological altera-
tion in one of the hemicortices. However, we know from our examination of
normal subjects that the VER in the 1–2 recording is by no means always
exactly the same as that in the 1–3 recording. This could be due to, for example,
asymmetry of the skull and/or of the cranial contents. But this means that, at
least in our test arrangement, objective demonstration of a difference in activity
between the two optic hemicortices is impossible.

2. In the group we examined, all patients were suffering (as indicated by the
visual field findings) from complete homonymous hemianopia; this is to say
that in all patients total loss of function of one of the optic hemicortices could
be assumed to exist. However, it may also be (if not in our patients) that the

most central area of the (hemianopic) visual field is still quite intact; this is known as 'macular sparing'.

Different explanations have been offered for this phenomenon. One possibility might be that the entire fovea of both eyes projects upon each of the two optic hemicortices. This, however, has not been demonstrated anatomically. Another possibility would be that the projection area of the fovea on the affected side is spared by a collateral circulation from the middle cerebral artery. If this were true, then in cases of 'macular sparing' both optic hemicortices could contribute in an approximately equal manner to the generation of the VER, and particularly of the VER after local (foveal) stimulation. After all, the VER is largely determined by the activity of the projection area of the central fovea in the area striata.

In three patients with homonymous hemianopia, we obtained VER curves after local (foveal) stimulation which, in the lead between the inion electrode and the electrode over the 'dead' cortex, showed a much lower amplitude than in the lead between the inion electrode and the electrode over the 'active' cortex (see also illustration patient I of this group). In one other patient, the same was observed in the VER recordings after full field stimulation. It is possible that the difference in activity between the two optic hemicortices was herewith expressed. However, this does not imply that in all cases of hemianopia due to a cerebrovascular accident it is possible to demonstrate a difference in activity between the two optic hemicortices by examination of the full field VER and/or the local (foveal) VER.

In the patients examined during the early period of our study, the 2–3 lead was not yet recorded; not until later was the recording of this lead added. In none of the cases in which this lead was recorded as well, did it make any contribution to the objective demonstration of a difference in activity between the two optic hemicortices.

Group IIb: Three patients examined after hemispherectomy

PATIENT I, male, born 19th July 1950

This patient underwent hemispherectomy 14 days before the electro-ophthalmological examination was carried out. A right-sided temporoparietal trephination was performed: superficially in the cortex of the posterosuperior portion of the temporal region, a diffuse tumour was found which showed the features of a malignant infiltrating growth. Total removal of the tumour was achieved. Pathological anatomical examination of the resected specimen identified the

growth as a grade III astrocytoma. The patient was given postoperative irradiation.

Examination

Visual acuity	OD 1,0, with red filter 1,0	OS 1,0, with red filter 1,0	
Media	no abnormality	no abnormality	
Fundi	no abnormality	no abnormality	
Visual fields	left-sided homonymous	same as OD	
(Goldmann)	hemianopia		
Colour discrimination	deuteranopia	deuteranopia	

(Note: patient reported having 'always been colour-blind')

Electro-ophthalmology ERG: local (foveal) stimulation with field size 8°, 5° and 3°; simultaneous recording of VER.
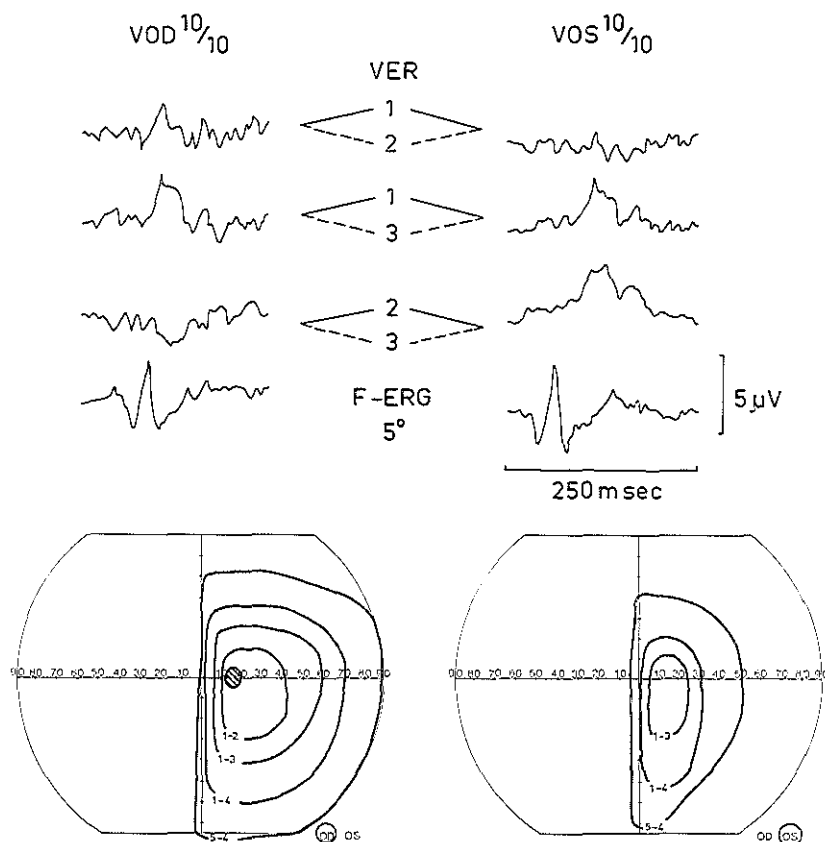
Fig. 56

Patient, male, age 19 years

Description (see also figure 56: 5°-recording):

ERG OD after local (foveal) stimulation: 4.1 μV: normal.
ERG OS after local (foveal) stimulation: 5.0 μV: normal.
VER OD after local (foveal) stimulation: all leads: discernible.
VER OS after local (foveal) stimulation: 1–2 lead: absent; 1–3 and 2–3 leads: discernible.

Discussion

Since only patient I in group IIb had a complete homonymous hemianopia as a result of the hemispherectomy, the results obtained in this patient are the most important.

The conclusion from this examination is that it was impossible, on the basis of the VER leads recorded (leads 1–2, 1–3 and 2–3), to establish with certainty which of the two optic hemicortices had been removed. This is explained in paragraph 1. of the discussion of patients of group IIa.

It was not possible to summarize the cases of the other two patients in a survey. Since these cases yielded no new information, they will be left out of discussion.

SUMMARY

To establish the diagnosis in cases of an acute affection of the optic nerve, the investigator must rely on functional examinations such as determination of visual acuity and of the visual field. Only when the process is localized at the optic disc abnormalities become apparent with the aid of the ophthalmoscope. Affections of longer standing may lead to atrophy of nerve fibres, and this may become visible in the fundus in that the disc is pale of appearance. However, not in all cases is the so-called disc atrophy associated with poor visual acuity: in these cases the functional findings seem to contradict the fundoscopic findings. Another example is the choked disc, which produces highly pathological fundoscopic features even though visual acuity and visual field are quite intact. The opposite situation is that of the acute stage of retrobulbar neuritis, in which the optic disc may present an entirely normal appearance whereas visual acuity and visual field are severely disturbed. Findings such as the above mentioned evoke the wish for an extended examination which includes methods supplying some information on the manner in which, under pathological circumstances, the optic nerve does or does not conduct. Recording visually evoked responses provides a possibility in this respect.

Visually evoked responses are known to be largely determined by photic stimulation of the central retina (VAN HOF 1960; COPENHAVER & PERRY 1964). However, stimulation of the peripheral retina likewise makes a contribution – be it much smaller – in illiciting the VER. This means that intactness of the central fovea, the maculopapillary fibre bundle in the optic nerve, and the projection of the fovea in the optic cortex, is a prerequisite for recording VERs.

On the other hand, the development of sophisticated recording techniques (e.g. with the aid of the computer) which make it possible to identify the VER amidst the ever-present background activity (the EEG), has enabled the investigator to record an ERG from a very small retinal area, e.g. the local photopic ERG of the central fovea (FERG). Simultaneous recording of FERG and VER makes it possible to examine the function of, exclusively, that part of the optic system that encompasses the fovea, the maculopapillary fibre bundle and the projection of the fovea in the optic cortex. Visual acuity is determined by this part of the optic system. It is the diminished visual acuity (and a central scotoma in the visual field) that, in many cases, characterizes an affection of the

optic nerve. If, under these pathological conditions, one can nevertheless record VERs after local (foveal) stimulation, and recognize pathological changes in the recordings, then it should be ascertained that these VERs have indeed been obtained by stimulation of the fovea. This can be achieved by recording the FERG, for which normal values are given in chapter VI.

Chapters II and III discuss the development of methods to record VER and FERG. The method used in our study is described in detail in chapter IV. Chapter V presents a description of the protocol of examination to which our patients were submitted, and lists the number of patients examined.

Chapter VII describes the electro-ophthalmological findings obtained in patients with optic neuritis. In the acute stage of optic neuritis (diminished visual acuity and a central scotoma in the visual field), no VER can be recorded after local (foveal) stimulation of the retina. The impairment of conduction, thus objectively demonstrated, may result from the development of an inflammatory-like oedema which impairs the capillary blood circulation in the optic nerve; one of the consequences of this situation is a pathological metabolism of the nerve tissue and release of toxins (e.g. BONAMOUR 1968). If in such cases it is possible to identify a VER in the recordings after full field stimulation of the retina, then we are dealing, we believe, with the contribution of the peripheral retina to the generation of the VER. In this context it is to be noted that, in the acute stage of optic neuritis, it is often surprising to see how well the patient can fix the (small) photic stimulus in spite of the poor visual acuity and the central scotoma in the visual field. If visual acuity and visual field fail to recover after the acute stage, then the VER after local (foveal) stimulation remains absent. This is a result of demyelination and atrophy of nerve fibres, particularly those of the maculopapillary bundle. In this stage examination does become more difficult because the patient's ability to fix the stimulus diminishes as poor visual acuity is of longer standing. Upon partial recovery from optic neuritis (e.g. visual acuity 0.6–0.7 and a relative central scotoma in the visual field), we have observed that the VER after local (foveal) stimulation can nevertheless remain absent. We believe that in these cases there has been demyelination of the fibres in the maculopapillary bundle, but that yet the majority of these fibres does still conduct, even over the segment of demyelination. The mode of conduction in the demyelinated segment differs from normal and may well resemble that in naturally unmyelinated fibres in the peripheral nervous system. A consequence of this might be that the conduction velocity diminishes. As a result, the conduction time of the nerve fibres can come to show interdifferences due to which depolarization of the projection of the fovea in the optic cortex takes place only gradually so that at no time a potential

occurs of sufficient amplitude to permit our apparatus to record it. In the case of complete recovery from optic neuritis, one can observe a return of the VER after local (foveal) stimulation to the extent that there is no longer a significant difference between the VER recorded after stimulation of the one (unaffected) eye and that recorded after stimulation of the other (affected) eye. We believe that electro-ophthalmological examination demonstrates in these cases that no demyelination as a result of the optic neuritis has occurred, or that, as a result of remyelination, a restitutio ad integrim has occurred.

Chapter VIII presents the results of an examination of twelve patients with LEBER's hereditary optic atrophy. The majority had regained fair-to-good visual acuity in at least one eye. In only one patient of this group were VERs identifiable in the responses after local (foveal) stimulation. We observed that in a few cases of LEBER's optic atrophy a visual acuity of 1.0 could be attained. In these cases a central scotoma in the visual field had in its exact centre an intact sparing corresponding to $\leqslant 1°$ subtended visual angle. The absence of the VER after local (foveal) stimulation is ascribed to the fact that only a small number of fibres in the maculopapillary bundle is still intact; impulses conducted by these few fibres, effect depolarization of so small a part of the projection of the central fovea in the optic cortex that a potential of sufficient amplitude to be recorded, is never produced.

In patients with traumatic optic atrophy, it was difficult to record ERG and VER after local (foveal) stimulation because all were examined long after the accident, so that visual acuity had long been poor. However, in one case (visual acuity 0.6 in the eye, of which the optic nerve was affected) a disturbance of conduction in the maculopapillary bundle could be demonstrated because the VER after local (foveal) stimulation of this eye was absent (chapter IX).

Simple glaucoma (chapter X) was not systematically studied. Two patients are discussed. The results of their examinations do not warrant the expectation that a more comprehensive examination by the techniques we used will reveal many new points of view on the disturbance of conduction of the nerve fibres in this condition. A patient with toxic opticoneuropathy due to ethambutol medication and one with juxtapapillary retinitis (JENSEN) are discussed in the same chapter.

Chapter XI describes the examination of patients with intracranially localized causes of disturbed vision. With the placements chosen for the scalp electrodes (see chapter IV), it proved impossible in patients with dysfunction of one optic hemicortex to demonstrate its inactivity versus the activity of the intact hemicortex. In patients with (incomplete) bitemporal hemianopia due to a hypophyseal process, the VER after local (foveal) stimulation was disturbed if the

maculopapillary fibre bundle had been affected by compression atrophy. This fact, however, was already known in these cases from examination of visual acuity and visual fields. In cases of choked disc, a normal VER after local (foveal) stimulation was found whenever visual acuity and visual fields were (still) adequate. Whenever the visual acuity was diminished as a result of secondary optic atrophy, the VER after local (foveal) stimulation was absent.

Voor het stellen van de diagnose bij acute aandoeningen in het verloop van de nervus opticus is de onderzoeker aangewezen op het functie-onderzoek, zoals de bepaling van de gezichtsscherpte en van het gezichtsveld. Alleen wanneer het proces gelocaliseerd is bij de papilla nervi optici zijn met behulp van de oog-spiegel afwijkingen zichtbaar. Als de aandoening langer bestaat kan zij lei-den tot het ontstaan van een atrofie van zenuwvezels en dit kan in de fundus zichtbaar worden, en wel door het dan bleke aspect van de papil. Toch is het niet in alle gevallen zo dat de z.g. papil-atrofie gepaard gaat met een slechte gezichtsscherpte: het functie-onderzoek lijkt dan in tegenspraak te zijn met de bevindingen bij fundoscopie. Een ander voorbeeld is de stuwingspapil, waarbij, bij een sterk pathologisch veranderd fundoscopisch beeld, de visus en het gezichtsveld geheel intact kunnen zijn. Dit staat tegenover het acute stadium van een neuritis retrobulbaris, waarbij het aspect van de papilla nervi optici geheel normaal kan zijn, terwijl de visus en het gezichtsveld ernstig gestoord zijn. Bevindingen als de bovenstaande roepen de wens op het onderzoek te kunnen uitbreiden met methoden, die enige informatie verschaffen over de wijze, waarop de nervus opticus onder pathologische omstandigheden geleidt – of niet geleidt. De registratie van de visually evoked responses biedt hiertoe een mogelijkheid.

Het is van de visually evoked responses bekend, dat zij voornamelijk worden bepaald door licht-stimulatie van de centrale retina (VAN HOF, 1960, COPENHAVER & PERRY, 1964). Maar ook stimulatie van de perifere retina heeft een – zij het veel kleiner – aandeel in het opwekken van de VER. Dit betekent dat het intact zijn van de fovea centralis, de maculo-papillaire vezelbundel in de nervus op-ticus en de projectie van de fovea in de optische cortex een eerste premisse is om VERs te kunnen registreren.

De ontwikkeling van verfijnde registratie-methoden (o.a. met behulp van de computer-techniek), die het mogelijk maakten de VER te herkennen te midden van de steeds aanwezige achtergrondsactiviteit (het EEG), stelde de onder-zoeker ook in staat een ERG te registreren van een zeer klein netvlies gedeelte, zoals b.v. het locale photopische ERG van de fovea centralis (FERG). De gelijktijdige registratie van het Fovea-ERG en de VER maken een functie-onder-zoek mogelijk van alleen dat gedeelte van het optische systeem, dat bestaat uit fovea, maculo-papillaire vezelbundel en de projectie van de fovea in de op-tische cortex. De gezichtsscherpte wordt door ditzelfde gedeelte van het visuele systeem bepaald. Het is de verminderde gezichtsscherpte (en in het gezichtsveld een centraal scotoom), waardoor in vele gevallen een aandoening van de nervus

opticus zich kenmerkt. Wanneer men onder deze pathologische omstandigheden in staat is toch VERs na locale (foveale) stimulatie te registreren en in de registraties pathologische veranderingen herkent, dient men er zeker van te zijn, dat deze VERs inderdaad verkregen zijn door stimulatie van de fovea. De registratie van het FERG, waarvoor in hoofdstuk VI de normale waarden worden opgegeven, biedt hiertoe de mogelijkheid.

In hoofdstuk II en III is ingegaan op de ontwikkeling van methoden om de VER en het FERG te registreren. In hoofdstuk IV wordt de methode, welke voor ons onderzoek is gebruikt, uitgebreid omschreven. Hoofdstuk V vormt een beschrijving van het protocol van onderzoek, waaraan onze patiënten werden onderworpen, met een opgave van het aantal patiënten, dat werd onderzocht.

In hoofdstuk VII worden de electro-ophthalmologische bevindingen beschreven bij patiënten met een neuritis optica. In het acute stadium van neuritis optica (verminderde visus en een centraal scotoom in het gezichtsveld) kunnen geen VERs geregistreerd worden na locale (foveale) stimulatie van de retina. Deze aldus objectief aantoonbare blokkade van de geleiding is mogelijk een gevolg van het optreden van een ontstekings-achtig oedeem, waardoor de circulatie van bloed via de capillairen in de nervus opticus wordt belemmerd, met als gevolg o.a. een pathologisch metabolisme van het zenuwweefsel en het vrijkomen van toxinen (o.a. BONAMOUR, 1968). Is in zo'n geval de VER na full field stimulatie van de retina wél in de registraties herkenbaar, dan menen wij te maken te hebben met het aandeel van de perifere retina in het opwekken van de VER. Aangetekend moet worden, dat het in het acute stadium van neuritis optica vaak verwonderlijk is, hoe goed de patient de (kleine) licht-stimulus kan fixeren, ondanks de slechte gezichtsscherpte en het centraal scotoom in het gezichtsveld. Indien na het acute stadium de visus en het gezichtsveld niet herstellen, dan blijft de VER na locale (foveale) stimulatie afwezig. Dit is het gevolg van demyelinisatie en atrofie van zenuwvezels, en wel in het bijzonder van die in de maculo-papillaire bundel. Het onderzoek wordt in dit stadium wél moeilijker, omdat bij langer bestaande slechte gezichtsscherpte het vermogen van de patient om de stimulus te fixeren vermindert. Bij een gedeeltelijk herstel van een neuritis optica (b.v. visus 0.6–0.7 en in het gezichtsveld een relatief centraal scotoom), zagen wij, dat ook dan de VER na locale, foveale stimulatie afwezig kon zijn. Wij menen, dat er in dit geval een demyelinisatie heeft plaats gevonden van de vezels in de maculo-papillaire bundel, maar dat desondanks het merendeel van de vezels nog wel geleidt, ook dus over het traject van de demyelinisatie. De wijze van geleiding in het gedemyeliniseerde gedeelte is anders dan normaal en komt mogelijkerwijs overeen met die in van nature ongemyeliniseerde vezels

in het perifere zenuwstelsel. Een gevolg hiervan zou dan zijn, dat de geleidings-snelheid daalt. De geleidingstijd van de zenuwvezels kan hierdoor onderlinge verschillen gaan vertonen, waardoor de depolarisatie van de projectie van de fovea in de optische cortex slechts geleidelijk plaats vindt en waardoor er nimmer op één moment een potentiaal ontstaat van voldoende hoogte om door onze apparatuur geregistreerd te kunnen worden. Treedt er een volledig herstel op van een neuritis optica, dan kan men een terugkeer waarnemen van de VER na locale (foveale) stimulatie en wel zó, dat er geen wezenlijk verschil meer bestaat tussen de VER geregistreerd na stimulatie van het ene (niet aangedane) oog en die na stimulatie van het andere (wel aangedane) oog. In deze gevallen menen wij, dat het electro-ophthalmologisch onderzoek aantoont, dat géén demyelinisatie als gevolg van de neuritis optica is opgetreden, ofwel, dat door het proces van remyelinisatie een restitutio ad integrim heeft plaatsgevonden.

In hoofdstuk VIII worden de resultaten weergegeven van het onderzoek bij een twaalftal patiënten met de heriditaire opticus atrofie van LEBER. De meeste van deze hadden een redelijke tot goede visus herkregen op tenminste één oog. Bij slechts één patient uit deze groep waren na locale (foveale) stimulatie VERs in de responsies herkenbaar. Wij zagen, dat bij de opticus atrofie van LEBER in enkele gevallen een visus 1.0 kon worden bereikt. In het gezichtsveld kwam dan een centraal scotoom voor, met precies in het centrum een intacte uitsparing, overeenkomend met $\leqslant 1°$ subtended visual angle. De afwezigheid van de VER na locale (foveale) stimulatie wordt toegeschreven aan het feit dat slechts een zeer gering aantal vezels in de maculo-papillaire bundel nog intact is; impulsen, door deze weinige vezels voortgeleid, bewerkstelligen depolarisatie van slechts een zó klein gedeelte van de projectie van de fovea centralis in de optische cortex, dat nimmer een potentiaal ontstaat van voldoende hoogte om te kunnen worden geregistreerd.

Het was moeilijk om bij patiënten met een traumatische opticus atrofie het ERG en de VER na locale (foveale) stimulatie te registreren, ten gevolge van het feit dat allen pas langere tijd na het trauma werden onderzocht en de visus dan ook allang slecht was. In een enkel geval – met visus 0.6 van het oog, waarvan de nervus opticus getroffen was – kon niettemin een stoornis in de geleiding van de maculo-papillaire vezelbundel worden aangetoond, doordat de VER na locale (foveale) stimulatie van dit oog afwezig was, (hoofdstuk IX).

Glaucoma simplex (hoofdstuk X) werd niet systematisch onderzocht. Twee patiënten worden besproken. De resultaten van deze onderzoeken wekken niet de verwachting, dat een uitgebreider onderzoek met de door ons gebruikte technieken veel nieuwe gezichtspunten zal bieden omtrent de stoornis in de geleiding van de zenuwvezels bij deze aandoening. Tot slot worden in ditzelfde

hoofdstuk besproken een patient met een toxische opticopathie t.g.v. etham-
butol gebruik en één met een chorioretinitis juxtapapillaris (JENSEN).

Hoofdstuk XI beschrijft het onderzoek bij patiënten met intra-craniëel ge-
localiseerde oorzaken van gestoord gezichtsvermogen. Het bleek onmogelijk
om met de gekozen plaatsing van de schedel electroden (zie hoofdstuk IV) bij
patiënten met een uitval van één helft van de optische cortex, de inactiviteit
daarvan aan te tonen t.o.v. de activiteit van de intacte helft. Bij patiënten met
een (incomplete) bitemporale hemianopsie t.g.v. een hypophyse proces was de
VER na locale (foveale) stimulatie gestoord indien de maculo-papillaire vezel-
bundel door drukatrofie was getroffen. Dát dit zo was, was in deze gevallen
echter al bekend uit het onderzoek van de gezichtsscherpte en de gezichts-
velden. In gevallen van stuwingspapil werden normale VERs na locale (foveale)
stimulatie gevonden indien de visus en de gezichtsvelden (nog) goed waren.
Was de visus verminderd als gevolg van een secundaire opticus atrofie, dan was
de VER na locale (foveale) stimulatie afwezig.

JOHANNES PAUL DE HAAS, geboren te Arnhem op 16 april 1939.

Opleiding aan het Stedelijk Gymnasium te Arnhem, (1951–1957).

Inschrijving als student in de medicijnen aan de Rijksuniversiteit te Leiden, (september 1957).

Doctoraal examen in de geneeskunde te Leiden, (december 1962).

Arts examen te Leiden, (februari 1965).

Reserve Officier van Gezondheid (mei 1965–september 1966); afdelings-arts van de 41e Afdeling Veldartillerie.

Opleiding tot oogarts bij PROF. DR. H. E. HENKES, hoofd van de afdeling Oogheelkunde van de Medische Faculteit te Rotterdam, (october 1966–october 1970).

Vestiging als oogarts te Vlaardingen, (october 1970); lid van de Medische Staf van het Holy-Ziekenhuis.

REFERENCES

ADIE, W. J. Acute retrobulbar neuritis in disseminated sclerosis. *Trans. ophthal. Soc. U.K.* 50: *262* (1930).

ADRIAN, E. D. & B. H. C. MATTHEWS. The Berger rhythm: potential changes from the occipital lobes in man. *Brain* 57: *355* (1934).

AGUILAR, M. & W. S. STILES. Saturation of the rod mechanism of the retina at high levels of stimulation. *Optica Acta* 1: *59* (1954).

AIBA, T. S., M. ALPERN & F. MAASEIDVAAG. The electroretinogram evoked by the excitation of human foveal cones. *J. Physiol.* 189: *43* (1967).

ANDERSON, W. A. D. Synopsis of pathology. Mosby, Saint Louis (1960).

ARDEN, G. B. & J. L. K. BANKES. Foveal electroretinogram as a clinical test. *Brit. J. Ophthal.* 50: *740* (1966).

—— & A. BARRADA. Analysis of the electro-oculogram of a series of normal subjects. *Brit. J. Ophthal.* 46: *468* (1962).

——, —— & J. H. KELSEY. New clinical test of retinal function, based upon the standing potential of the eye. *Brit. J. Ophthal.* 46: *449* (1962).

ARMINGTON, J. C. c.s. Summation of retinal potentials. *J. Opt. Soc. Amer.* 51: *877* (1961).

—— Adaptational changes in the human electroretinogram and occipital response. *Vision Res.* 4: *179* (1964).

—— Spectral sensitivity of simultaneous electroretinograms and occipital responses. *Vision Res.*, Suppl. 1: *225* (1966).

ASHER, H. The electroretinogram of the blind spot. *J. Physiol.* 112: *40 pp.* (1951).

BALEN, A. TH. M. VAN. The electro-encephalographic response to light stimulation and its significance for ophthalmological diagnostics. Thesis Utrecht. Klomp & Bosman, Rotterdam (1960). (Summary in English).

BANKES, J. L. K. The foveal electroretinogram. *Trans. ophthal. Soc.* U.K. 87: *249* (1968).

BEINHOCKER, G. D. et al. Electroperimetry. *Trans. Bio-Med. Engin. BME* 13: *11* (1966).

BEMENT, S. L. & J. B. RANCK JR. A quantative study of electrical stimulation of central myelinated fibers. *Exp. Neurol.* 24: *147* (1969).

BENEDICT, W. L. Retrobulbar neuritis and disease of the nasal accessory sinuses. *Arch. Ophthal.* 9: *893* (1933).

BERLIN. *Ber. dtsch. ophthal. Ges.* 12: *9* (1879).

BIERSDORF, W. R. & D. A. DILLER. ERG in macular degeneration. *Am. J. Ophthalm.* Vol 68, 2: *269* (1969).

BONAMOUR, G. c.s. La papille optique. Masson, Paris (1968).

BOYNTON, R. M. & L. A. RIGGS. The effect of stimulus area and intensity upon the human retinal response. *J. exp. Psychol.* 42: *217* (1951).

BRINDLEY, G. S. & G. WESTHEIMER. The spatial properties of the human electroretinogram. *J. Physiol.* 179: *518* (1965).

BROWN, K. T. The electroretinogram: its components and their origin. *Vision Res.* 8: *633* (1968).

BRUNETTE, J.-R. & G. BERNIER. Study of a family of Leber's optic atrophy with recuperation. In: Progress in ophthalmology. Excerpta Medica Foundation, Amsterdam (1969).

BUNGE, R. P. Glial cells and the central myelin sheath. *Physiol. Rev.* 48: *197* (1968).

CARR, R. E. & P. HENKIND. Ocular manifestations of Ethambutol. *Arch. Ophthal.* 67: *566* (1962).

CARROLL, F. D. Optic neuritis; a 15-year study. *Amer. J. Ophthal.* 35: *75* (1952).

CHACKO, L. W. An analysis of fibre-size in the human optic nerve. *Brit. J. Ophthal.* 32: *457* (1948).

CIBIS, P. Ueber die Aetiologie und Häufigkeitsverhältnisse der Neuritis retrobulbaris. *Klin. Mbl. Augenheilk.* 102: *205* (1939).

CIGÁNEK, L. L'influence de la fréquence de la stimulation photique sur le potentiel évoqué chez l'homme. *Rev. Neurol.* 99: *198* (1958).

—— Postdécharge rythmique corticale chez l'homme évoquée par les stimuli photiques. *Rev. Neurol.* 99: *196* (1958).

—— Potentiels corticaux chez l'homme évoqués par les stimuli photiques. *Rev. neurol.* 99: *194* (1958).

—— The EEG response (evoked potential) to light stimulus in man. *Electroenceph. clin. Neurophysiol.* 13: *165* (1961).

CONE, W. V. & J. A. MACMILLAN. In: Penfield's cytology and cellular pathology of the nervous system. *N.Y.* 2: *839* (1932).

COOPER, S., R. S. CREED & R. GRANIT. Note on the retinal action potential of the human eye. *J. Physiol.* 79: *185* (1933).

COPENHAVER, R. M., G. D. BEINHOCKER & N. W. PERRY JR. Visual evoked retinal and occipital potentials. *Docum. Ophthal.* 18: *473* (1964).

—— & N. W. PERRY Jr. Factors affecting visually evoked cortical potentials such as impaired vision of varying etiology. *Invest. Ophthal.* 3: *665* (1964).

DAWSON, G. D. A summation technique for the detection of small evoked potentials. *Electroenceph. clin. Neurophysiol.* 6: *65* (1954).

DEUTMAN, A. F. The hereditary dystrophies of the posterior pole of the eye. Thesis Rotterdam. van Gorcum, Assen (1971).

DEVOE, R. G., H. RIPPS & H. G. VAUGHAN. Cortical responses to stimulation of the human fovea. *Vision Res.* 8: *135* (1968).

DODT, E. & K. H. JESSEN. The duplex nature of the retina of the nocturnal gecko as reflected in the ERG. *J. gen. Physiol.* 44: *1143* (1961).

DOESSCHATE, J. TEN. Visual acuity and distribution of percipient elements on the retina. *Ophthalmologica* 112: *1* (1946).

DOWLING, J. E. Organization of vertebrate retinas. *Invest. Ophthal.* 9: *655* (1970).

DREYER, H. Über Ätiologie und Häufigkeitsverhältnisse der Neuritis retrobulbaris. *Klin. Mbl. Augenheilk.* 110: *170* (1944).

—— Über Ätiologie und Häufigkeitsverhältnisse der Neuritis retrobulbaris. *Klin. Mbl. Augenheilk.* 112: *93* (1947).

DUKE ELDER, S. & G. I. SCOTT. Diseases of the lens and vitreous; Glaucoma and hypotony. *System of Ophthalmology*, Vol. *XI*. Kimpton, London (1969).

—— & —— Neuro-ophthalmology. *System of Ophthalmology*, Vol. *XII*. Kimpton, London (1971).

FEINSOD, M., H. ROWE & E. AUERBACH. Changes in the electroretinogram in patients with optic nerve lesions. *Docum. Ophthal.* 29: *169–200* (1971).

——, —— & —— Enhanced retinal responses without signs of optic nerve involvement. *Docum. Ophthal.* 29: *201–211* (1971).

GASTAUT, H. & H. RÉGIS. Visually-evoked potentials recorded transcranially in man. In: Proctor, L. D. & W. R. Adey, (eds.): 'The analysis of central nervous system and cardiovascular data using computer methods'. Washington, NASA, p. 7–34 (1965).

GASTEIGER, H. Gegenwartsprobleme der Augenheilkunde. Thieme, Leipzig (1937).

GORNIG, H. & S. BISCHOF. Zur Altersabhängigkeit einiger Sehnervenerkrankungen. *Z. Alternsforsch.* 22: *291* (1969).

GOURAS, P. C.S. Electronic computation of the human retinal and brain responses to light stimulation. *Ann. N.Y. Acad. Sci.* 115: *763* (1964).

—— & K. LINK. Rod and cone interaction in dark adapted monkey ganglion cells. *J. Physiol.* 184: *499* (1966).

HAAS, J. P. DE, G. H. M. VAN LITH & H. E. HENKES. The ERG and the VER of the macular region in cases of disturbance of the visual nervous system; Proceedings 7th ISCERG Symposium, Istanbul 1969; ed. by D. Basar and U. Bengisu. Istanbul, Faculty of medecine, p. 51 (1971).

—— Electrophysiological examination of central scotomata due to pathological changes in the optic nerve. Second Mackenzie Memorial Symposium, 1971. Glasgow, Scotland, in press.

HAM, A. W. Histology, 6th edition. Lippincott, Philadelphia (1969).

HAYREH, S.S. Blood supply of the optic nerve head and its role in optic atrophy, glaucoma, and oedema of the optic disc. *Brit. J. Ophthal.* 53: *721* (1969).

HENKES, H. E. & A. TH. M. VAN BALEN. Techniques of recording of the hitherto unrecordable ERG in the human eye. In: Electroretinographia; Proc. Symp. Luhacovice 1959; ed. by J. Vanysek. Lekarska Fakulta University J. E. Purkyne, Brno, p. 21 (1960).

—— & L. H. VAN DER TWEEL. Amplification sélective du flicker E.R.G. *E.R.G. et Champ Visuel 161* (1962).

——, —— & J. J. DENIER VAN DER GON. Selective amplification of the E.R.G. *Ophthalmologica* 132: *140* (1956).

HIERONS, R. & T. K. LYLE. Bilateral retrobulbar optic neuritis. *Brain* 82: *56* (1959).

HOEVE, J. VAN DER. Optic nerve and accessory sinuses. *Arch. Ophthal.* 51: *210* (1922).

—— Roentgenography of the optic foramen in tumors and diseases of the optic nerve. *Amer. J. Ophthal.* 8: *101* (1925).

—— Röntgenphotographie des Foramen opticum bei Geschwülsten und Erkrankungen des Sehnerven. *Graefes Arch. Ophthal.* 115: *355* (1925).

HOF, M. W. VAN. The cortical response to photic stimulation. *J. electroenceph. clin. neurophysiol.* 11: *611* (1959).

—— Open-eye and closed-eye occipito-cortical response to photic stimulation of the retina. *Acta physiol. pharmacol. neerl.* 9: *443* (1960).

——, J. VAN HOF-VAN DUIN & W. J. RIETVELD. Enhancement of occipito-cortical responses to light-flashes in man during attention. *Vision Res.* 6: *109* (1966).

HOGAN, M. J. & L. F. ZIMMERMAN. Ophthalmic pathology; an atlas and textbook. Saunders, London (1962).

IMAY, Y. & D. MORIWAKI. A probable case of cytoplasmic inheritance in man; a critique of Leber's disease. *J. Genet.* 33: *163* (1936).

JACOBSEN, J. Ein Beitrag zur Ätiologie der Neuritis optica. Inaug.-Diss. Med. Fak. Hamburg (1964).

JACOBSON, J. H. Clinical electroretinography. Thomas, Springfield (1961).

——, K. KAWASAKI & T. HIROSE. The human electroretinogram and occipital potential in response to focal illumination of the retina. *Invest. Ophthalm.* 8: *545* (1969).

KENNEDY, C. & F. D. CARROL. Optic neuritis in children. *Arch. Ophthal.* 63: *747* (1960).

KWITTKEN, J. & H. D. BAREST. The neuropathology of hereditary optic atrophy (Leber's disease): the first complete anatomic study. *Amer. J. Path.* 34: *192* (1958).

LENZ, F. Ueber die Krankhaften Erbanlagen des Mannes. Jena (1912).

LITH, G. H. M. VAN & H. E. HENKES. The local electric response of the central retinal area. In: Advances in electrophysiology and -pathology of the visual system: Proc. VIth ISCERG Symp., Erfurt 1967: ed. by E. Schmöger. Thieme, Leipzig, p. 163 (1968).

—— & —— The relationship between ERG and VER. *Ophthal. Res.* 1: *40* (1970).

—— The combined use of the macular electroretinogram (M-ERG) and the visually evoked responses (VER). *Ophthalmologica* 162: *208* (1971).

LUNDSGAARD, R. Leber's disease: a genealogic, genetic and clinical study of 101 cases of retrobulbar optic neuritis in 20 danish families. *Acta Ophthal.* Suppl. XXI. Nordisk Forlag, Copenhagen (1944).

MCDONALD, W. I. & T. A. SEARS. Effect of demyelination on conduction in the central nervous system. *Nature* 221: *182* (1969).

——, —— Focal experimental demyelination in the central nervous system. *Brain* 93: *575* (1970).

—— & ——The effects of experimental demyelination on conduction in the central nervous system. *Brain* 93: *583* (1970). .

MEADOWS, S. P. Doyne Memorial Lecture: Retrobulbar and optic neuritis in childhood and adolescence. *Trans. ophthal. Soc. U.K.* 89: *603* (1969).

MONNIER, M. Retinal, cortical and motor responses to photic stimulation in man. *J. Neurophysiol.* 15: *469* (1952).

NAGATA, M. & Y. HONDA. Macular ERG in central serous retinopathy. *Jap. J. Ophth.* 1: *9* (1971).

ØSTERBERG, G. Topography of the layer of rods and cones in the human retina. Busck, Copenhagen (1935).

OTRADOVEC, J. & J. VOTOČKOVÁ. Etiologie akutnich neuritis optiku. *Sborn. lék.* 64: *234* (1962).

PATON, L. & G. HOLMES. Pathology of papilloedema: an histological study of sixty eyes. *Brain* 33: *389* (1910–1911).

PEN, R. D. & W. A. HAGINS. Signal transmission along retinal rods and the origin of the electroretinographic a-wave. *Nature* 223: *201* (1969).

PERRY, N. W. JR. & D. G. CHILDERS. The human visual evoked responses: method and theory. Thomas, Springfield (1969).

PETERS, A. The structure of myelin sheaths in the central nervous system of Xenopus Laevis (Daudin). *J. biophys. biochem. Cytol.* 7: *121* (1960).

—— The node of Ranvier in the central nervous system. *Quart. J. exp. Physiol.* 51: *229* (1966).

PIETRUSCHKA, G. Über Häufigkeit und klinische Kriterien sowie therapeutische Ergebnisse bei vasculäre Opticopathien. Ber. Tagung Oto-Neuro-Ophthal., p. 288 Dresden (1962).

POLYAK, S. L. The retina. University Press, Chicago (1941).

—— The vertebrate visual system. University Press, Chicago (1957).

PRINGLE. *Brit. J. Surg.* 4: *373* (1917).

RAWSON, M. D., L. A. LIVERSEDGE & G. GOLDFARB. Treatment of acute retrobulbar neuritis with corticotrophin. *Lancet* 2: *1044* (1966).

RIPPS, H. & H. G. VAUGHAN. The spectral sensitivity of evoked potentials from the retina and cortex of nocturnal and diurnal monkeys. *Vision Res.* 9: *895* (1969).

RODGER, F. C. Unilateral involvement of the optic nerve in head injuries. *Brit. J. Ophthal.* 27: *23* (1943).

SCHÖNENBERGER, F. Beitrag zur Kenntnis der homochron-hereditären Opticus-atrophie. *Arch. Julius Klaus Stiftung* 2: *59* (1926).

SCHREINEMACHERS, H. P. & H. E. HENKES. Relation between localized retinal stimuli and the visual evoked response in man. *Ophthalmologica* 155: *17* (1968).

—— Some specific findings in the VER and its use in the diagnosis of ophthalmological abnormalities. In: Advances in electrophysiology and -pathology of the visual system; Proc. VIth ISCERG Symp., Erfurt 1967; ed. by E. Schmöger. p. 171, Thieme, Leipzig (1968).

SCHWEINITZ, G. DE. The toxic amblyopias. Philadelphia (1896).

SEEDORFF, T. Leber's disease. *Acta Ophthal.* 46: *4* (1968).

—— Leber's disease II. *Acta Ophthal.* 46: *985* (1968).

—— Leber's disease III. *Acta Ophthal.* 47: *23* (1969).

SENUS, A. H. C. VAN. Leber's disease in the Netherlands. Thesis Leiden. Junk, Den Haag (1963).

SUGAWARA, S. Etiologic observation of optic neuropathies. The relationship of retrobulbar neuritis to multiple sclerosis. *Acta soc. ophthal. Jap.* 62: *304* (1958).

TURNER, J. W. A. Indirect injuries of the optic nerve. *Brain* 66: *140* (1943).

UZMAN, B. G. & G. M. VILLEGAS. A comparison of nodes of Ranvier in sciatic nerves with node-like structures in optic nerves of the mouse. *J. biophys. biochem. Cytol.* 7: *761* (1960).

VOGT, A. Ueber geschlechtsgebundene Vererbung von Augenleiden. *Schweiz. med. Wschr.* 52: *77* (1922).

WALLACE, D. C. A new manifestation of Leber's disease and a new explanation for the agency responsible for its unusual pattern of inheritance. *Brain* 93: *121* (1970).

WALSH, F. B. Clinical neuro-ophthalmology; second ed. Williams & Wilkins, Baltimore (1957).

WALTER, W. GREY, V. J. DOVEY & H. SHIPTON. Analysis of the electrical response of the human cortex to photic stimulation. *Nature 158*: *540* (1946).

WEERDT, C. J. DE. Neurological studies on Leber's optic atrophy. Thesis Leiden. van Denderen, Groningen, (1969).

WEIGELIN, E. Local circulation in papilloedema. Second Mackenzie Memorial Symposium, 1971. Glasgow, Scotland, in press.

WHITE, L. E. The location of the focus in optic nerve disturbances from infection. *Ann. oto-rhino-laryng.* 37: *128* (1928).

WILMER, W. H. Chronic retrobulbar neuritis. *Arch. Ophthal.* 4: *817* (1930).

WILSON, J. Leber's hereditary optic atrophy; a possible defect of cyanide metabolism. *Clin. Sci.* 29: *505* (1963).

Name / sex	age (years)	affected eye(s)	aetiology	VOD	VOS	local OD F-ERG	local OD VER	local OS F-ERG	local OS VER	full light OD ERG	full light OD VER	full light OS ERG	full light OS VER	full dark OD ERG	full dark OD VER	full dark OS ERG	full dark OS VER	notes
L.B.-V. ♀	23	OS	?	1,1	1/60	+	+	-	-	+	+	+	±					
				1,1	1,1	±	+	+	+	±	+	±	+					6 weeks after 1st examination
A.B. ♂	46	OS	?	0,9	1/300	+	±	±	-	+	+	+	±					
A.B.-A. ♀	35	ODS	M.S.	0,3	0,3	+	±	+	±									
	37			1,0	1,0	+	±	+	±	+	+	+	+					2 years after 1st examination
T.B. ♂	44	ODS	?	0,9	0,9	+	±	±	±									
H.D.-K. ♀	30	ODS	M.S.(?)	1,1	1,1	+	±	+	±									optic neuritis ODS 2 years before examination
J.E. ♂	66	OS	alcohol tabacco ?	1,1	0,4	+	±	+	±	+	±	±	-					
P.F. ♂	46	ODS	alcohol tabacco ?	0,3	0,3	-	-	-	-	-	±	-	±					
C.G. ♂	47	ODS	alcohol tabacco ?	1/60	2/60	+	±	+	±									
A.H.-B. ♀	48	ODS	MS	0,3	1/60	-	+	-	-	±	+	-	±					
				0,4	1/60	+	±	-	-	±	+	-	±	±	+	±	±	4 months after 1st examination
N.H. ♂	38	OD	M.S.(?)	0,1	1,0	+	-	+	-									3 years ago: optic neuritis OS
	40			0,5	1,0	+	-	+	±					+	-	+	±	1½ years after 1st examination
W.H.-H. ♀	43	OD	?	1/60	1,1	+	-	+	+					+	-	+	+	
				0,8	1,1	+	-	+	+					+	+	+	+	8 days after 1st examination
				1,1	1,1	+	±	+	+	+	+	+	+					4 weeks after 1st examination
				1,1	1,1	+	±	+	+	+	±	±	+					4 months after 1st examination
H.H.-B. ♀	26	OD	M.S.	0,1	1,0	±	-	±	±									
	27	ODS		5/60	0,2	-	-	±	-	±	±	-	±					11 months after 1st examination
W.H. ♀	22	ODS	?	1/60	perc.-	+	±?	+	±	±	±	+	±					
				1/60	1/60	+?	±	+	+									3 weeks after 1st examination
				0,7	0,2	+	±	+	±									6 weeks after 1st examination
				1,0	0,3	+?	±	+?	±									8 weeks after 1st examination
				0,7	0,7	+	±	+	+	+	+	±	±					8 months after 1st examination
Th.H.-S. ♀	52	OS	?	1,0	3/60	+	+	+	-									
A.H.-K. ♀	31	ODS	M.S.?	0,5	0,5	+	+	+	+									reconvalescense
				0,8	0,8	+	+	±	+									4 months after 1st examination
	32			0,9	0,9	+	+	+	+									1 year after 1st examination
J.H.-W. ♀	50	OD	?	perc.-	1,0	-	-	-	+	+	±	+	+	+	±	+	+	
C.H. ♀	43	OD	?	perc.+	1,0	+	±	+	+									
	45	ODS		0,1	0,6	±	±	+	±									18 months after 1st examination
				0,1	0,6	+	±	+	±									21 months after 1st examination
M.H.-W. ♀	19	OD	?	perc.±	1,0	-	-	+	+									
	20			1,0	1,0	+	+	+	+	±	+	±	+					16 months after 1st examination
T.K. ♂	23	OD	M.S.	0,6	1,1	+	±	+	+									
				1,1	1,1	+	+	+	+									1 week after 1st examination
				1,1	1,1	+	+	+	+									7 months after 1st examination
				1,1	1,1	+	+	+	+									14 months after 1st examination

I Continuation

Name	sex	age (years)	affec-ted eye(s)	aetiology	VOD	VOS	local (foveal) stimulation OD F-ERG	OD VER	OS F-ERG	OS VER	full field stimulation light adapted state OD ERG	OD VER	OS ERG	OS VER	dark adapted state OD ERG	OD VER	OS ERG	OS VER	
B.K.	♂	64	OD	?	1/60	1,1	+	−	+	+									
					0,3	1,1	+	±	+	+	+	±	+	+					7 months after 1st examination
					0,3	1,1	+	−	+	+	±	±	+	+	+	±	+	±	13 months after 1st examination
L.N.-D.	♀	39	OD	M.S.?	1/300	1,1	±	−	±	+					+	±	+	+	
Th.N.	♂	54	ODS	alcohol ?	perc.±	5/10	+	±?	±	±?									
A.N.-L.	♀	37	ODS	?	1,0	1,0	±	−	±	±	+	±	+	±	+	±	+	±	
							±	±	+	±	+	±	+	±					3 months after 1st examination
K.O.	♂	31	OD OS?	MS?	2/60	0,8	+	−	+	±	+	+	+	+					
N.P.	♀	17	ODS	?	0,2	0,2	+	±	+	±					+	+	+	+	
							+	−	−	−	+	±	−	±	+	±	+	+	4½ months after 1st examination
J.P.-R.	♀	31	OD	M.S.	perc.+	1,0	+	−	+	+									
					1,0	1,0	+	+	+	+									14 months after 1st examination
G.P.-H.	♀	25	ODS	?	0,4	0,8	±	−	±	±	+	−	±	−?					
P.P.	♀	58	ODS	tobacco ?	0,8	0,7	+	+	±	±									
					1,0	1,0	+	+	+	±									14 months after 1st examination
J.Q.	♂		ODS	?	0,5	perc.-	−	+	−	−	−	+	±	−	−	+	−	±	
A.Q.	♂	32	ODS	M.S.	0,1	4/60	+	−	+	−					±	±	±	±	
							±	−	−	−					−	±	+	±	15 days after 1st examination
							+	−	+	−	±	±	±	±					6 months after 1st examination
E.R.	♀	43	OD	?	1/60	1,1	+	±	+	+	±	±	+	+	+	±	+	+	
					0,8	1,1	+	±	+	+									16 days after 1st examination
					0,8	1,1	+	±	+	+									2 months after 1st examination
					0,7	0,9	+	+	+	+									13 months after 1st examination
H.S.	♀	19	OS	?	1,0	0,7	+	+	+	+									
					1,0	1,0	±	±	+	+									20 months after 1st examination
J.S.	♂	29	ODS	?	0,9	0,8	±	−	±	−	±	±	−	±	+	±	+	±	
					0,3	0,3	+	−	+	−	±	±	±	±					4 months after 1st examination
W.S.-A	♀	24	OD	M.S.?	1/60	1,1	+	−	+	+	+	±	+	+	+	±	+	+	
							±	−	+	±	±	−	+	+	±	−	+	+	7 weeks after 1st examination
							−	−	+	±	−	−	+	+					8 months after 1st examination
A.S.	♀	21	OD	M.S.?	0,1	1,1	+	+?	+	+									
					1,1	1,1	+	+	+	+									25 months after 1st examination
H.V.-V.	♀	32	OS	?	1,1	0,1	+	+	±	±	+	+	+	±					
					1,1	1,1	+	+	+	+									6 months after 1st examination
M.W.	♂	28	OD	?	1/60	1,1	+	−	+	+	+	±	+	+					
					1,1	1,1	−	±	+	+									9 months after 1st examination
K.W.	♂	49	OS	?	1,1	1/60	+	+	+	−	+	+	+	±					
							+	+	±	−									1 week after 1st examination
C.W.-E.	♀	48	OS	?	1,1	3/60	+	−	+	−									
					3/60	1/60	−	−	−	−	+	±	+	−	+	±	+	±	20 months after 1st examination

II LEBER's HEREDITARY OPTIC ATROPHY

Name	sex	age	VOD	VOS	local (foveal) stimulation				full field stimulation								
									light adapted state				dark adapted state				
					OD		OS		OD		OS		OD		OS		
					F-ERG	VER	F-ERG	VER	ERG	VER	ERG	VER	ERG	VER	ERG	VER	
A.A.	♂	31	0,8	0,9	+	–	+	–					+	±	+	±	
C.B.	♂	47	0,8	6/60	±	–	+	–					±	+	±	+	scotopic} photopic} ERG:normal, EOG:normal
H.H.	♂	43	2/60	0,3	–	–	–	–					–	–	–	–	
Th.H.	♂	46	0,5	0,9	+	±?	+	±?					+	+	+	+	
W.M.	♂	66	4/60	5/60	±¹⁾	–	+¹⁾	–	±	–	±	±	–	–	–	±	scotopic} photopic} ERG:normal, EOG: normal
N.R.	♂	67	0,8	0,9	–	–	±	–					+	±	+	±	
W.R.	♂	52	0,3	5/60	±	–	–	–					+	±	+	±	
F.V.	♂	24	0,2	1,0	–	±	+	±									
			0,2	0,3	–	±	–	–	–	±	–	±	±	±	–	±	6 months after 1st examination
C.V.	♂	32	1,0	0,4	+	–	+	–	±	±	–	±	+	±	+	±	scotopic} photopic} ERG: normal, EOG: normal
J.V.	♂	64	0,8	0,7	–	–	–	–					+	±	+	±	

1) 8°-registration: <u>subnormal</u>

III PAPILLOEDEMA (CHOKED DISC) DUE TO VARIOUS CAUSES

Name	sex	age (years)	VOD	VOS	aetiology	local (foveal) stimulation				full field stimulation							
										light adapted state				dark adapted state			
						OD		OS		OD		OS		OD		OS	
						F-ERG	VER	F-ERG	VER	ERG	VER	ERG	VER	ERG	VER	ERG	VER
F.-J., J.	♀	47	1,0	1,0	tumour	+	+	+	+								
H.M.T.	♀	48	1,0	1,0	tumour	+	+	+	+	±	+	+	+	+	+	+	+
M.-B.M.	♀	44	1,0	1,0	cortical phlebitis	+	+	+	+								
P.U.	♂	29	1,0	1,0	tumour	+	+	+	+								
K.-E., M.C.	♀	24	1,0	1,0	cortical phlebitis	+	+	+	±								
S.L.Q.	♂	25	1,0	1,0	?	+	+	+	+								
S.D.	♂	20	0,8	0,3	aquaduct stenosis	+	+	+	±								

IV HOMONYMOUS HEMIANOPIA DUE TO A CEREBRO-VASCULAR ACCIDENT

Name	sex	age (years)	VOD	VOS	right- or left-sided hemianopia	local (foveal) stimulation						full field stimulation											
						OD			OS			light adapted state						dark adapted state					
						F-ERG	VER		F-ERG	VER		OD			OS			OD			OS		
												ERG	VER		ERG	VER		ERG	VER		ERG	VER	
							1-2	1-3		1-2	1-3		1-2	1-3		1-2	1-3		1-2	1-3		1-2	1-3
E.M.	♂	73	0,7	0,6	left-sided	+	–	±	+	±	±												
G.-L., G.	♀	63	0,4	0,6	left-sided	±	±	+	+	+	+												
H.L.	♀	58	0,9	0,9	right-sided	–	±	±	–	±	±												
M.A.C.	♂	70	0,3	0,5	left-sided	±	+	+	–	+	+							+	±	+	+	±	+
M.J.	♂	72	1,0	1,0	right-sided	+	–	–	+	–	–							+	±	±	+	±	±
P.W.	♂	27	1,0	1,0	right-sided	+	+	–	+	+	–												
P.Chr.	♂	73	1,0	1,0	left-sided	±	+	±	–	+	+	+	±	+	+	±	+						
P.J.	♂	54	1,0	1,0	right-sided	+	±	–	±	±	–												
S.Th.	♂	53	1,0	1,0	left-sided	±	±	±	–	±	±												
V.J.M.	♀	47	1,0	1,0	left-sided	+	+	+	+	+	+							–	+	+	–	+	+
V.J.	♂	64	1,0	1,0	right-sided	+	+	+	+	–	+												