CHANGES IN THE ELECTRORETINOGRAM IN PATIENTS WITH OPTIC NERVE LESIONS

by

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ABSTRACT

Sixty-nine cases of optic nerve atrophy were examined electrophysiologically. 42% displayed enhanced ERGs together with reduced or absent visual evoked potentials. Eight cases of these with conditions resulting from blunt head injury, brain tumor, encephalitis and multiple sclerosis are presented in detail.

The distribution of the b-wave and a-wave amplitudes of the pathological ERG was studied and compared with normal ERGs. The b-wave was taken as criterion for retinal sensitivity for reasons explained. Possible underlying mechanisms of the electrophysiological data are speculated considering that 55% of the cases displayed reduced ERGs. The data seem to support the hypothesis that in the intact visual system impulses propagated along centrifugal optic nerve fibers inhibit retinal activity at the bipolar cell level, an effect rivaled by the growing retinal sensitivity during dark adaptation. In the absence of the efferent effect in optic nerve involvement, the ERG recovery would be unrivaled resulting in enhanced ERGs. An inhibition of this assumed inhibitory feedback on the retina by light adaptation is postulated and supported by evidence from animal experiments found in the literature. This hypothesis and alternative hypotheses are applied to the cases examined.

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The occurrence of reduced ERGs is explained by an involvement of the bipolar and receptor cells due to a progressive degeneration of possibly existing intraretinal centrifugal fibers. In favor of this is the significant diminution of the a-wave in contrast to the generally normal a-wave values found in cases with enhanced ERGs as compared with the ERG of normal persons.

INTRODUCTION

The participation of the retinal ganglion cells in the clinical electroretinogram (ERG) is generally considered negligible. Experimental evidence and clinical findings in conditions where the ganglion cells were degenerated (GRANIT & HELME, 1939; KARPE, 1945; NOELL, 1953; MÜLLER-LIMMROTH, 1959; BROWN, 1968), point to the first two neurons in the retina as being responsible for its elicitation. However, experimental and clinical observations show that a disturbance in the impulse propagation through the optic nerve fibers, the axons of the ganglion cells, often causes alterations which are reflected by the ERG in the retinal activity of the corresponding eye. In some cases the ERG becomes larger than that produced in the eye with intact central connections and often reaches 'supernormal' amplitudes (DIETERLE & BABEL, 1955; JACOBSON & GESTRING, 1958a, 1958b; SUZUKI, 1959; STRAUB & RANK, 1959; STRAUB, 1961; ABE, 1962; NAGAYA et al., 1962; GILLS, 1966a; FEINSOD & AUERBACH, 1969). In other cases it may remain normal or does not attain normal values (EBE, 1964).

A disturbance in the nervous conduction between retina and cortex is demonstrated by a greatly reduced or even extinct visual evoked potential (VEP) in the cortex. The existence of centrifugal fibers in the optic nerve, which are thought by some of the authors to synapse with the amacrine cells (RAMÓN Y CAJAL, 1892–3; COWAN & POWELL, 1963; WOLTER, 1965; WOLTER & KNOBLICH, 1965; BROOKE et al., 1965; HONRUBIA & ELLIOT, 1968), seems to point to a negative feedback system in the normal visual system (GRANIT, 1955; DODT, 1956). There are other contrary reports, however, where no negative feedback was found, which make the subject controversial (BRINDLEY & HAMASAKI, 1962; MITA, 1962;EBE et al., 1964; BRINDLEY & HAMASAKI, 1966).

Because of these differences in opinion, it seemed to us necessary to evaluate the clinical material of 69 cases of optic nerve atrophy examined up to this date in our laboratory, and to try to draw some conclusions as to the function of the intact visual system. In this electrophysiological study, the data of all cases

examined are provided and critically compared. In addition, a typical group of eight patients with optical nerve affections of various causes, whose ERG was larger than that found in the intact visual system and whose VEP was absent, is presented in detail. All cases except one displayed ophthalmoscopic evidence of optic nerve atrophy either prior to the examination or thereafter.

METHODS

In all 69 cases examined as well as in the 54 normal persons whose ERG data are included here, the pupils were maximally dilated (Mydriaticum Roche). ERGs to single stimuli were recorded simultaneously from both eyes. The VEP was recorded after simultaneous stimulation of both eyes as well as of each eye individually. The examinations were carried out in an electrically shielded cage with the patient in a recumbent position. For the ERG recordings a contact lens containing a silver ring electrode (HENKES) was fixed to each eye, and an indifferent silver disc electrode was fastened to the mid-supraorbital rim above each eye. The VEP was derived bipolarly from the occipital scalp between two 9 mm silver disc electrodes, which were placed at the inion and 5 cm above. A ground electrode was attached to one ear lobe.

A photostimulator (van Gogh SI-1A or Grass PS-2) was used which activates a xenon discharge lamp. The flash duration was about 10 μsec. The light source was centered at 20 cm in front of the patient's eyes.

For ERG recordings a condenser-coupled dual-beam CRO (Tektronix 502) was used. The electrodes were connected to the CRO through AC preamplifiers (Grass PS-5) whose filters were set at 0.1 cps and 2000 cps (Fig. 1 in: AUERBACH, 1967). For the recordings of the VEP responses to 70 flashes delivered at a frequency of about 1/sec were averaged on the Computer of Average Transients (CAT) (model 400B). The averaged responses were displayed on the screen of the CRO, which was set for X-Y tracings, and photographed with a Grass camera (C4). For the few VEP examinations carried out before the CAT was available, DAWSON's (1954) photographic method was employed for averaging. The single ERG responses were also photographed from the CRO screen. Sweeps and camera shutter were synchronized to coincide with the onset of the stimulus.

The ERG was repeatedly recorded during the steady state of light adaptation. The recovery of the ERG from a five-minute light adaptation was followed for about 30 minutes of dark adaptation. Single stimuli were used in order not to

light-adapt the eye. They were applied at intervals of at least 30 seconds (AUERBACH, 1964).

Since visual adaptation is reflected by the changes in the amplitude of the b-wave (see discussion), the values of the ERG recordings used in the following refer essentially to the amplitude from the initial negative (downward) peak of the a-wave to the positive peak of the b-wave. However, the a-wave was also considered; it was measured from the baseline down to the initial negative peak. Under our test conditions, the normal values for the amplitude of the b-wave at the end of the recovery (i.e., after about 30 minutes in the dark) are essentially between 430 μV and 550 μV, 80% to 85% of the final amplitude having recovered after ten minutes in the dark, while those for the a-wave range between 100 μV and 200 μV (AUERBACH, 1962, 1964, 1967). These values are based on a large number of examinations of which the results from 98 eyes in 54 normal subjects are presented in the histogram of Fig. 1. The normal averaged VEP, of which the first 250 msec were recorded, has a latent period of 20–25 msec and displays a peak-to-peak amplitude of 4 – 10 μV between the initial positive potential, which is essentially a radiation response component from geniculo-cortical fibers (CREUTZFELDT et al., 1969), and the subsequent negative-positive complex wave of the primary response. The late potentials of the VEP which follow the primary response have not been considered in these measurements.

RESULTS

In all cases of optic nerve involvement examined, an extinct VEP or one of very small amplitude and lengthened latency were found. 42% of these, i.e. 29 cases, displayed an ERG with enhanced b-waves, usually in both eyes (see Table I and Fig. 2). Of the remaining 58%, ERGs with subnormal b-waves were recorded in 38 cases, again generally in both eyes (Table II and Fig. 2); and only in two cases the ERGs of both eyes displayed normal amplitudes, shape and recovery in the dark (Table III and Fig. 2).

In the histogram of Fig. 2, which demonstrates the values of the b-wave of all 69 cases, it can be seen that the two groups of pathological ERGs (shaded bars) are well separated from each other. While the amplitudes of the subnormal b-waves reach maximal values of 400 μV, those of the enhanced b-waves range between 560 μV and 800 μV (see also the scatter diagram of Fig. 4). The gap between the two pathological groups which appears in the histograms of Fig. 2 is almost ideally filled by the measurements of the b-wave amplitudes from

TABLE I

Patients with enhanced retinal responses and defective visual evoked potentials.

No.	Age (Years)	Sex	Diagnosis	ERG (μV) right eye a	ERG (μV) right eye b	ERG (μV) left eye a	ERG (μV) left eye b	VEP
1	6	m	Cause unknown; mental retardation	130	620	160	630	s.d.
2	7	f	Premature birth and anoxia; mental and motor retardation	100	780	100	620	d.
3	1	m	St. after encephalitis	110	600	50	610	e.
4	6	m	St. after encephalitis	120	600	120	610	s.d.
5	32	f	St. after encephalitis	300	730	300	770	e.
6	17	f	Multiple Sclerosis	170	610	150	580	Rt-n Lt-e
7	23	f	Multiple Sclerosis	210	610	210	620	e.
8	28	f	Multiple Sclerosis	160	660	220	710	e.
9	35	f	Multiple Sclerosis	110	560	150	600	Rt-e Lt-s
10	41	f	Multiple Sclerosis	120	460	180	590	Rt-s Lt-s
11	42	f	Multiple Sclerosis	100	610	100	610	e.
12	49	m	Multiple Sclerosis	300	590	290	500	d.
13	15	f	Bilateral retrobulbar neuritis	210	640	180	620	n.
14	33	f	Left retrobulbar neuritis	210	480	180	600	n.
15	26	f	Right retrobulbar neuritis	250	690	280	610	Rt-s.d. L-n
16	49	f	Diabetes; bilateral optic neuritis	100	600	110	620	s.d.
17	62	m	Recurrent bilateral optic neuritis	180	780	180	680	s.d.
18	27	f	Tuberculum sellae meningioma	290	680	290	750	e.
19	35	f	Right frontotemporal brain tumor; Diabetes	180	800	200	750	s.d.
20	45	m	St. after head injury	160	600	180	660	d.s.
21	42	m	Traumatic right optic nerve atrophy	190	690	150	480	Rt-e Lt-n
22	15	f	Right exophthalmus; Unknown origin	120	600	120	610	Rt-e Lt-n
23	7	f	Unknown cause	180	580	120	700	d.s.
24	7	f	Unknown cause	120	650	150	720	s.
25	39	m	Unknown cause	210	630	190	610	e.
26	12	f	Unknown cause	150	580	110	560	s.
27	14	f	Unknown cause	170	570	120	510	s.d.
28	15	m	Unknown cause	150	710	180	700	d.s.
29	35	m	Unknown cause	120	670	120	690	d.

TABLE II

Patients with subnormal retinal responses and defective visual evoked potentials.

No.	Age (Years)	Sex	Diagnosis	ERG (μV) right eye a	ERG (μV) right eye b	ERG (μV) left eye a	ERG (μV) left eye b	VEP
1	½	m	Unknown cause; retarded developm.	20	130	30	150	e.
2	¾	f	Unknown cause; retarded developm.	120	290	5	210	e.
3	1½	f	Unknown cause; retarded developm.	100	480	60	300	s.d.
4	3	m	Unknown cause; retarded developm.	70	310	30	310	e.
5	4	f	Unknown cause; retarded developm.	10	290	10	290	e.
6	5	f	Unknown cause; retarded developm.	90	170	60	170	e.
7	2	f	Cerebral palsy	150	320	110	270	e.
8	4	m	Cerebral palsy	100	240	120	240	e.
9	3	m	Oxycephaly	100	350	120	370	e.
10	28	m	Craniostenosis	60	280	100	280	s.d.
11	33	m	St. after encephalitis	100	300	50	220	e.
12	5 m.	m	St. after bilateral subdural hematoma	170	350	120	300	s.
13	6	f	Craniopharyngioma	60	200	20	200	e.
14	20	f	Craniopharyngioma	70	170	115	220	s.
15	33	m	Pituitary adenoma	120	310	180	310	e.
16	43	m	Pituitary adenoma	150	380	120	320	e.
17	47	f	Pituitary adenoma	100	310	120	320	s.d.
18	45	f	Tuberculum sellae neningioma	50	400	80	400	Rt-e Lt-n
19	47	f	Bilateral occipital meningioma	20	350	70	350	e.
20	54	m	St. after luetic meningitis	120	400	120	500	e.
21	62	f	Opticochiasmatic arachnoiditis	160	380	190	350	s.d.
22	26	m	Bilateral optic neuritis	120	290	120	280	s.
23	28	f	Left retrobulbar neuritis	180	400	150	280	Rt-e Lt-n
24	30	m	Bilateral retrobulbar neuritis	20	310	20	290	s.d.
25	43	f	Bilateral retrobulbar neuritis	80	350	100	380	e.
26	22	f	Multiple Sclerosis	80	300	80	400	s.d.
27	36	m	Trauma to skull; nyctalopia	100	180	100	190	Rt-e Lt-s
28	29	m	Methyl alcohol poisoning	120	310	90	310	e.
29	68	m	Methyl alcohol poisoning	20	180	110	300	e.
30	42	m	Glaucoma	100	390	50	400	s.d.
31	47	m	Glaucoma	30	210	50	250	e.
32	7	f	Unknown cause	100	320	90	370	e.
33	7	f	Unknown cause	30	325	100	400	e.
34	12	f	Unknown cause	70	380	100	400	s.d.
35	13	m	Unknown cause	90	350	50	250	e.
36	14	m	Unknown cause	100	330	150	400	s.
37	23	m	Unknown cause; meningitis?	80	250	120	350	e.
38	32	m	Unknown cause	150	400	150	400	e.

TABLE III

Patients with normal retinal responses in both eyes and defective visual evoked potentials.

No.	Age (Years)	Sex	Diagnosis	ERG (μV) right eye a	ERG (μV) right eye b	ERG (μV) left eye a	ERG (μV) left eye b	VEP
1	24	m	Right retrobulbar neuritis	190	480	180	480	Rt-e Lt-n
2	51	f	Trauma in operation to left optic nerve	170	500	250	480	Rt-n Lt-sd

n: normal
d: delayed
s: subnormal amplitude
e: extinct

normal subjects (Fig. 1, right). The contingency table for the three groups by potentials gives a chi-square (χ^2) with $P > 0.001$. The determination of the normal distribution of the b-wave amplitudes made it possible to assign with confidence the two pathological cases displaying normal b-waves in both eyes and the seven cases in which a normal b-wave was found solely in one eye (see empty and dotted bars respectively in Fig. 2).

The measurements of the b-wave in the ERGs of the 69 cases with defective VEPs were divided in the histograms of Fig. 3 into those belonging to ERGs with subnormal b-waves (left), those belonging to ERGs with enhanced b-waves (center), and those belonging to cases with both monocular and binocular ERGs (right). A comparison with the histogram of Fig. 1 (left), which demonstrates the distribution of the a-wave amplitudes in normal subjects, shows that the amplitudes of the group with enhanced b-waves (Fig. 3, center) quite well tallies with the normal values of the a-wave although in a relatively small number of cases high amplitudes (between 260 μV and 300μV) were obtained, which in no case were attained by the a-waves of the ERGs from normal persons. On the other hand, the distribution of the a-wave values from the group with subnormal b-waves (Fig. 3, left), differs considerably from the distribution of the a-wave values in both the normal group (Fig. 3, right and Fig. 1) and the group with enhanced b-waves (Fig. 2, center). A distinct shift in the a-wave amplitudes to smaller values can be noticed here.

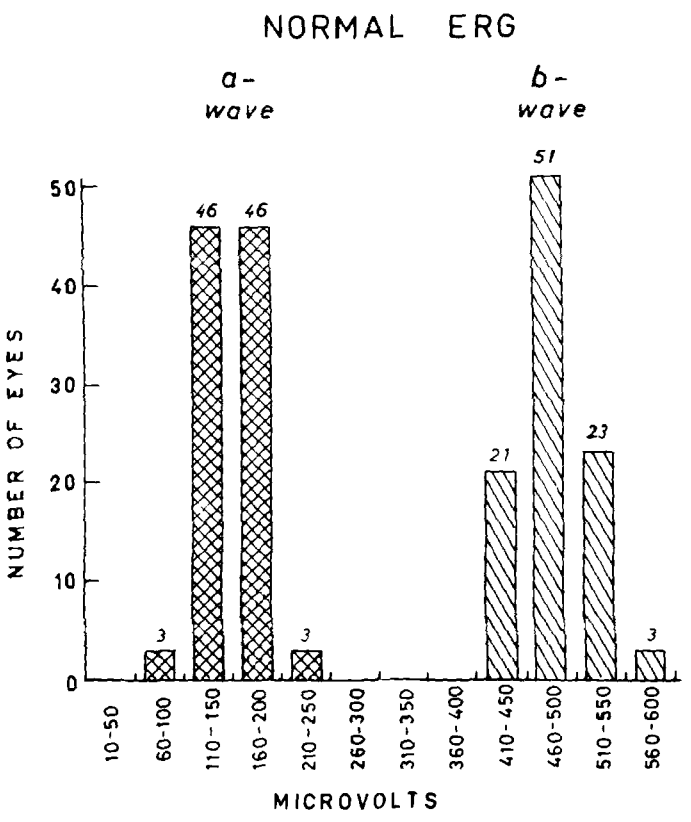

Fig. 1 Histogram of the distribution of the a- and b-wave amplitudes in 98 eyes of 54 normal subjects.

In the scatter diagram (Fig. 4), the values of the a-wave were plotted against those of the b-wave. The scattered points from the values of the ERGs with subnormal b-waves (open circles) and of the ERGs both of normal persons (open triangles) and of pathological cases whose one eye showed an ERG within the normal range (dotted triangles) show positive correlation between the a- and b-values about a line with a slope approximately 0.3. The values of subjects with enhanced b-waves do not fit about this line but tend to fall below it, because most of these subjects have a-wave values in the normal range with a few, however, having the highest values (compare Fig. 3, right). The values of right and left eyes for each subject are connected by a thin line. The most

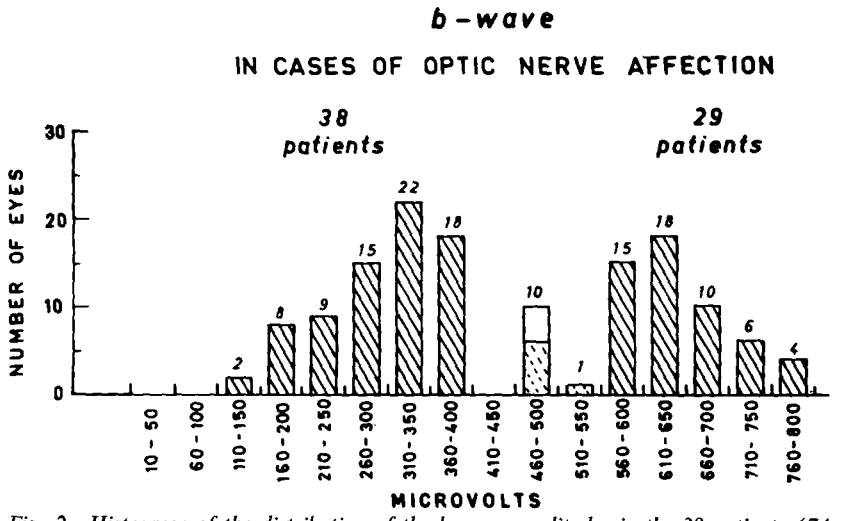

Fig. 2 Histogram of the distribution of the b-wave amplitudes in the 38 patients (74 eyes) displaying subnormal ERGs (between 110 μV and 400 μV), in the 29 patients (53 eyes) displaying enhanced ERGs (from 560 μV to 800 μV), and in the two patients with normal ERGs in both eyes (empty bars). The dotted bars in the center belong to seven patients with a normal ERG in one eye.

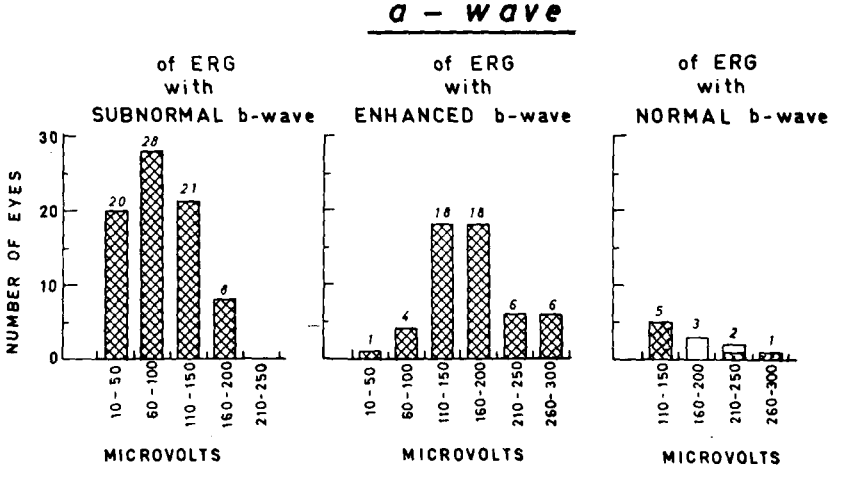

Fig. 3 Histogram of the distribution of the a-wave amplitudes in patients displaying subnormal b-waves (left) and enhanced b-waves (center). The a-waves of patients displaying normal b-waves (right) are divided into those with normal b-waves in both eyes (empty bars) and with normal b-waves in one eye (dotted bars).

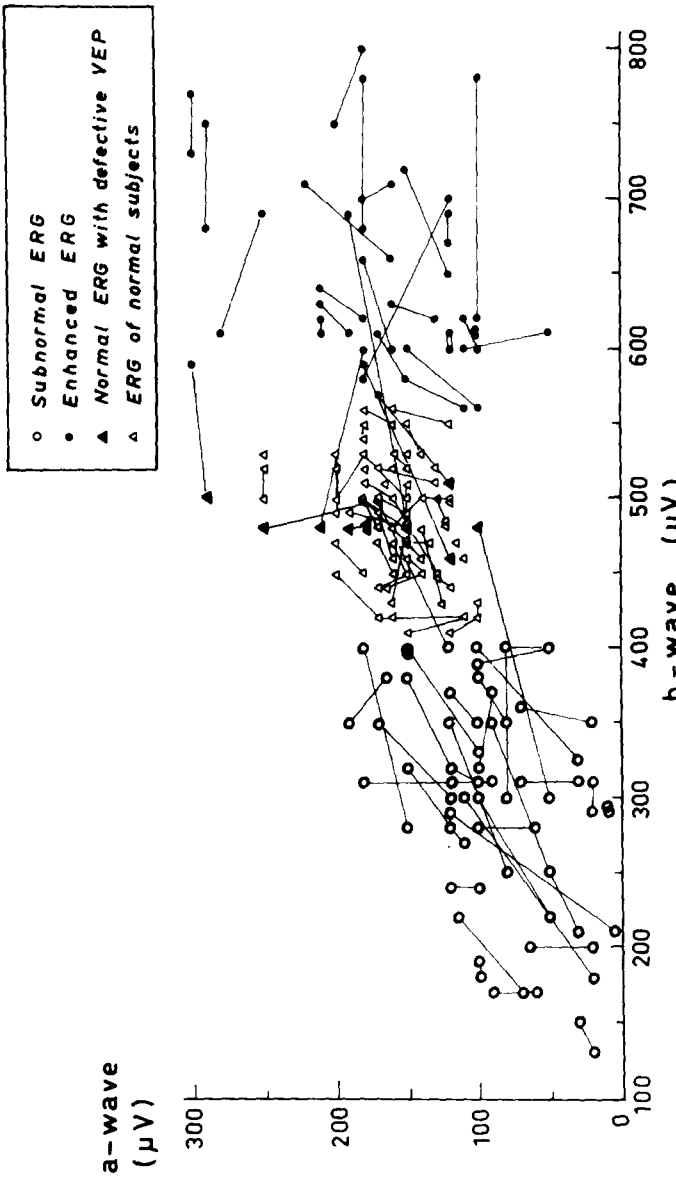

Fig. 4 Scatter diagram of the b-wave amplitudes against the a-wave amplitudes. Both eyes of each patient or subject are connected by thin lines. (See description in Text).

striking observation is the close correspondence in values for both eyes from normal subjects in contrast to those with subnormal or enhanced ERGs.

One fact should be emphasized regarding the ERG in normal persons. Under our testing conditions in which the stimulating light source was centered between the two eyes, the amplitudes of the b-wave were practically equal, or very similar, for the right and the left eyes. The greatest discrepancy obtained was 6% to 7%. This similarity was not always found with the a-wave. Here too, usually very small differences were found between the right and the left eyes, though there were discrepancies up to 27%. This occurred even in cases where the b-waves were almost equal. Slight differences in the angle of incidence of the stimulating light into the two eyes are probably responsible for these discrepancies, since the a-wave, which represents the late receptor potential (BROWN, 1968), is apparently more dependent on the incidence angle of the light than the b-wave, which is considered to be generated in the bipolar layer. In fact, this observation is made very often in our routine examinations unavoidably the patient frequently changes his head position slightly during the test.

Because of the fact that an enhancement of the b-wave of the ERG is still a matter of controversy (see Introduction), it was thought advisable to describe in greater detail eight of the typical cases, which demonstrate this enhancement.

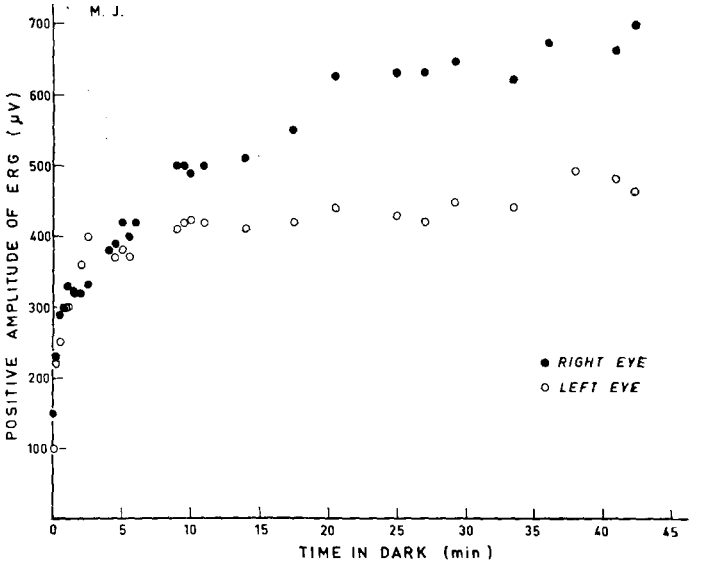

Fig. 5 The recovery of the b-wave of the ERG in the dark from a 5 minute light adaptation. The ERG of the blind right eye recovers to higher amplitudes than the ERG of the left eye. The recovery is practically equal for the first five minutes in the dark (patient 1).

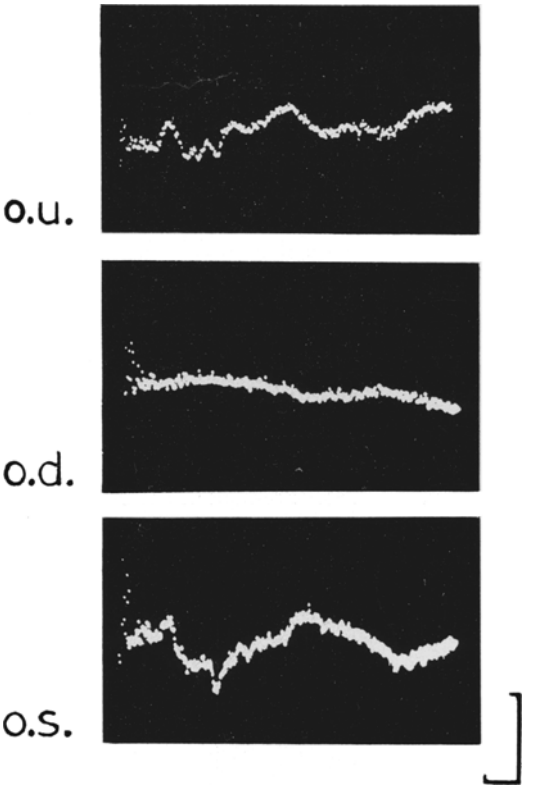

Fig. 6 The VEP of Patient 1 produced by binocular and the two monocular stimulations (average of 70 responses). The VEP to binocular stimulation (o.u.) is of normal shape but of low amplitude. It is very similar to the VEP elicited when the left eye alone (o.s.) was stimulated. When the blind right eye (o.d.) was stimulated the VEP was extinct. Calibrations: 10 μV, 20 msec.

CASE REPORTS

Patient 1 (M. J.): a 42-year-old man was unconscious for four days as a result of a blunt right head injury. When he regained consciousness, he was restless and confused for several weeks, and complained of loss of vision in the right eye. No fracture was found upon skull X-ray. On examination, the pupils of both eyes were of normal size and reacted normally to light. Visual acuity in the left eye was 6/9 and the visual field was normal. Both fundi were normal.

The ERG in the light and the ERG recovery during dark adaptation were measured two months after the accident while the patient was still in a confused state. The ERG in the light was normal. Its recovery during dark adaptation in the left eye was practically complete after about 40 minutes, reaching normal amplitudes. The responses of the right eye increased at about the same rate as those of the left eye for the first five to seven minutes in the dark. Thereafter the b-wave of the right ERG continued to grow during the following 35 minutes or so to considerably higher amplitudes than those attained by the left ERG (Fig. 5). The difference between the steady-state b-wave amplitudes, 690 μV in the right eye and 480 μV in the left eye, was far in excess of the usual variation between the eyes. The most striking finding was the VEP, which was normal after stimulation of the left eye and absent after stimulation of the right eye (Fig. 6). The former was practically equal to the VEP elicited by binocular stimulation.

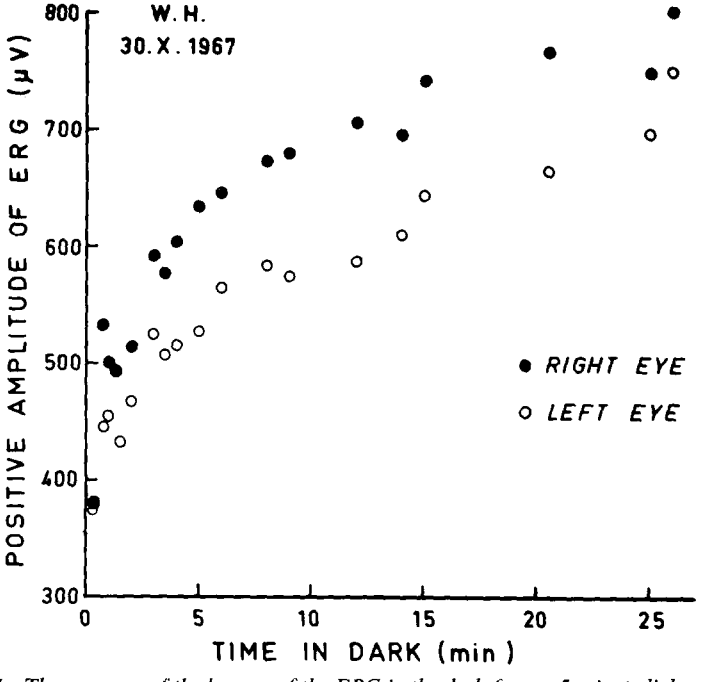

Fig. 7 The recovery of the b-wave of the ERG in the dark from a 5-minute light adaptation. The ERGs of both eyes are supernormal, that of the right eye to a greater extent. They do not seem to have attained their steady state in the dark after the 25 minutes examined (patient 2).

Six weeks after these examinations, primary optic nerve atrophy was found in the right eye.

Patient 2 (W. H.): a 34-year-old woman, who suffered from juvenile diabetes, complained of blurred vision in both eyes. Visual acuity was 6/9 in both eyes. Examination of the visual fields of both eyes revealed restrictions and an enlarged scotoma around the optic papillae. Fundoscopy showed secondary optic atrophy in the right eye. Slight pallor of the left optic disc could almost pass as normal. The neurological examination did not reveal any abnormality but right brachial angiography and pneumoencephalography demonstrated a space-occupying lesion in the depth of the right fronto-temporal lobe.

The ERGs of both eyes were normal in light adaptation. They recovered during dark adaptation to supernormal values. The recovery of the right ERG was extremely fast, and attained supernormal amplitudes already within the first five minutes. These responses were at each phase larger than those of the left eye, and reached after 25 minutes 800 μV as against 750μV in the left eye. The course of both recovery curves makes it very likely that the steady state was not yet achieved when the measurements were discontinued (Fig. 7). The VEP from stimulation of either eye was of long latency and small amplitude. The patient refused surgical treatment. After a month, secondary optic atrophy was also found in the left eye.

Patient 3 (S. S.): a 27-year-old woman came to the clinic complaining of blurred vision in her right eye. Three years ago, during her first pregnancy, she had almost completely lost vision in her left eye. On examination, complete primary optic atrophy was found in the left eye. A less advanced optic nerve atrophy showed in the right eye, where pallor was more pronounced in the temporal part of the optic papilla while the nasal part was still slightly rose-colored. Visual acuity in the right eye was 5/21 while in the left eye only light perception remained. The right visual field displayed a defect in the lower temporal quadrant. All neurological examinations were negative.

The electrophysiological examinations revealed normal ERGs in the light, and supernormal ERGs at the end of the recovery of more than 50 minutes (about 680μV in the right eye and 750 μV in the left eye) together with an extinct VEP following stimulation of the left eye. The VEP after stimulation of the right eye was extremely small (less than 1 μV).

During the subsequent days vision in the right eye rapidly deteriorated.

Angiography revealed a tumor in the region of the sella turcica. Surgery exhibited a tuberculum sellae meningioma which was removed.

At re-examination six weeks after surgery, the visual acuity of the right eye had improved to 5/12 and its visual field was almost complete. There was no change in the left eye.

The electrophysiological examination also showed a great improvement. The ERG in the light was normal in both eyes. However, the recovered ERG of the right eye was now around 400 μV, which is slightly below the lower limit of normalcy, and that of the left about 450 μV. An easily measurable VEP was elicited through stimulation of the right eye; its latency was normal and its amplitude was about 4 μV. No VEP could be produced through stimulation of the left eye.

Patient 4 (M. S.): the 32-year-old woman became blind in both eyes at the age of eight, a month after she suffered from a severe febrile illness. Nothing more is known of the case history. Fundoscopy revealed primary optic nerve atrophy

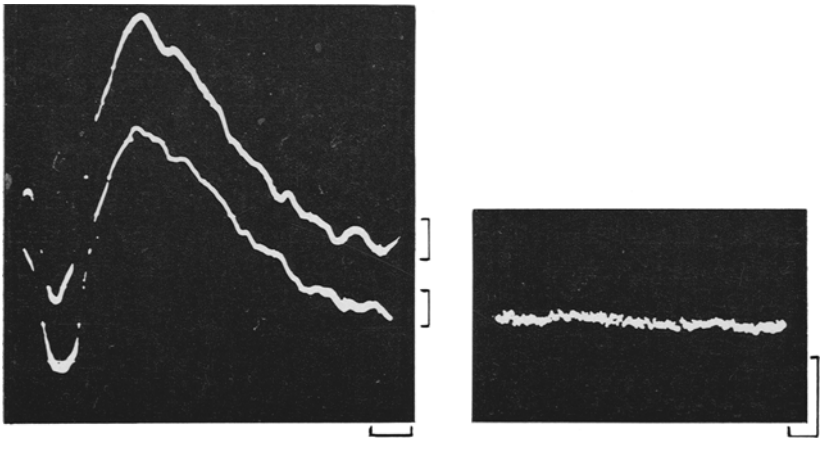

Fig. 8 Supernormal ERGs (left) from right eye (upper trace) and from left eye. Calibrations: 100 μV, 20 msec. The VEP (right) is extinct. Calibrations: 10 μV, 20 msec. (patient 4).

in both eyes which was assumed to be due to measles encephalitis or a similar disease (WALSH, 1957).

The amplitude of the ERGs grew quickly during dark adaptation in both eyes to supernormal values of 730 μV in the right eye and 770 μV in the left eye. The VEP after binocular stimulation was extinct (Fig. 8). The ERG in the light was normal.

Patient 5 (F. G.): eleven years before the present examination this woman (now 42-years old) suffered for several days from an episode of blindness in her left eye. Two years later, vision was lost permanently in that eye and a primary optic atrophy was found. According to the patient, six years later her right eye also became blind for a few weeks. Pneumoencephalography and cerebral angiography carried out then did not reveal any abnormality. Two years prior to the present examination she began to suffer from recurrent attacks of spastic paraparesis.

Ophthalmological examination of her present condition showed a primary optic atrophy in the left eye and a dilated pupil which still reacted to light. There was no abnormal finding in the fundus of the right eye, whose visual acuity was 5/5 and whose visual field was normal. Moreover, a spastic paraparesis affecting mainly the left leg, was found together with hyperactive tendon reflexes and Babinski's sign. The diagnosis of Multiple Sclerosis was made.

The ERG in the light was normal in both eyes. During dark adaptation the ERG of both eyes recovered in 26 minutes to supernormal amplitudes of around 610 μV. The VEP was normal when the right eye was stimulated and extinct on stimulation of the left eye.

Patient 6 (M. R.): this 35-year-old patient suffered at the age of 17 from blurred vision in both eyes. After cortisone treatment for three weeks, binocular vision returned to normal. Six years later, in 1954, she lost vision in both eyes a month after delivery of her first child. The condition improved after steroid treatment. At that time an exploratory craniotomy was performed (in France) because of bitemporal hemianopsia and bilateral optic atrophy, and a leptomeningitis hemorrhagica around the optic nerve was found. In 1957, four months after the delivery of her second child she lost vision again in both eyes for one month. In 1959 a transient right hemiplegia occurred which lasted one month. Two years later whe became quadriparetic for several weeks, and a spasticity of the left leg remained as a residual. In 1962 the right eye was found to be completely blind

while the left eye permitted only finger counting at 30 cm. There was also a spastic paraparesis with marked decrease in the deep sensations. In the following years the visual acuity of her left eye deteriorated further still, and in 1966 only low vision in the lower temporal quadrant of the visual field was left. This was lost in 1967 but returned after ACTH treatment. The diagnosis of Multiple Sclerosis was made.

The last examination carried out in 1967 revealed a bilateral optic atrophy. While the right eye was completely blind, she could still count fingers at 30 cm in the lower temporal quadrant of the left eye. The pupils were wide and not reacting to light. There was a convergent squint of the right eye. In addition, complete paralysis of the right sixth nerve was found as well as a marked spasticity in the left side of the body and hyperreflexia of all tendon reflexes with bilateral Babinski's sign. The abdominal reflexes were absent and all deep sensations were disturbed.

During dark adaptation the ERGs of both eyes attained supernormal amplitudes; they were of around 600μV in the left eye; those attained by the right eye were slightly smaller. The ERGs in the light were of normal amplitudes. The VEP was absent when the right eye was stimulated and very small on stimulation of the left eye.

Patient 7 (W. M.): when first examined in 1966, the patient was 28 years old. Until the age of 25 she was in good health. At that time she lost vision almost completely within three days in the right eye after suffering for a few days of a sore throat and right retrobulbar pain. Treatment with ACTH and steroid preparations was unsuccessful. Two years later, vision was lost also in the left eye under similar circumstances, and ACTH, steroids and retrobulbar injections of papaverine were of no help.

On examination in 1966, i.e. seven months after loss of vision in the left eye, both pupils were found widely dilated and unresponsive to light. While the left eye was amaurotic, there was still some light and movement perception in the right eye. Ophthalmoscopically, optic nerve atrophy was found in both eyes. Other physical and neurological examinations, such as the EEG, cerebral angiography and pneumoencephalography, were normal. Multiple Sclerosis was suspected at this time.

The ERG in the light was normal in both eyes. The ERG recovery was more extended during dark adaptation than normal. The immediate increase in amplitude after discontinuation of light adaptation was abnormally large. The

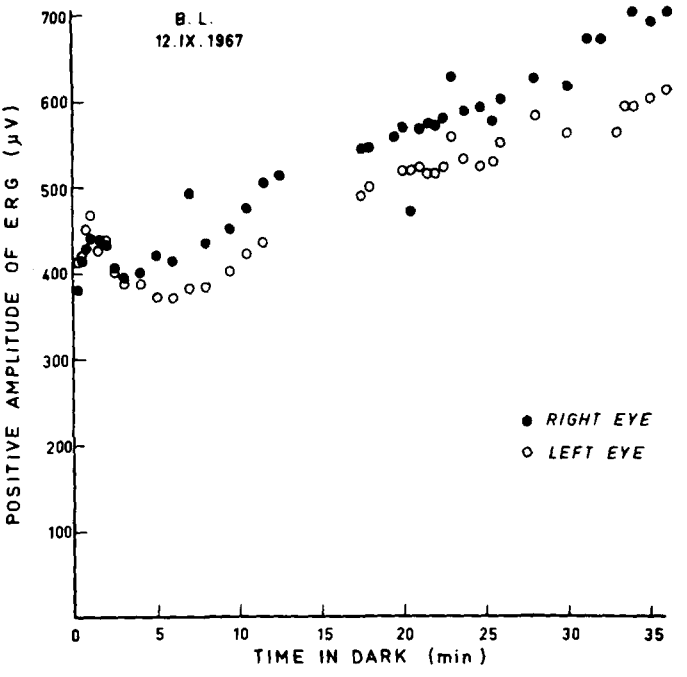
B. L.
12. IX. 1967
POSITIVE AMPLITUDE OF ERG (μV)
700
600
500
400
300
200
100
0
5
10
15
20
25
30
35
TIME IN DARK (min)
RIGHT EYE
LEFT EYE

Fig. 9a

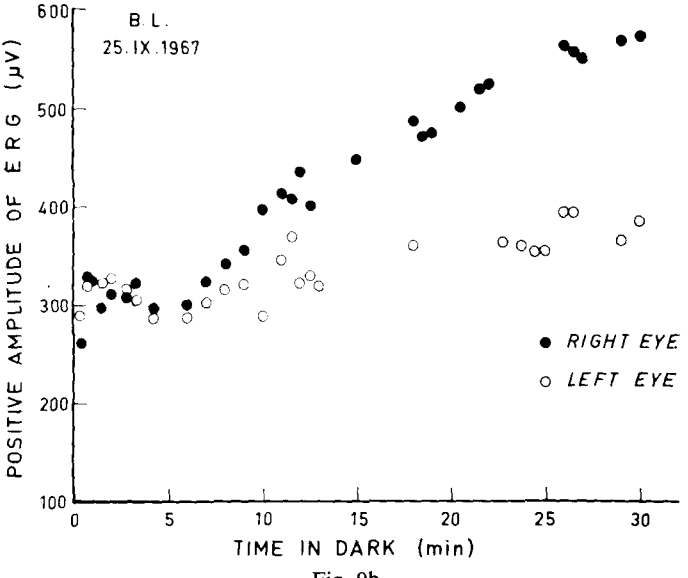
B. L.
25. IX. 1967
POSITIVE AMPLITUDE OF ERG (μV)
600
500
400
300
200
100
0
5
10
15
20
25
30
TIME IN DARK (min)
RIGHT EYE
LEFT EYE

Fig. 9b

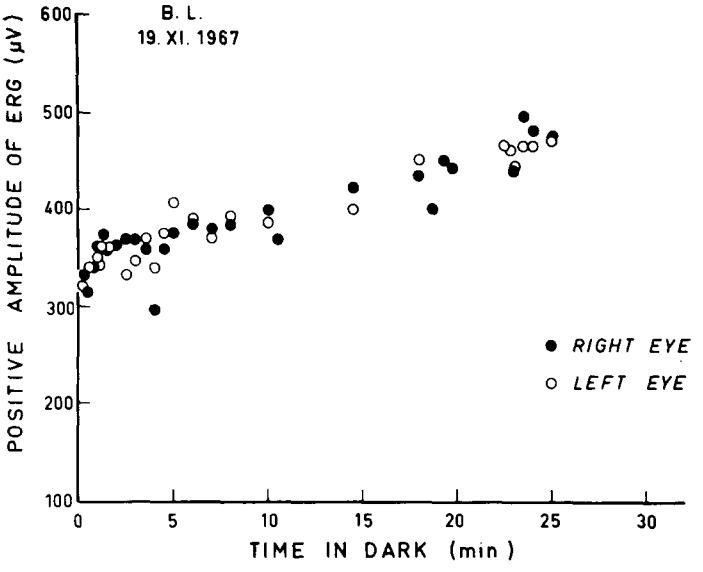

Fig. 9c

Fig. 9 The recovery of the b-wave of the ERG in the dark from a 5-minute light adaptation (patient 8).

(a) From recordings taken on the day the patient lost vision in her right eye for the first time. The ERGs from both eyes attain supernormal values. Steady state values are not yet reached within the 35 minutes tested.

(b) From recordings taken a few days later when vision returned to normal; while the ERG from the left eye is now subnormal, that of the right eye is still enhanced. The course of the recovery is about equal in both eyes for the first five to seven minutes in the dark.

(c) Control examination about two months later showing an identical but somewhat abnormal ERG recovery from both retinae. Although the steady state is not yet attained at the end of the test, it is unlikely that the values will ultimately surpass the normal range.

responses became supernormal in both eyes already within the first five minutes, and after 23 minutes the ERG of the right eye attained amplitudes of 660 μV and that of the left 710 μV. No VEP could be elicited by binocular stimulation. Moreover, the alpha rhythm could not be interrupted by light flashes. A transfrontal exploratory craniotomy performed a few days later displayed both optic nerves to be pale, thin and atrophic, but the chiasma appeared normal.

Three years later (at the age of 31), after having been operated for breast cancer, she began to suffer from intermittent pareses and paraesthesias in both

legs, and from urinary retention. The abdominal reflexes were reduced, the patellar and ankle reflexes were hyperactive and Babinski's sign could be bilaterally elicited. The paresis in her left leg was very marked. There was now no vision left in both eyes. No other cranial nerves were affected. The final diagnosis of Multiple Sclerosis was made.

Repeated ERG and VEP examinations showed the same results as those obtained three years ago.

Patient 8 (B. L.): the 26-year-old woman suffered during her first pregnancy from headache. At the sixth month diplopia occurred due to paresis of the right abducent nerve, which disappeared after two weeks. However, a few days later she suddenly lost vision in the right eye completely, while the visual acuity in the left eye was 5/5 and the visual field normal. After ACTH treatment vision gradually returned, and ten days later visual acuity was 5/5 in both eyes with normal visual fields.

Seven days after a normal delivery, vision failed again in the right eye, and there was also pain in the distribution of her right trigeminal nerve. In addition, palsy of the right abducent nerve reappeared. Prompt ACTH treatment was successful, and her complaints disappeared within two weeks. Repeated fundoscopies did not reveal any abnormal finding during these episodes of visual loss. The clinical diagnosis of Multiple Sclerosis was made.

During this period of time repeated electroretinographic examinations were carried out. The first test was performed when vision in her right eye was lost the first time. The course of recovery was about equal in both eyes during the first five minutes. Thereafter the response of the right eye became larger. During dark adaptation the ERG of both eyes was enhanced and achieved supernormal amplitudes within the 36 minutes examined, that of the right eye being larger than that of the left. However, both ERGs had not recovered completely within this period (Fig. 9a). A few days later, when vision in both eyes was normal again, the ERG recovery of the left eye was slightly subnormal but the responses of the right eye were still enhanced and did not reach the steady state within the 30 minutes examined. Again the recovery was about equal in both eyes for the first five minutes or so in the dark (Fig. 9b). About two months later the ERG recovery in both eyes was practically equal during the 25 minutes tested. The amplitudes attained were in the normal range although the recovery was slightly delayed and was not complete after 25 minutes (Fig. 9c). During all tests the ERGs were normal in the light.

The VEP displayed subnormal amplitudes and lengthened latency when each eye was stimulated separately, but increasingly so when the right eye alone was stimulated.

During the second period of amaurosis in her right eye a similar course of events could be traced electroretinographically.

Finally, one more patient who suffered from bilateral optic atrophy following encephalitis may be mentioned. An enhanced ERG recorded from both eyes turned to subnormal values for both the b- and the a-waves in the course of one year (case No. 3 in Table 1).

DISCUSSION

In all cases reported here the common denominator for the electrophysiological findings was an involvement of the optic nerve which necessarily includes the retinal ganglion cells. However, as mentioned already, the ganglion cells are thought not to contribute to the generation of the major components of the ERG (GRANIT & HELME, 1939) when the conventional recording methods are employed. But there is no evidence that the slow potentials, which in addition to the spike potentials are generated by the ganglion cells (ARDEN & BROWN, 1965; BROWN, 1968), do not contribute to the ERG. These potentials may be detected by more sensitive methods than the conventional ones.

Due to the controversy found in the literature regarding the enhancement of the b-wave, it was felt desirable to discuss in greater detail the various aspects of this phenomenon together with the subnormality of the ERG found in other cases of optic nerve atrophy.

The present findings seem to indicate that in certain conditions the contribution to, or the influence on, the ERG of the neurons more central than the first two retinal neurons can yet be detected by the use of conventional recording methods. As a consequence, a rivalry between the efferent influences and the visual adaptation in the retina, which increases in the dark, may be supposed to occur in the intact visual system. In order to demonstrate this, the recovery of the ERG during dark adaptation from a preliminary light adaptation occurring in the intact visual system must be compared with the recovery in a visual system defective at levels higher than the first two neurons. For this reason, the changes in the recovery of the positive wave of the ERG during the process of dark adaptation were mainly studied, although changes in the negative wave were also proved to be of importance.

The b-wave and its connection to visual adaptation

The gross ERG, the evoked response of the retina, represents the summation of the potentials generated in the cells of the first two neuronal layers of the retina (NOELL, 1953; BROWN, 1968), their interneural interaction (LIPETZ, 1961) and the summed activity of the retinal areas illuminated (BRINDLEY, 1956, 1957). Although the b-wave was mainly considered, its relationship to the negative a-wave, which is the late receptor potential and likely to be generated in the inner limbs of the receptor cells (BROWN & WATANABE, 1962a, 1962b), was studied in the pathological condition and compared with the normal case. The oscillatory potentials (AUERBACH, 1968) and the complex nature of the positive wave (AUERBACH, 1962, 1967) were not considered. The grouping of the pathological cases into subnormal and enhanced ERGs, using the overall amplitude of the b-wave as the criterion, was done for the following reasons.

The quantum absorption in the visual pigments initiates the visual events and is linked to the generation of the early receptor potential (BROWN & MURAKAMI, 1964a, 1964b), a component faster than the a-wave. However, it has been convincingly demonstrated that visual adaptation is not reflected by phenomena in the outer and inner limbs of the receptors (LIPETZ, 1961; RUSHTON, 1963; RUEHTON & WESTHEIMER, 1962). It was shown by the experiments of CRAIK & VERNON as early as 1941 and by JOHNSON & RIGGS (1951) that visual adaptation is a function of the retina, but it was RUSHTON (1960) who later suggested that there may be a 'pool of excitation' in the retina into which the receptors 'can pour their excitation'. This reasoning, among other experimental facts, points away from the early and late receptor potentials as reflecting visual adaptation. It points to elements in the inner nuclear layer as the site of visual adaptation, probably to the bipolar cells. Further evidence emphasizes this point such as DOWLING's (1963, 1967) recordings of the a- and b-waves as a function of log intensity, and the close relationship between the changes in the b-wave amplitude during dark adaptation and the psychophysically measured dark adaptation (KARPE & TANSLEY, 1948; AUERBACH & BURIAN, 1955; BEST & BOHNEN, 1956). The bipolar cells may generate the b-wave (NOELL, 1954; BROWN & WIESEL, 1961; BROWN, 1968) or participate in its generation. However, there is recent evidence from intracellular recordings in the retina of the mudpuppy which points rather to the Müller cells as the origin of the b-wave (MILLER & DOWLING, 1970). At the present stage of knowledge, we feel that it would be too early to try to apply and to include these important findings to the considerations on the human retinal mechanisms hypothesized in this paper.

Conditions displaying enhanced retinal responses

Enhanced ERGs concerning particularly the b-wave are found also in experimental and pathological conditions different from the one described here and not directly connected with the cerebral visual pathways (JACOBSON, 1961). Briefly mentioned are several of these conditions such as hyperventilation (ALPERN et al., 1955) and tobacco smoking (STRAUB & WINKELMANN, 1960). Enhanced ERGs likewise occur sometimes in vascular disturbances which also involve the a-wave. In the early stages of asphyxia and anemia the ERG is enhanced. This is probably due to increased excitability in single nerve fibers and synapses following hypoxia. It is found in cases of complete arterial (HENKES, 1954a) and venous occlusion (HENKES, 1953), where it may appear transiently, and more prolonged when the blood supply is only slightly impaired. This can be explained by a temporarily increased excitability of neural connections in hypoxia (HENKES, 1957). The same interpretation has been given with regard to arterial hypertension and arteriosclerosis (HENKES, 1954b, HENKES & VAN DER KAM, 1954), where enhanced ERGs are sometimes temporarily found. Similarly, an enhanced ERG appears transiently in siderosis, with locally raised excitability having been suggested as a cause (KARPE, 1957). Finally, there is an enhanced ERG in cases of hyperthyroidism, which significantly diminishes during antithyroid treatment (PEARLMAN & BURIAN, 1964), and for which no adequate explanation has been proposed. In none of these conditions is the optic nerve primarily involved.

The enhanced ERG occurring in a large percentage of optic nerve affections reported in this study is characteristically associated with a diminution or absence of the VEP, and is almost certainly not due to the same or analogous processes as in the cases discussed above.

Hypothetical mechanisms governing retinal function

(possible significance of efferent cerebral and retinal pathways)

The presence of centrifugal neural connections between the CNS and the retina, possibly involving the amacrine cells (RAMÓN Y CAJAL, 1892–3; POLYAK, 1957), has been histologically demonstrated in the pathological and in the intact human visual systems (WOLTER, 1965; WOLTER & KNOBLICH, 1965; HONRUBIA & ELLIOTT, 1968; SACKS & LINDENBERG, 1969) as well as in other animal species (RAMÓN Y CAJAL, 1892–3; HONRUBIA & ELLIOTT, 1968; VENTURA & GALLEGO,

1953; COWAN & POWELL, 1963). Neural fibers, probably extraretinal in origin, have been demonstrated in the retina of the chimpanzee by POLYAK (1957), who designated them as centrifugal fibers. Moreover, there is electrophysiological evidence for the existence of such efferent pathways in the retina of the cat (GRANIT, 1955) and of the rabbit (DODT, 1956). These findings may provide the basis for the interpretation of the pathologically enhanced retinal response in that a negative feedback system may be active in the control of the retinal response in the normal visual system, which rivals the increasing retinal sensitivity during dark adaptation.

This hypothesis implies that impulses travelling along efferent fibers inhibit the retinal activity which is reflected by the ERG. These impulses either may be due to spontaneous activity or may be elicited by the afferent sensory input. As a consequence, an inhibition should occur at a level where the efferent fibers synapse with the retinal cells such as the ganglion cells and possibly the amacrine cells. POLYAK's centrifugal bipolar cells, which he found in the primate retina, and which differ morphologically from the centrifugal bipolars, may be affected (POLYAK, 1957). They have been tentatively assigned by POLYAK (1957, p. 249) to be of inhibitory nature and to transmit 'influences from the ganglion cells, and possibly from the centripetal bipolars, back to the photoreceptors'. The likelihood of POLYAK's hypothesis seems to be backed by our findings of changes in the a-wave values in the subnormal ERGs as compared to the values in the normal ERG (see below).

The electron microscopic studies of BROOKE et al. (1965) on centrifugal fibers in the monkey's visual system following severance of the optic tract, revealed degenerated fibers in the optic nerve fiber layer, the ganglion cell layer, the inner plexiform layer down to the inner nuclear layer. Although there is not yet anatomical proof that these centrifugal fibers synapse with retinal nerve cells, the following speculations may explain at least part of our results.

Assuming that impulses along these centrifugal fibers activate the amacrine cells, the reciprocal synapses, which have been demonstrated in the primate retina (DOWLING & BOYCOTT, 1965) at the junctions of the amacrine and the bipolar cells, are possibly the site of the assumed negative feedback, that is, the site where these impulses exert their inhibitory influence. Although DOWLING, in contrast to others mentioned above, could not find evidence for the existence of centrifugal connections in the primate retina, some of the ideas discussed here are essentially based on his work (DOWLING, 1967), and they may explain the assumed modulation of bipolar activity induced by efferent impulses leading

to decreased bipolar sensitivity. They are also in keeping with PEDLER's comment to DOWLING and BOYCOTT's presentation (1965). Presynaptic interaction in the inner plexiform layer provided by the amacrine cells would then close the circle in that the efferent influence would spread to the bipolar-ganglion cell junction and change its sensitivity. However, there may be additional influences in that the tight junction which DOWLING and BOYCOTT found between bipolar processes and ganglion cell somata may cause backfiring into the bipolar cells. Also, there may be some significance in the observation that the bipolar terminals make not only axo-somatic contacts with ganglion cell somata but also axodendritic contacts with a possibly small number of ganglion cell dendrites.

Now, in the absence of the assumed modulation of retinal activity from efferent impulses or in their diminished activity, the postulated rivalry with the increasing retinal sensitivity in the dark would either stop, or the two rivalling processes would remain unimpeded (or only partially impeded), and the ERG would be enhanced.

The abolition of this negative feedback would explain the occurrence of an enhanced ERG, were there not an even greater number of cases of optic nerve atrophy in which the retinal response is reduced. So, without rejecting this interpretation, which at present seems merely a suggestive hypothesis with no direct evidence, we end up with grave doubts. These doubts, however, do not belittle the diagnostic value of this symptom, since, if an enhanced ERG in the absence of a VEP is found, it makes a diagnosis of optic nerve pathology very likely.

As an alternative hypothesis, mainly based on the interruption of afferent impulse propagation, a progressive degeneration of the centrifugal fibers may be assumed to involve the synaptic connections in the inner plexiform layer between bipolar, amacrine, and ganglion cell dendrites and axons (DOWLING, 1965). This would result in both pre- and postsynaptic effects by modulating or by making ineffective a negative feedback within the retina itself. The retinal response would then be enhanced as in the first patient presented above as long as the degeneration does not involve the bipolar cells. If the degeneration would progress beyond the amacrine and the ganglion cells, ultimately affecting the bipolar cells themselves, a reduced retinal response should result. This does not appear unlikely in view of the possible existence in man of the abovementioned intraretinal centrifugal fibers described by POLYAK (1957). With diminished function of the bipolar cells, a deteriorating effect would then spread to the

receptor cells. In fact, as seen in Fig. 3 (left), the distribution of the a-wave values has significantly shifted to smaller amplitudes as compared with the distribution of the values of the b-wave in the enhanced ERGs, which, in turn, are very similar to the normal values (compare Fig. 3, center, with the normal a-wave distribution in Fig. 1).

Finally, the two assumed neural mechanisms may act in unison, resulting in a double arrangement of negative feedback in the normal visual system. In the absence of the efferent input into the retina, a disinhibition may occur in the dyad synapse between bipolar, and amacrine and ganglion cell processes.

However, the measurements in patients 4, 5, 6 and 7 seem to negate the hypothesis that progressive degeneration of the centrifugal fibers may ultimately involve the bipolar cells and the receptors. The periods of time that these patients were afflicted with the disease were far too extended (24 years, 11, 18 and 6 years respectively) to permit the unequivocal assumption of a further intraretinal progress of the degeneration as a consequence. We did not find in these advanced cases a reduced retinal response or a tendency to become reduced. There is, however, the case mentioned at the end of the Case Reports where such a diminution of the enhanced ERG as a whole occurred. Although postsynaptic degeneration is only known to occur in the lateral geniculate body, this does not exclude the possibility of its occurrence in the retina. In the case of reduced ERGs in optic nerve affections, we are unable to find any mechanism other than an involvement of the bipolar cells, which would account for this finding.

Discussion of the clinical material presented

The optic nerve affection in the eight patients presented was due to different etiologies. In the first case, the monocular amaurosis together with an absent VEP as the result of a closed-head injury points to unilateral interruption of ascending impulse propagation in the optic nerve. The enhanced ERG strengthens the arguments discussed above in pointing to an involvement of the descending fibers. The occurrence of enhanced ERGs was reported in patients after surgical section of the optic nerve (SUZUKI, 1959; STRAUB & RANK, 1959; STRAUB, 1961; GILLS, 1966a). Moreover, several authors have provided histological evidence that such blunt head injuries may lead to complete severance of the optic nerve within an intact dural sheath (WALSH, 1966; LISCH, 1967; SCHNEIDER, 1968). We assume this to be the case here. It is emphasized that the marked enhancement of the ERG in the first patient was found before retro-

grade degeneration reached the optic papilla.

In the second patient the binocular ERG enhancement was found at a time when visual function was still quite good, i.e. when the optic nerves still transmitted to the brain, although there were already abnormal findings in the visual fields. However, the enhancement was demonstrable in the left ERG prior to clear-cut signs in the optic papilla.

The third patient suffered from a tumor which pressed on the optic chiasma. Because of the far more advanced effect on the left eye, it is apparent that the tumor did not exert pressure symmetrically on the optic connections. With the removal of the tumor, function began to return to the less severely affected fibers from the right eye. The begining of the restoration of function of the afferent fibers from the right eye can be seen both in the improvement of vision and the visual field, and in the VEP produced by stimulation of the right eye. The striking diminution of the ERG amplitude following the operation can be explained by renewed efficacy of efferent inhibitory fibers. However, the amplitude of the ERG also decreased in the practically blind left eye, despite the advanced optic nerve atrophy. Since no VEP could be elicited through the left eye, almost all of the afferent pathways must be non-conducting. Efferent fibers may have escaped damage, or the bipolars may have been involved by progressive degeneration.

The history of the four patients suffering from Multiple Sclerosis (Case Reports of patients 5 to 8) is of special interest. The results from patients 5, 6 and 7 are at variance with a recent study of this condition. GILLS (1966b) examined the retinal responses in 27 cases of advanced Multiple Sclerosis and found in the great majority a reduced ERG. He did not find an enhancement of the ERG in any of his cases*. These three cases included in this report are all at an advanced stage of the disease.

The eighth patient was examined during and after the first two attacks of Multiple Sclerosis with almost identical results. The enhanced ERG from the right eye at the beginning of each attack together with the loss of vision in her right eye is likely to be due to an area of demyelinization in the right optic nerve with an accompanying edema, an occurrence described in the literature (GRINKER & SAHS, 1966). The enhanced ERG in her left eye is unlikely to be due to a similar affection of the optic nerve since vision was normal and the visual field

* A survey of a much larger material on Multiple Sclerosis is in preparation.

complete. It points rather to the seat of the patch of demyelinization being close to the chiasma producing a spread of the edema to the left optic nerve sufficient to damage the centrifugal fibers descending here, but insufficient to block the impulse propagation of the afferent fibers. The fact that vision returned to normal in her right eye points to a recovery of the afferent fibers in the right optic nerve consequent to the receding edema assumed to be present. The fact that the ERG of the right eye remained enhanced for a certain period of time despite the return of normal vision may be explained by a missing inhibitory influence along the centrifugal fibers. It may be that these connections were more affected in this case by the pathological process than the centripetal connections. Interesting is the temporary subnormal ERG recorded in the left eye after vision returned to the other eye. The inhibitory influence may have been temporarily stronger than normal or the bipolar cells may have been temporarily involved. It should be stressed that this course of events is unlikely to be due to a chance finding since they repeated themselves twice.

Experimental studies on animals

Several animal studies have been carried out in which the optic nerve was experimentally severed. In the majority of these (JACOBSON & GESTRING, 1958a, 1958b; ABE, 1962; NAGAYA et al., 1962), an enhanced retinal response was obtained from the eye with the cut optic nerve as compared with that from the intact eye. The study of BRINDLEY & HAMASAKI (1962), however, differs sharply in that the authors were unable to observe any difference in the cat ERG amplitude before and after the severance of the optic connections. Similarly the unpublished observation of DUBIN, EASTER and DOWLING mentioned by DOWLING (1967) also differs. They found that adaptation, measured by the b-wave of the ERG, was normal in eyes with severed optic nerves and degenerated ganglion cells. DOWLING concluded that ganglion cells and centrifugal fibers are probably not involved in visual adaptation. Due to lack of detail, we cannot discuss this finding.

From our results the explanation of this discrepancy seems to be in the adaptive stage of the animal in which the recordings were performed. While JACOBSON & GESTRING (1958a, 1958b) observed both in cats and in monkeys an enhanced ERG after ten minutes of dark adaptation, BRINDLEY & HAMASAKI (1962) recorded at a nearly constant degree of light adaptation.

Our measurements in following the recovery of the retinal response were

carried out during dark adaptation, a procedure which we found to be of great advantage. In our cases of unilateral involvement of the optic nerve, the ERG recovery of the b-wave of both eyes was practically equal during at least the first five minutes in the dark. Thereafter, as can be seen in the recovery curves of Figs. 5 and 9b, the amplitude of the ERG from the eye with the affected optic nerve gradually increased to a larger extent than that from the other eye. This implies that the hypothetical inhibitory effect of the centrifugal fibers itself would become inhibited by the effect of light adaptation. Disinhibition in the form of a release from inhibition would then occur after the discontinuation of the light adaptation.

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