PHOTIC RESPONSES OF THE PRIMARY VISUAL PATHWAY IN CAT

EFFECTS OF ADAPTATION, AROUSAL, AND REPETITIVE STIMULATION UPON PHOTIC RESPONSES OF THE PRIMARY VISUAL PATHWAY IN THE CAT

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Roy Herbert Steinberg, M.D.

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To My Parents

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CHAPTER I

GENERAL INTRODUCTION

> ...We might come nearer to the neural mechanism of consciousness if we knew something about the neural mechanism of attention, and clearly one of the first points is to decide what happens in the brain when the attention is directed one way or another... (Adrian 1937)

A physiological distinction between the sensory transmission and integration of attended from non-attended stimuli is still awaited. We do not know "...what happens in the brain when the attention is directed one way or another..." In fact, neurophysiologists are still trying to establish the more basic distinction between sensory transmission and integration in wakefulness as opposed to sleep. The relevant physiological processes must first be identified at this level of analysis as it is clear that the delicate control operative in focusing the attention relies on the presence of a state of attentive wakefulness. Bremer (1936) and Rheinberger and Jasper (1937) defined a pattern of electrical activity associated with wakefulness and orientation (low voltage fast activity or arousal) in the initial

electroencephalographic recordings from the intact brain of experimental animals. Investigations in which the evoked response technique was first employed also distinguished differences in sensory function between wakefulness and sleep.[1] The present investigation was undertaken to further define characteristics of sensory transmission unique to the aroused state.

Variations in the state of arousal were studied in two ways: (1) Arousal was induced by high frequency electrical stimulation of the midbrain reticular formation in acute preparations; (2) natural fluctuations in the sleep-wakefulness cycle and arousal induced by non-painful sensory stimuli were studied in chronic freely-moving preparations.

Transmission in the primary pathway of the visual system was analyzed. Receptor stimulation (flash stimulation of the retina) of the unanesthetized preparation was chosen in preference to the use of electrical stimulation and anesthesia in order to approximate more closely the conditions of normal function. However, this created

1. Evoked potential, evoked response and population response are used synonymously throughout this work.

the necessity of dealing with the complexity inherent in the photic evoked response as recorded from visual cortex (Claes 1939; Marshall et al 1941). Further, response definition is obscured in unanesthetized preparations by the background surface activity of the electroencephalogram.[2] Recent work employing computer averaging techniques has demonstrated that a more reliable response to light can be recorded from the cerebral cortex in cat (Brazier 1957, 1958). Therefore, in the present investigation a computer technique was employed for response analysis.

In addition, analysis of the cortical response was also facilitated by monitoring its input from the optic radiation. Parallel recording at several levels of the primary visual pathway was also advisable in order to accurately localize the transmission sites effected by arousal. Responses were therefore simultaneously recorded from four different loci: visual cortex, optic radiation-lateral geniculate nucleus, optic tract, and cornea (electroretinogram).

2. As a result, in recent discussions of the evoked potential from the cerebral cortex (Bremer 1961; Granit 1962; Motokawa 1963) the potential elicited by light has been relatively neglected.

The use of repetitive flash stimulation was required by the average evoked response method, and repetition itself has been considered an important variable producing response changes related to attention (vide infra). Therefore, alterations related to repetition per se were also analyzed.

Early in this study a difficulty arose regarding the interpretation of certain response alterations. Optic tract responses, under conditions of strict stimulus control (vide infra), appeared to change in form during repetitive flash stimulation and occasionally the change seemed related to the onset of arousal. This problem was complicated further by the transmission of the changes to the lateral geniculate nucleus and occasionally to visual cortex. However, an analysis of this problem resulted in the description of optic tract response alterations (oscillations) which were not related to arousal but which were a function of repetition and finally of light adaptation. This analysis is presented in Chapter III. Chapter IV describes response changes at the lateral geniculate nucleus-optic radiation and visual cortex related to fluctuations in arousal level. Preceding these two data chapters is the complete

presentation of the methods employed (Chapter II). A summary of the experimental findings is presented in Chapter V.

CHAPTER II

METHODS

Experiments were of two types - acute and chronic. Methods for the acute series are presented first followed by a section outlining procedures unique to the chronic experiments. Certain procedural details omitted in METHODS will be found in the RESULTS sections.

I. ACUTE EXPERIMENTS

Acute experiments were performed on thirty-six cats weighing 2.0 - 3.5 kg. Surgical sleep was induced with intravenous thiopental (Pentothal, 12.5 mg/kg) and trachea, femoral vein, and femoral artery (systemic blood pressure was continuously monitored in six cats) were cannulated. During surgery additional doses of thiopental i.v. were administered when needed. After placement in the stereotaxic instrument (earbars lubricated with Xylocaine-jelly) the semilunar ganglion and surrounding rootlets of the trigeminal nerve were liberally infiltrated with Procaine injected into the area of the foramen rotundum bilaterally. All metal-to-skin pressure points and all wound margins were also infiltrated.

The nictitating membranes were bilaterally resected and the cortex partially exposed by craniotomy and removal of dura. The exposed cortex was protected with a 1-2 mm layer of an innocuous oil-jelly mixture (one-half part petroleum jelly and one-half part paraffin oil). With this procedure the cortical temperature remained at 1°C below rectal temperature while the latter was maintained at 36-38°C with an automatic heating pad (Krnjević and Mitchell 1961). At the completion of surgery the animal was paralysed with intravenous gallamine triethiodide (Flaxedil) and thereafter artificially respirated. Recording began 2-3 hours after the last dose of thiopental.

Stimulation

All experiments were performed in a soundproofed room from which stray light was also excluded. The pupils were dilated with an ophthalmic solution of hyoscine hydrobromide (1 or 2%, 1-2 drops) and the cornea protected with opaque plastic contact occluders.

Photic stimulation. At the beginning of this study it was observed that mydriasis induced by parasympathetic block was never complete. The wide opening of the mydriatic

pupil (9-11 mm) invariably dilated an additional 1-4 mm with stimulation of the midbrain reticular formation (RF stim.).[1] Therefore additional precautions were taken to secure complete control of the relation between pupil size and photic stimulus: (1) In the first eight experiments the eye was illuminated by a tiny lamp (Pinlite) placed in direct apposition to the cornea on the inner surface of an opaque contact-occluder (vide infra). (2) Use of an artificial pupil (23 cats), i.e. a 1-4 mm circular opening in the center of an opaque plastic contact-occluder placed on the cornea. A collimated beam of light (vide infra) of 1-4 mm diameter was then passed through the artificial pupil. (3) In five experiments the superior cervical ganglion was excised on one side at the beginning of the experiment (4 cats) or twenty-four hours earlier (1 cat). The atropinized pupil of these sympathectomized preparations never dilated further to brain stem stimulation and the 1-10 mm diameter light beam was now passed directly through the natural pupil. This technique was completely effective as demonstrated in Figures 26 and 31, an

1. Sympathetic excitation must always enlarge the para-sympathectomized pupil when the preparation is otherwise intact. This was first described for the atropinized pupil by Claude Bernard (1858). A complete discussion and full bibliography of this phenomenon is given in Loewenfeld (1958).

experiment in which the pupil was photographed as a control before, during, and after RF stim. Here an infrared light source illuminated the preparation and single frames were taken at 1/sec. using infrared sensitive film (Nikon F camera with a 250 exposure motor drive).

Blue-white flashes of 10 microsecond duration and at repetition rates of 1/10 sec. to 5/sec. were obtained from a Grass PS-1 photic stimulator. A long-duration flash, employed in on-off testing, was formed from a 350 msec. train of 10 microsec. flashes at a repetition rate of 100/sec. (train duration was gated by a Bird 70-92B stimulator). The xenon lamp (PST - 2) was contained in a special housing and lens system which provided a point source and collimated beam of 1-15 mm diameter. The source was placed 30 centimeters from the eye and the image focused on the corneal surface. Intensity of flash at the cornea could not be accurately measured, however, peak intensity was about 750,000 c.p.. Intensity was diminished by the reduction steps available from the stimulator (50%, 25%, 12%, 6%) and with Wratten neutral density filters covering a five log unit range. Stimulus reliability was usually monitored by deflecting part of the beam onto a photodiode (RCA 20-3-5-2.0). However,

in several experiments the flash monitor of the PS-1 stimulator was employed.

A 100 watt lamp, thirty centimeters from the eye, was the source of background light for adaptation.

Reticular formation stimulation. Electrodes were placed in the midbrain reticular formation (left), contralateral to the side of lateral geniculate nucleus-optic radiation recording (LGN - OR), at Horsley-Clarke coordinates F 1-3, L3, H 2.5. The position of the electrodes was adjusted for the location producing activation at minimal stimulus parameters. Steel bipolar electrodes of the type used for depth recording (vide infra) with tip separations of 0.5 - 1.0 mm in the vertical plane and 0 - 2.0 mm in the horizontal plane were used. Square-wave pulses at 150/sec., 0.1 - 3.0 msec., 1V - 10V, were obtained from a Grass S4 stimulator.

Recording

The electroretinogram (ERG) was recorded by a platinum disc electrode (1 mm diameter) placed directly on the corneal surface.

Potentials from the visual cortex (VC) were recorded with 0.2 - 0.3 mm silver ball electrodes. For depth

recording, bipolar Formvar-coated steel wires, 0.25 mm sharpened to a tip diameter of 50 micra with 0.5 mm tip exposure and vertical tip separation of 0.5 - 1.0 mm, were employed. All responses were usually recorded monopolarly, referred to large silver plate electrodes (1 cm diameter) attached to each temporalis muscle.

The optic tract (OT) at the optic chiasm (OC) was located by placing the electrode at Horsley-Clarke coordinates F 13, H -5.5, L 1.5 (atlases of Jasper and Ajmone Marsan 1954, and Snider and Niemer 1961) and adjusting the position for the production of an optimal, i.e., minimal stimulus parameters of 0.1 msec., 0.5V, homolateral cortical evoked response (Chang 1952). Additional adjustment for the flash-evoked response was rarely needed. Stimulation of the optic tract was then used for locating the border between LGN and OR (Method presented in Chapter IV).

Spike potentials from optic tract axons were recorded with tungsten microelectrodes (Hubel 1957) of 1-20 megaohm resistance and 1-2 micron tip diameter. The electrode was placed in the optic tract by direct insertion through the intact cortical surface and underlying brain tissue. Special procedures for reducing

"pulsations" were not needed, however, in one experiment the cortical surface was sealed with agar. Unit discharges were amplified with a Bak-type unity gain cathode follower (Bak 1958).

In all experiments population and unit responses were displayed on a cathode-ray oscilloscope (Tektronix 551) with the preamplifiers (Tektronix 122) set for a frequency response of .2 - 1 kc (population response) and 80 c - 10 kc (unit response). Electrocorticogram and other continuous measures, such as systemic blood pressure and cortical temperature, were recorded on an Offner Type T electroencephalograph.

The data from each experiment was stored on seven channel magnetic tape (Ampex, Series FR-100A). Responses were also photographed either during the experiment or from the taped record. Average evoked potentials were estimated with the Computer of Average Transients (Mnemotron Corp.). Computed data will be referred to as <u>averages</u>, although the CAT only performs a summation process. The CAT was also used to compute post-stimulus histograms, interval histograms, and rate of the unit discharges. Either a Sanborn Twin Viso Recorder or an Esterline Angus S601S Speed Servo Chart Recorder plotted the computer output on paper.

Histology

At the end of each experiment a direct current (150 microamperes for 10 sec.) was passed across the paired tips of the depth electrodes. The animal was killed by an overdose of thiopental i.v. and the brain perfused through the carotid arteries with normal saline followed by a ferrocyanide-formalin-alcohol mixture (Jasper and Ajmone Marsan 1954). After fixation in formalin, serial paraffin sections (20 micra) were made through electrode tracts and stained alternately for cells by Nissl and for myelinated fibers by Weil techniques. Electrode tips were located by the Prussian blue reaction.

II. CHRONIC EXPERIMENTS

Seven cats were studied; three neuraxially intact and four with surgical section of the optic chiasm and corpus callosum (Myers 1955; Magni et al 1960). The latter group is included as the animals did not differ from the normal cat regarding the observations of this study.

12-18 ball-type extradural electrodes (Formvar-coated stainless steel wire, tip diameter 0.2 - 0.3 mm) were implanted in each animal and attached to Winchester

subminiature connectors. Bipolar separations of 2-3 mm were employed as well as a modified bipolar arrangement wherein the active electrode was referred to a placement vertically oriented in the overlying bone at a horizontal separation of 1 mm. In every case, references for monopolar recordings were also available from frontal sinus and lambdoidal ridge. The placements on visual cortex (at Horsley-Clarke coordinates Fr 0 to -6, L 2 to 3) were verified at autopsy and were within or upon the lateral border of area striata as defined by Otsuka and Hassler (1962).

Photic stimulation was provided separately for each eye by the contact-occluder method (Mishkin et al 1959; Evarts 1960). Contact occluders which conformed to the shape of the corneal surface and scleral rim were formed of opaque black vinyl plastic 1/32" thick. A small tungsten filament light source (Pinlite, type 30-30, Kay Electric, Pine Brook, N.J.) was imbedded in the center of the inner concave surface. This tiny incandescent lamp (0.1" in length and 0.03" in diameter) was driven by a circuit which provided a bias of 0.5 - 1.0 V and thereby reduced latency of incandescence (Doty 1958). The bias produced a slight pinpoint of

orange light. When a rectangular pulse of 0.5 V, 10 msec., was applied, peak intensity was reached in 6 msec., maintained for 5 msec., and full nigrescence reached in an additional 10 msec. At these parameters, representing the maximal intensity used, a peak of only 40 millilamberts (mL) was attained at the corneal surface. This was estimated by directly apposing a small photodiode (vide supra) to the inner surface of the occluder. Current across the filament was monitored during the experiment.

Each cat was studied during a period of 4-8 months after a period of accommodation of 7-14 days. All experiments were performed with the animal placed in a soundproofed room with oneway observation window. An ophthalmic solution of hyoscine hydrobromide (1 or 2%, 1-2 drops) was instilled in each eye 2-3h before the placement of the contact occluders (the pupillary reflex to light was tested at the beginning and conclusion of each experiment). The contact occluders were then placed in apposition to the corneal surface of each eye (nictitating membranes had been resected).

Amplitudes for all identifiable components of the computed responses were measured peak to peak and where

possible, baseline to peak. Latencies were calculated from the onset of current to the lamp to the peak of the measured deflection. The latency from the initial change in baseline was calculated, when possible, for the initial deflection.

CHAPTER III

OSCILLATORY ACTIVITY AND LIGHT ADAPTATION IN THE OPTIC TRACT

> The optic nerve is unlike any other nerve in that the receptor elements in the retina are not in immediate connection with the fibers of the nerve but are linked to them through a chain of neurons and synapses. (Adrian and Matthews 1928)

I. INTRODUCTION

In the first report of successful optic nerve recordings rhythmic activity was described (in eel, Adrian and Matthews 1928). These oscillations began a few seconds after the onset of illumination and when fully developed had a frequency of 15/sec. (max. - 25/sec.). A few minutes later the frequency fell to 5-6/sec. These investigators recognized the similarity of this phenomenon to that described by Fröhlich in 1914 for the cephalopod eye. Here, oscillations were at a frequency of 20-90/sec. and were maintained for as long as six minutes after the <u>off</u> of the light, the frequency then dropping to 20-40/sec. Oscillatory potentials at a frequency of 100-150/sec. were recorded from the optic nerve of cat by Granit (1933).

Following this initial report they have been mentioned by several investigators (Bartley and Bishop 1942; Noell 1953), but the first systematic investigation was reported by Doty and Kimura in 1963. They confirmed the finding of high frequency oscillations recorded in the population response from the optic nerve of cat. Stimulus artifacts and injury discharges were excluded as the source of this remarkably regular phenomenon. The frequency was 50-160/sec., with the higher frequencies occurring in the less narcotized (pentobarbital) preparations. Strychnine eliminated all rhythmic activity (0.3 mg/kg i.v. or 0.01% - sprayed on the exposed retina). Frequency was independent of flash intensity but the oscillations were more prominent when strong flashes of light were used. In addition, they suggested a relation to repetitive stimulation. "Under all conditions there is a distinct tendency for the amplitude and regularity of even the first few flashes to be augmented by repeated flashing (0.3/sec.), so that the responses to the first 1-3 flashes are often different from subsequent ones." Recently, Yokoyama et al (1964) described 100/sec. oscillations from the optic nerve of the albino rabbit. The relation to repetitive stimulation was not as clear. The response

varied at different stimulus frequencies with optimal development at 1/3 - 1/sec. but with a reduction of the clarity of the response at frequencies above 2/sec. They considered adaptation as one factor of importance in this variability but also reported the presence of oscillations during both light and dark adaptation.

The enhancement of the oscillatory response at high stimulus intensities and the relation to repetitive stimulation suggests a dependency on photopic mechanisms. Although a scarcity of evidence exists, some additional support for this contention can be found in the literature.

Oscillatory potentials have been identified in the electroretinograms of a large number of species, both invertebrate and vertebrate.[1] Yonemura et al (1963)

1. In many species where optic nerve recordings to photic stimuli have not been obtained, retinograms have been recorded. Rhythmic waves recorded in the ERG and optic nerve may or may not be the same phenomenon, e.g., due either to electrical "pickup" or to a common physiological generator. In intra-retinal microelectrode recordings both Tomita and Funaishi (1952) and Brindley (1956) identified oscillations located between the receptor and ganglion cell layers, suggesting a generator in this anatomical area. In rabbit, oscillations were recorded simultaneously in ON and ERG by Yokoyama et al (1964). The behavior of these two rhythmic records showed a clear correlation under varying stimulus conditions. Therefore, oscillations recorded in the ERG are apparently related to the ON phenomena. Regardless of the validity of this identity both records certainly reflect significant retinal events.

identified them in cat, rabbit, guinea pig, pigeon, chicken, tortoise, and bullfrog at periods of 4.5, 4.5, 10, 8, 10, 20, and 45 milliseconds respectively. They were described in man by Cobb and Morton (1953) at a frequency of 100-150/sec. Armington (1954) recorded the ERG of the turtle (pseudemys) whose retina is cone-dominant. Oscillations were present in the record and were selectively enhanced by chromatic stimuli of long wavelengths. This sensitivity at the red end of the spectrum suggested the involvement of a photopic process to the author. However, multiple peaks in the electro-retinogram are also present in guinea pig (Yonemura et al 1963) and rat (Cone 1964), both of whom have rod-dominant retinae. In man, on the other hand, photopic ERG components have been described by Rendahl (1958). These components are, in fact, the oscillatory potentials noted earlier by Cobb and Morton (1953). In cases of achromatopsia where there is rod monochromatism the oscillatory potentials are missing or substantially diminished (Rendahl 1964; Nagata 1964; Jacobson et al 1963).

The oscillations of the optic tract (or optic nerve) population response result from the synchronous discharge of many different fibers (Adrian and Matthews 1928).

Grüsser and Rabelo (1958) described grouping of the discharge of single ganglion cells in the retina of the unanesthetized cat but did not relate them to the population response oscillations. Grouped unit discharges at the peaks of oscillatory waves, separated by discharge-free intervals were reported by Doty and Kimura (1963) and Yokoyama et al (1964). Crapper and Noell (1963) showed very clear recordings of single units firing in repetitive bursts, in-phase with oscillatory activity.

Further investigation of the behavior and origin of these oscillations was indicated, for as a patterning of the ganglion cell discharge, they provide information about properties of transmission between receptor and ganglion cell and are a distinct component of information flow from ganglion cell to higher centers. Intensive analysis of the functional properties of these centers demands a thorough identification of the characteristics of their input. In addition, when repetitive stimulation is employed in studies concerned with integrative functions such as habituation and learning, characteristics of the input to the higher centers must be accurately known, e.g., variability of cortical evoked responses may result from variability already present in the optic radiations, etc..

In this section a detailed analysis of the oscillations with respect to repetitive stimulation and light adaptation was undertaken. Population responses were supplemented by recordings from individual optic tract fibers in order to investigate ganglion cell behavior.

II. RESULTS

Repetitive Stimulation

The responses recorded in the optic tract to a 10 microsecond flash were of two principle forms - simple or non-oscillatory and complex or oscillatory.[2] Transitions between these polar types were seen. Evolution from the non-oscillatory to the oscillatory response was observed during periods of repetitive stimulation of the dark adapted preparation. The appearance of oscillations occurred more rapidly at higher frequencies of stimulation. Figure 1 illustrates the response at increasing flash frequencies. Computer summation of the initial twenty-five responses in each series demonstrated more prominent and shorter latency oscillations at the higher frequencies

2. The oscillatory form will be referred to as the oscillatory response (Osc-R).

(2/sec., 5/sec.). At these frequencies (flash intervals of 500 msec. and 200 msec. respectively) oscillations appeared in the second or third response (Figure 1, center). This was particularly striking at 5/sec. where a fully developed Osc-R seemed to arise de novo in the third or fourth response. With further stimulation response stabilization occurred. The degree of oscillation was always a function of stimulus frequency. At lower frequencies (1/5 sec., 1/10 sec.) there was often no evolution to the Osc-R. However, intensity played an important role for at higher intensities oscillations would eventually appear after several hundred flashes were administered.

The oscillatory frequency was highly consistent between preparations. In ten animals at a flash frequency of 2/sec. the range was 80-110/sec. and the median 100/sec. Oscillatory frequency did not alter with intensity over a range of five log units above b wave (the prominent corneal positive component of the ERG) threshold. However, at any one intensity level the degree of oscillation was a function of the number of flashes previously administered. In addition, frequency of oscillation did not vary with flash rate.

Alterations in the form of the b wave were also observed during repetitive stimulation. A notching of the initial ascending limb or peak sometimes appeared during a repetitive series, however, this phenomenon was inconsistent among the preparations. At high stimulus frequencies (2/sec. and 5/sec.) there was a decrease in b wave amplitude of the averaged ERG. Examination of the individual responses demonstrated that at 5/sec. a sharp decrease in b wave amplitude occurred in the second response with gradual amplitude stabilization in responses five to ten (Figures 1 and 3). This has been called b wave suppression (Arden et al 1958). The rapid "growing in" of oscillations at 5/sec. paralleled the stabilization of the b wave. However, additional increases in amplitude of the oscillations sometimes occurred without any further change in b wave amplitude.

Adaptation level

Between repetitive trials (animal placed in the dark) return to the non-oscillatory form was noted. The return was more complete at long intertrial intervals when re-stimulation again produced evolution to the oscillatory form (Figure 2, B). If continuous light

replaced darkness between repetitive trials, the response behaved differently. Following removal of the adapting light, repetitive flashes immediately produced the Osc-R (Figure 2, A). During the series, this initially well developed response did not further improve.

It was soon apparent that light adaptation strongly enhanced the development of oscillatory activity. This was clearly evident when sustained light was substituted for darkness between trials. The evolution within repetitive trials could also be explained on this basis, i.e., light adaptation occurring more rapidly at higher stimulus frequencies where a larger number of flashes were presented per unit time. The rapid development of the oscillations at 2/sec. and 5/sec. was associated with b wave suppression and the latter has itself been related to light adaptation (vide infra). However, a facilitatory effect on the basis of repetitive stimulation qua repetitive stimulation, i.e., augmentation, could also play a role.

A more thorough analysis of this hypothesis was undertaken by sampling at fixed intervals while the retina was dark adapting following a period in the light. Samples consisted of short duration bursts of repetitive flashes. The duration of the sample and the intersample intervals

were set at levels which would least interfere with the on-going process of dark adaptation. A representative example from this analysis is presented in Figures 4 and 5. In Figure 4 the computer average of each test sample (25 responses at 2/sec.) is illustrated. The first sample to follow light adaptation (2') and, indeed, the first response of this sample (Figure 5, 2', #1) was oscillatory. However, during the first 6' - 8' in the dark the prominence of the Osc-R increased while during the next 34' (8' - 42') a progressive decrease occurred. The response was minimal in the 42' and 50' samples. In the samples following (58' - 82'), oscillations appeared at a long latency, and the response stabilized for there was now little variation between samples.

The individual responses within each sample were also examined (Figure 5). The progression noted in the averaged response was also noted for the individual response (#'s 1, 2, and 25 of each sample are illustrated). In addition, within each sample (#1 to #25) progression to a more developed oscillatory response occurred. This, within sample progression, was at a minimum in the initial samples following light adaptation (2' - 8').

Plotting peak b wave amplitude against time (Figure 6, top) related b wave recovery to the stages of oscillatory response change. The initial enhancement of the Osc-R was associated with an early, rapid phase of b wave recovery. Similarly the period of Osc-R decrease was associated with a second, slower phase of b wave recovery which followed a kink in the curve (6' - 10').[3] The long-latency oscillations developed and the optic tract response stabilized at the end of this second phase - the point of b wave amplitude stabilization. Comparison of the 8' averaged optic tract response with the 82' response revealed that latency of the initial positive peak and of oscillatory potentials was shorter at 8' (Figure 6, bottom).

Summary. The Osc-R was present immediately after light adaptation but further enhancement occurred during the first minutes in the dark. At this phase of maximal development (8') the response had an earlier latency than the later, dark adapted response (82'). In addition the

3. If after exposure to a bright light the retina is allowed to dark adapt, recovery of sensitivity can be plotted against time in the dark (log threshold measurement). It was first shown by Kohlraush (1922) that the recovery curve has a kink, the first part attributed to cone recovery and the second to rod recovery (Hecht 1937).

Osc-R was associated with the early phase of b wave recovery and is evidence for a relation of the Osc-R to the recovery of cone-system sensitivity. The second and slower phase of b wave recovery was temporally related to the progressive decrease of the Osc-R. The progressive decrease of the Osc-R with time, despite sampling with repetitive flashes, provided evidence that response enhancement during a repetitive series was not a function of repetition per se.

Recording in the albino rat

The rat retina contains approximately one cone receptor for each 100-400 rods (Walls 1934) in comparison to a cone-rod ratio of one to three in cat (Granit 1943). In order to explore the relationship between cone-system function and the Osc-R, recordings were obtained from this rod-dominant retina.

The method was unchanged for these experiments except that anesthesia was with intraperitoneal pentobarbital (Nembutal). Recordings were obtained three hours after the final dose when the animal was but lightly anesthetized. Successful recordings are reported for only one preparation. In this experiment although the response consisted of more

than one wave (Figure 7) no rapid oscillations were seen. The response at 1/5 sec. was almost identical to the response at 5/sec. In addition, there was no observed correlation between light adaptation and oscillatory components. However, there was an increase in amplitude of the initial positive deflection at 5/sec., #26-50. The response after 45 min. dark adaptation was not strikingly different from the response following 1 min. of light adaptation.

Unit responses from optic tract

A number of questions now arose regarding the origin of the Osc-R which could most adequately be studied by recording the activity of single ganglion cells: (1) Do the oscillations result from groups of different ganglion cells discharging at variable latencies from the stimulus or are individual ganglion cells firing repetitively? (2) Do the same ganglion cells discharge under scotopic and photopic conditions?

Successful microelectrode recordings from single optic tract axons were obtained in six preparations. The discharge patterns of twenty units were analysed. In all of these units regular grouping of discharges

was observed (Figure 8). The intergroup period was 10 msec. (range - 8 msec. - 20 msec., N - 20), corresponding to a frequency of 100/sec. The dominant response pattern to a single 10 microsecond flash began at a relatively short latency (Figure 8). Three to six bursts or groups were followed by a long-duration inhibitory period. The first burst had a latency of 13-40 msec. (mean - 16 msec., N - 14). It was of long duration and unit discharge was always at a high rate (rates as high as 900/sec. were seen). Three to five additional bursts followed containing fewer discharges at a slower rate and succeeded by an inhibitory period of 50-150 msec. (N - 14). A secondary period of excitation followed the inhibition and secondary inhibition followed by tertiary excitation was occasionally seen.

When the population response was recorded simultaneously with the unit discharge, a close relation between the two was observed (Figure 8, B and C). The period of oscillation and the intergroup period were identical in any one preparation. Notice in Figure 8, C that single discharges correspond to the low amplitude oscillations which occur immediately before the inhibitory period.

However, well developed grouping was not always present and in this respect also paralleled the behavior of the Osc-R. Two examples of differentiation to a grouped response are illustrated (Figures 9 and 10). In Figure 9, responses of a 2/sec. series clearly demonstrate a change in the response pattern between responses one and eight. The initial high frequency burst was present in the first response (high frequency initial bursts were present in all unit responses regardless of the number of previous flashes and/or adaptive state). Following this initial burst in response #1, a series of individual discharges occurred which were not grouped. Each subsequent response was relatively more grouped as inhibitory periods were "built in." (In responses #3-6, occasional discharges were seen prior to the first burst. These were actually part of the response [or were spontaneous discharges] to the preceding flash and indicated that the period of delay between flash and first burst was not an inhibitory period). In Figure 10 a similar series is shown for a different preparation. Here, the eye was not as well dark adapted prior to the onset of the repetitive series and more rapid differentiation to the grouped response occurred. Observe, in addition, that the previously

described long-duration inhibitory period also was enhanced during repetitive stimulation. After the third flash no discharges followed the last group (a single discharge at a latency of 80 msec.; see also Figure 11, B). This long-duration inhibition was actually present in the response to the first flash but with repetition, became sharper in onset, at a shorter latency (from the inspection of 500 msec. sweeps).

Post-stimulus histograms were obtained for selected units from the taped data. These histograms clearly demonstrated the regularity of the groupings and the sharpness of the intergroup inhibitory periods. In Figure 11, A, the histograms for the first ten responses (1-10) and the last ten responses of a 5/sec. series are compared. The differentiation of the grouped response was remarkable and is also illustrated in the histogram for the entire series of sixty-seven responses (inset B illustrates the same change in the individual response).

The relation of these post-stimulus histograms to the averaged population response was also confirmed. In Figure 12, a comparison of this type is illustrated.[4]

The grouped patterning of unit discharges was

4. The population response was not simultaneously recorded with the unit but at a time when the electrode resistance had decreased. However, electrode location was unchanged.

enhanced by adaptation to a sustained light. Low frequency stimulation (1/10 sec.) was used in order to prevent light adaptation during the scotopic sample and to permit the eye to dark adapt following exposure to sustained light (Figures 13 and 14). A series of twenty responses was recorded following thirty-six minutes of dark adaptation (Figure 13, Before). All responses of this series showed minimal grouping after the initial burst (a second group was just discernible). After a sustained light exposure of only one minute (After) marked grouping was seen in the first response sampled at a 10 sec. delay from the off of the light (Figure 13, After, 1). Notice that the succeeding responses tended to revert to the ungrouped pattern, especially at the end of the series (#15, 20), recorded at 160 sec. and 210 sec. after the off of the one minute adapting light. The post-stimulus histograms at analysis times of 125 msec. and 500 msec. also revealed this light adaptation effect (Figure 14). The inhibitory and post-inhibitory excitation periods, which followed the initial short latency response, were not greatly altered by light adaptation in this unit (Figure 14, 500 msec.).

Summary. The periods for grouping of single unit discharges and for oscillations in the population response were identical. The same unit discharged under both scotopic and photopic conditions. Differentiation of unit discharge patterns to the grouped form was enhanced by repetitive stimulation or by exposure to an adapting light.

Spontaneous oscillations

The Osc-R referred to a series of oscillatory potentials which appeared as a feature of the evoked response to a 10 microsecond light flash. Other oscillations were seen which did not immediately present this clear relationship to single flashes. Their frequency and behavior indicated, however, that they probably originated from a common source.

Oscillations often followed the initial population response (non-oscillatory) of a 5/sec. series (Figure 15). They occurred, therefore, prior to the appearance of the oscillations of the evoked response complex, e.g., the Osc-R of response #4-25. Yet the frequency of these "spontaneous" oscillations was identical to the Osc-R frequency. In addition, the Osc-R was actually observed

to arise out of these background oscillations (response #3) when they were visible in the record as in Figure 15. It suggests that, in fact, the Osc-R did not arise de novo but actually was a part of an already "ongoing" oscillatory process. The "spontaneous" oscillations were long latency sequelae of the initial flashes.

After sustained exposure to adapting light, oscillations were also seen in the population response record prior to the onset of repetitive flash stimulation (Figure 16, A). During flash stimulation, the Osc-R was at the same frequency as the background oscillations and arose from them (Figure 16, B). Note in addition that suppression of these oscillations following the initial evoked response highlighted the periods of primary and secondary long-duration inhibition described for individual unit responses.

During repetitive stimulation, and after response stabilization, oscillations were usually confined to the initial evoked response (Osc-R), however, after many stimuli they often appeared at longer latencies (Figure 17, A, #318). The late oscillations were usually at one-half the frequency of early oscillations (Figure 17, A and B).

Evidence for grouping of unit discharges, apart from the short latency response, was also found. In

Figure 18, A, grouped firing accompanied long latency oscillations. In units which discharged at initially long latencies, following a period of primary inhibition (Figure 18, B), grouping was also seen. The period was, however, approximately twice that of the short latency grouping.

Grouping was also seen in individual units during both the short latency response and the secondary excitatory phase following inhibition (Figure 19, B and C). When this occurred, the post-inhibitory grouped discharge period was usually double that of the early response.

Post-stimulus histograms for the long latency unit of Figure 18, B are presented in Figure 19, A. The probability of unit discharge decreased with time. This decrease occurred in a regular manner and can be described as a damping of the drive to grouped patterning of the discharge.

On-Off pattern

On-Off responses were determined for fifteen units with long duration flash illumination (350 msec.) of the entire retinal field (a 100/sec. burst of 10 microsecond flashes for 350 msec.). During this testing the adaptation

level of the eye was not well controlled and could be described as "partial light adaptation." Eleven On, two Off, and two On-Off units were encountered. Of the eleven On units only four showed a distinct inhibition at the off of the flash. All of the On units responded with short-latency excitation to the 10 microsecond flash (Grüsser and Rabelo 1958).

Under photopic conditions all units exhibited grouping regardless of their on-off categorization. The stability of these categories under varying conditions of adaptation was not studied (see Barlow et al 1957). The long-duration inhibitory periods, identified in the response to the 10 microsecond flash, were often present in the response to the 350 msec. flash (Figure 20). However, at times these inhibitory periods were obliterated by sustained firing at the grouped frequency. In Figure 20, A, two inhibitory periods followed the initial excitatory response to the 10 microsecond flash (lower trace), however, the second inhibitory period was obliterated in response to the 350 msec. flash (upper trace). In other units, all inhibitory periods were obliterated (the relation of this effect to adaptive state was not determined).

Figures 1-20

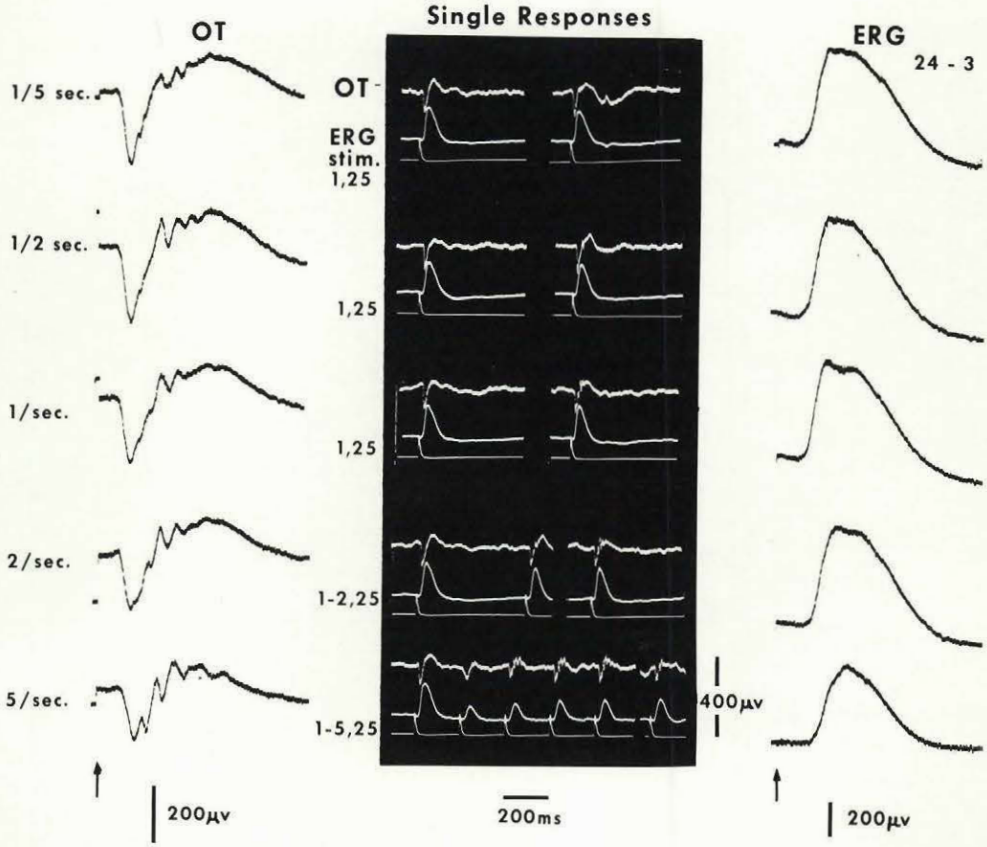


Fig. 1

Oscillatory response development at different flash rates, 1/5 sec. to 5/sec.; samples of averaged evoked responses (left and right) and single responses (middle). Each average has been computed from 25 individual responses (N-25) to 10 microsec. flashes at an analysis time of 125 msec. In this and all subsequent figures (unless otherwise indicated) photic stimuli were presented to the left eye while recording the right optic tract response, monopolarly, and the electroretinogram from the left cornea. The flash was administered at the beginning of each sweep (arrows). Deflection in this and all subsequent figures (unless otherwise indicated) was negative up at the active electrode in OT, and positive up in ERG.

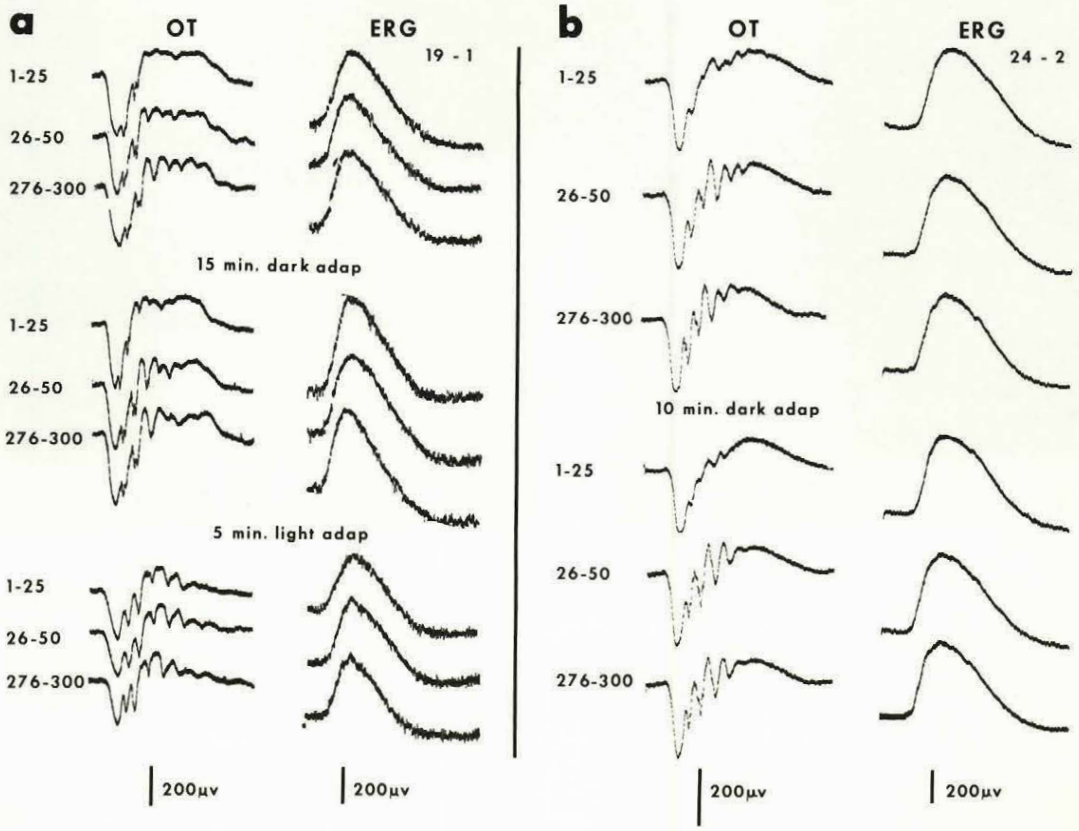


Fig. 2

Oscillatory response change with sustained dark and light adaptation in two preparations. A: Average evoked responses (N-25) following 30 min. dark adaptation (top), 15 min. re-dark adaptation (middle) and 5 min. sustained light adaptation (bottom); flash rate 2/sec. and analysis time 125 msec. B: Samples after $1\frac{1}{2}$ h. dark adaptation (top), and 10 min. re-dark adaptation (bottom) at same parameters, in another preparation.

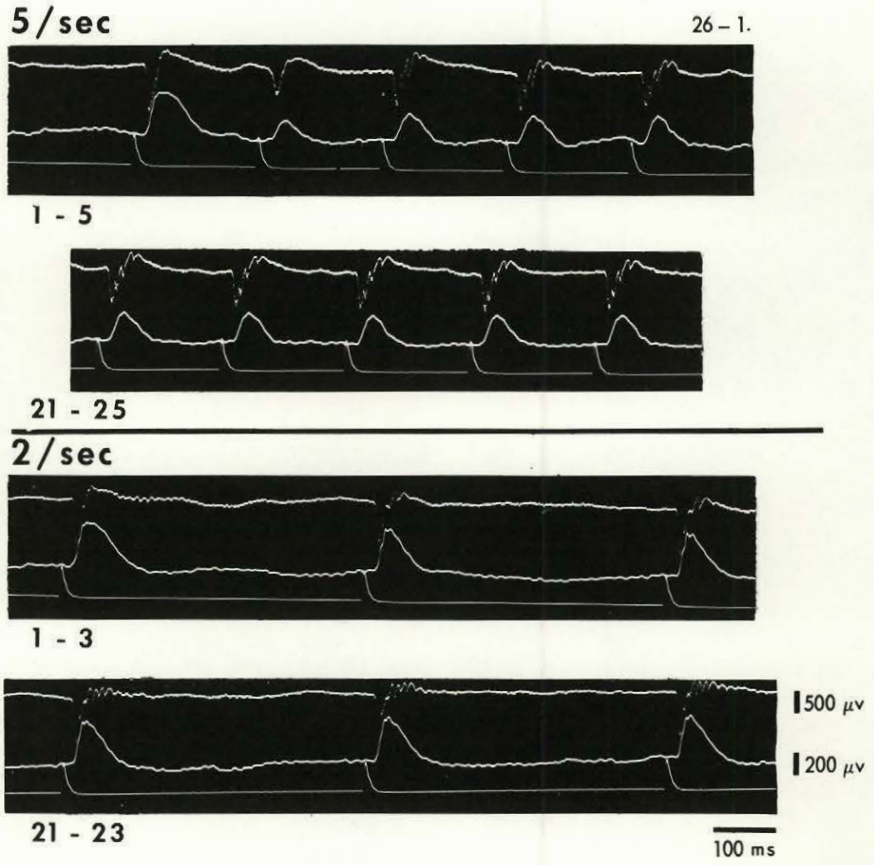


Fig. 3

Oscillatory response development at two flash rates, 5/sec. (top) and 2/sec. (bottom). Flashes were presented after 1½ h. dark adaptation and with 5 min. re-dark adaptation between samples. In each record the order is: OT (top), ERG (middle) and flash monitor (bottom).

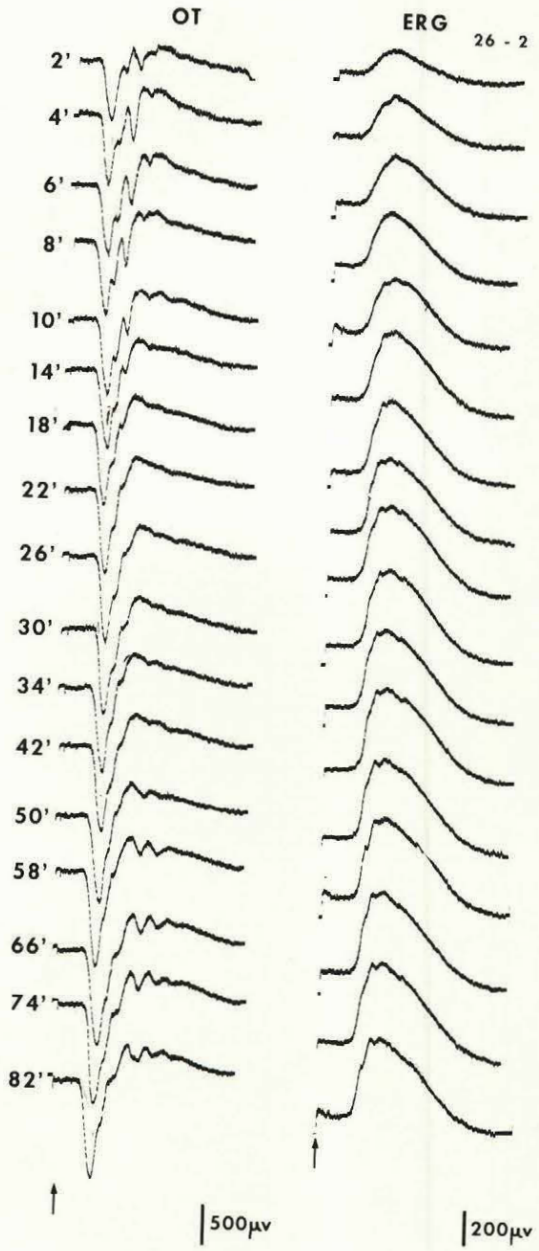


Fig. 4

Alterations of OT and ERG responses after 15 min. of sustained light adaptation. After this period of light adaptation responses were sampled in the dark at either 2 min. (0-10'), 4 min. (10'-34'), or 8 min. (34'-82') intervals. Each average was computed from the entire sample of 25 responses at 2/sec., at an analysis time of 125 msec.

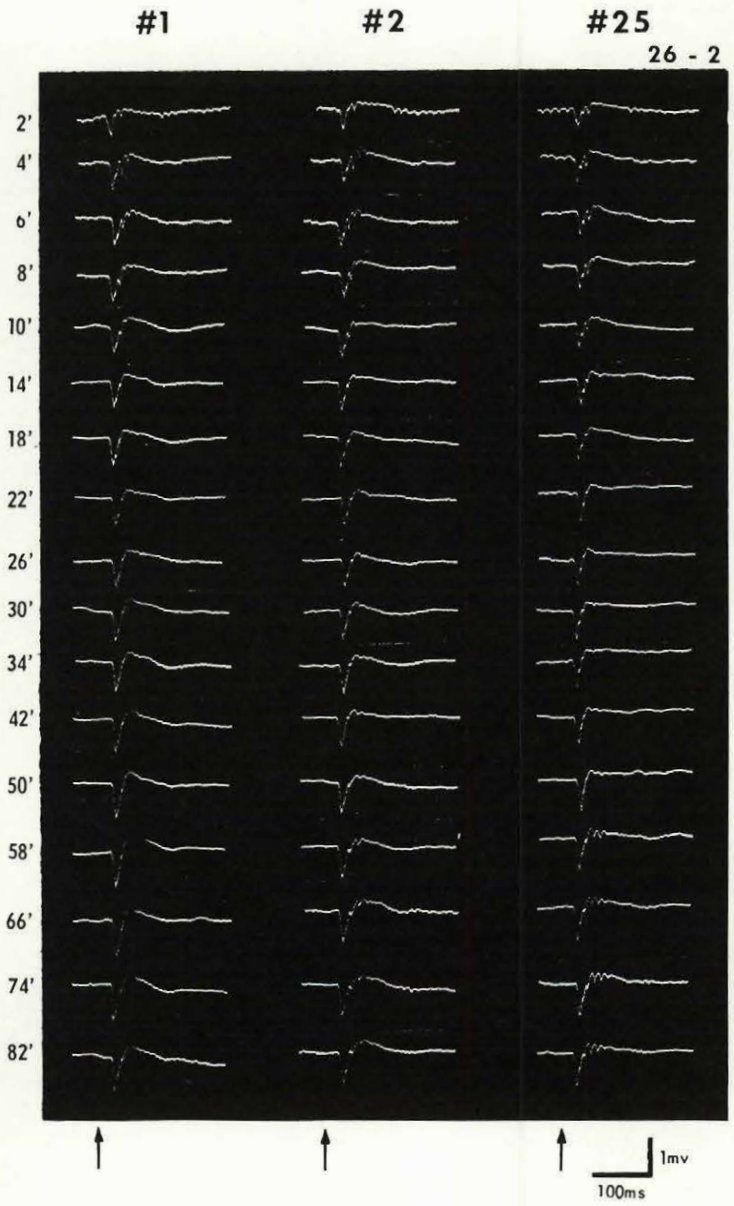


Fig. 5

Individual OT responses, #1, #2, #25, from each averaged sample presented in Fig. 4.

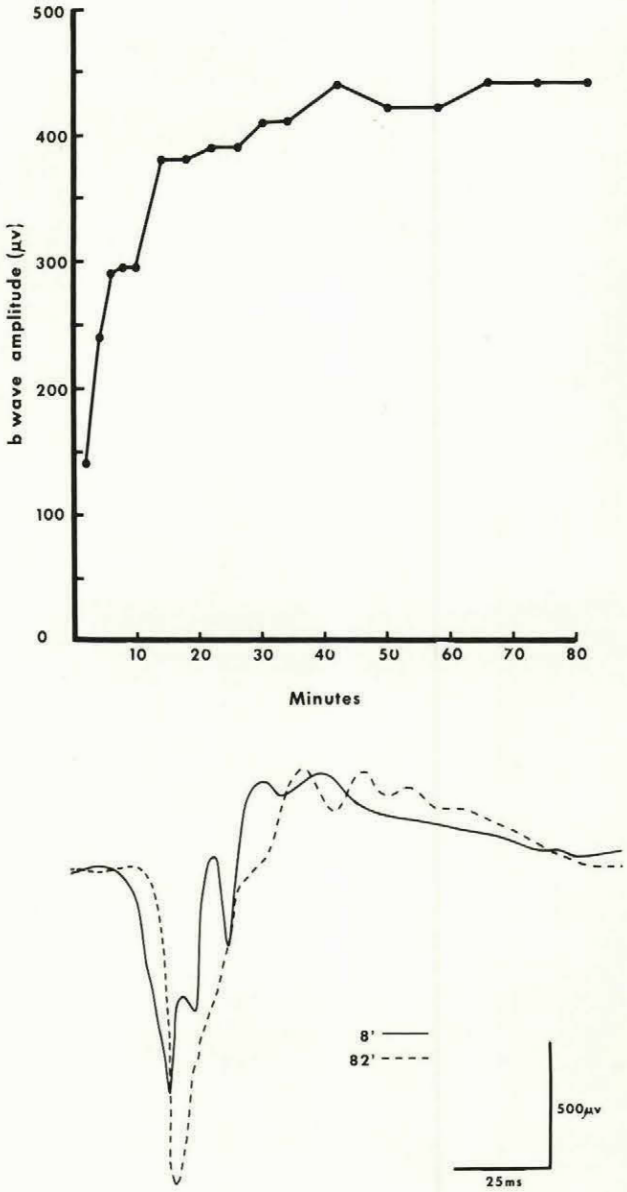


Fig. 6

Top: Recovery of b wave amplitude during dark adaptation. Peak b wave amplitude of the averages presented in Fig. 4 (ordinate) were plotted against time (abscissa).
Bottom: Superimposition of averaged OT responses at 8' and 82' (the averages of Fig. 4 were magnified and traced).

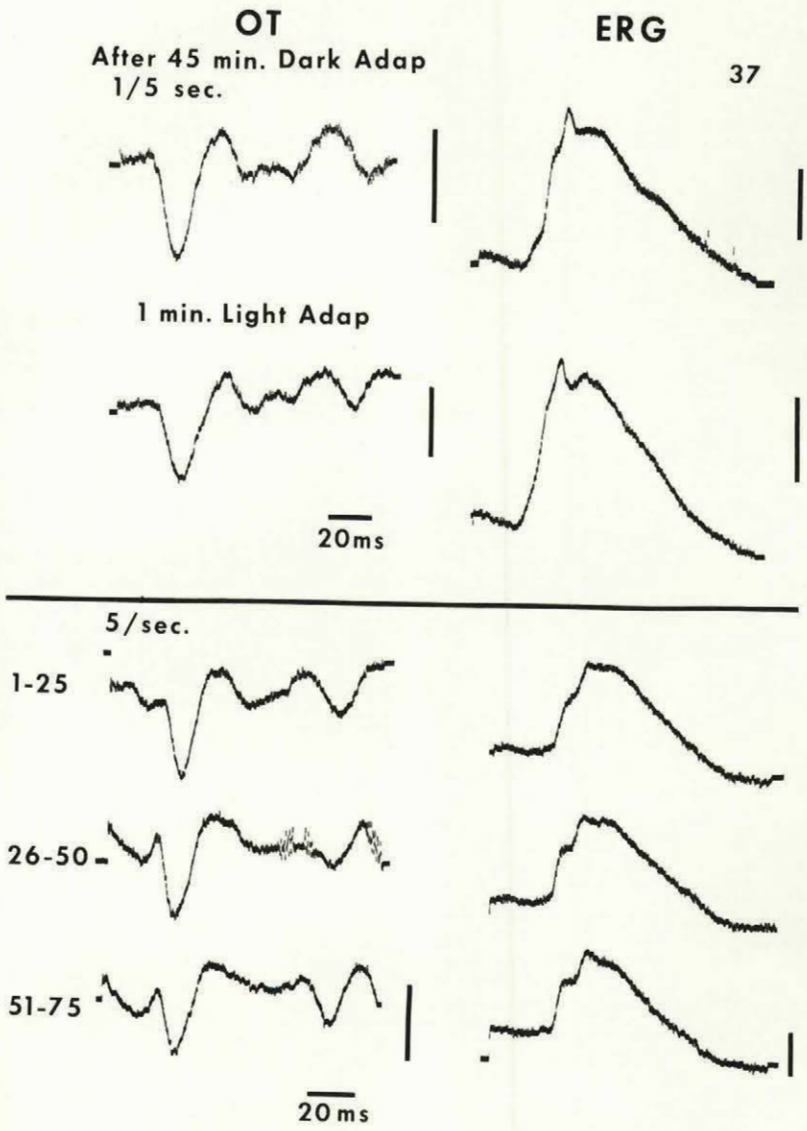


Fig. 7

OT and ERG responses from albino rat at different flash rates, 1/5 sec. (top) and 5/sec. (bottom), and under conditions of dark (45 min.) and light (1 min.) adaptation. Each average had been computed from 25 single responses recorded from right OT (bipolar) to flash stimulation of left eye.

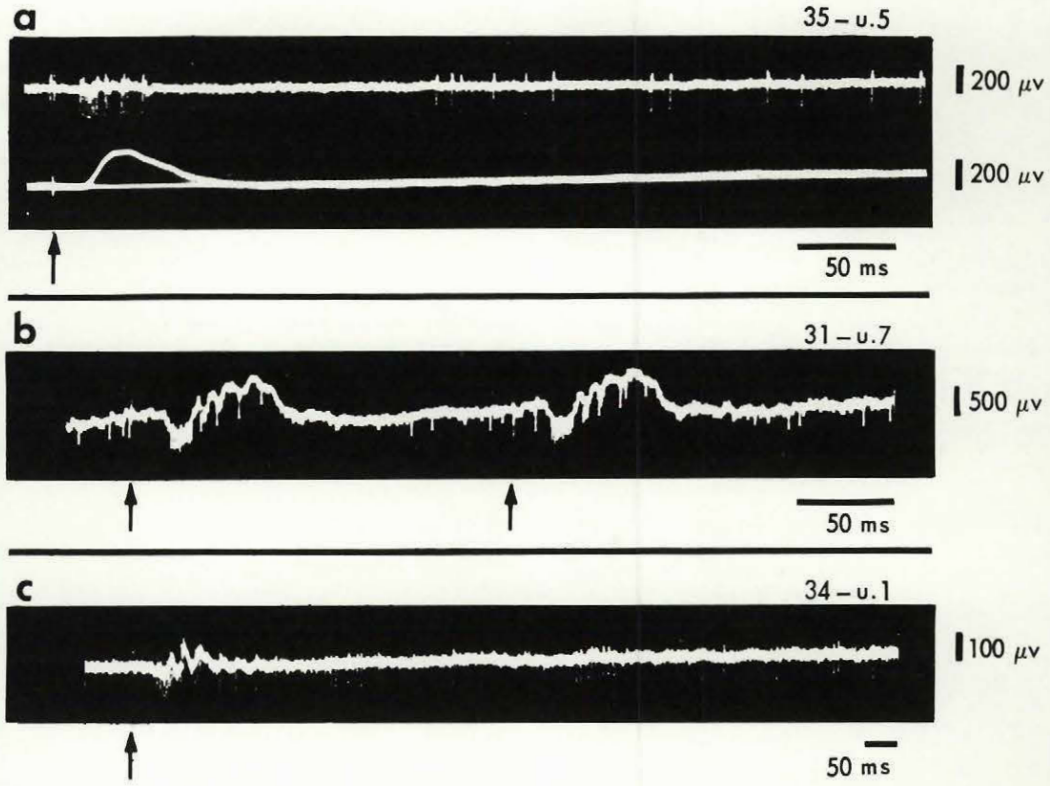


Fig. 8

Discharge patterns of three OT units. A: Flash rate 2/sec., response #13, B: 5/sec., #60, 61, (amplifiers set for low frequency response, .2c-1kc), C: 1/2 sec., #20. Polarity: negative up.

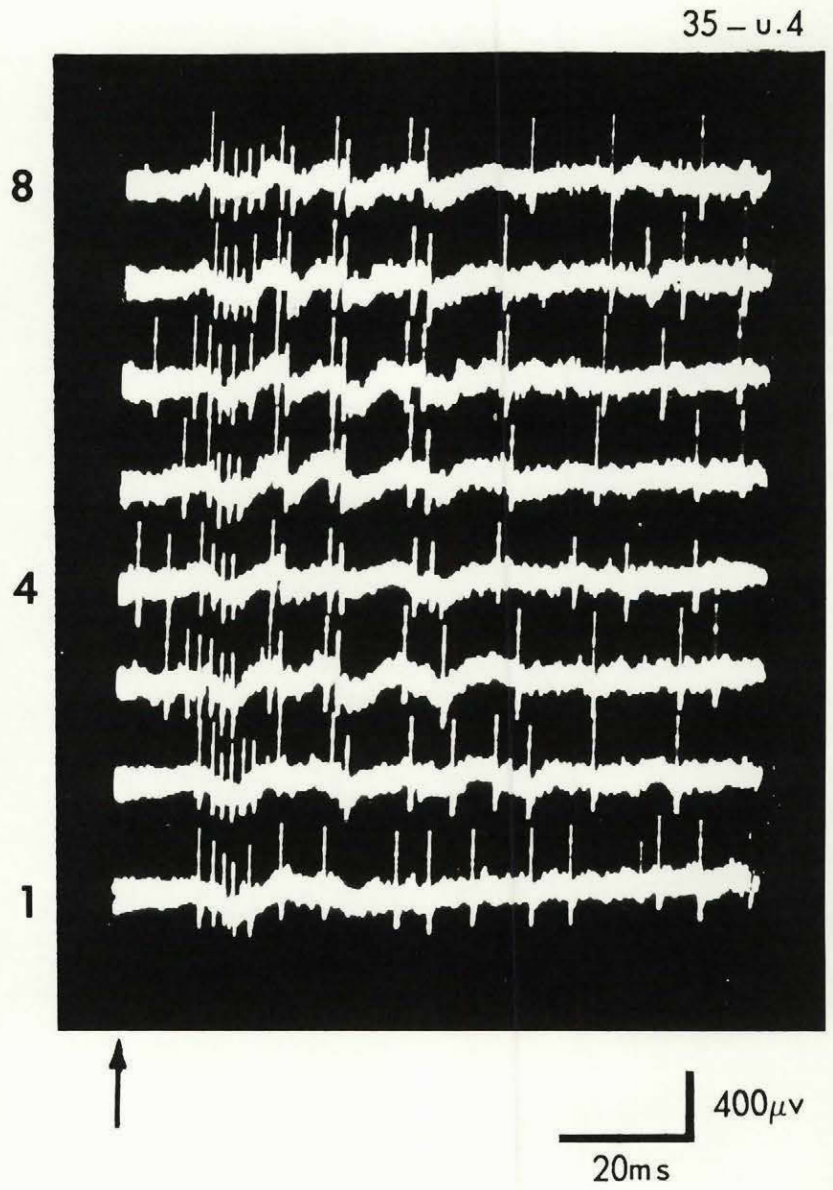


Fig. 9

Grouping of unit discharge during repetitive stimulation. Responses #1-8 (read from bottom to top) of a sample at 2/sec. after 10 min. dark adaptation. Sweep duration: 100 msec. Polarity: positive up.

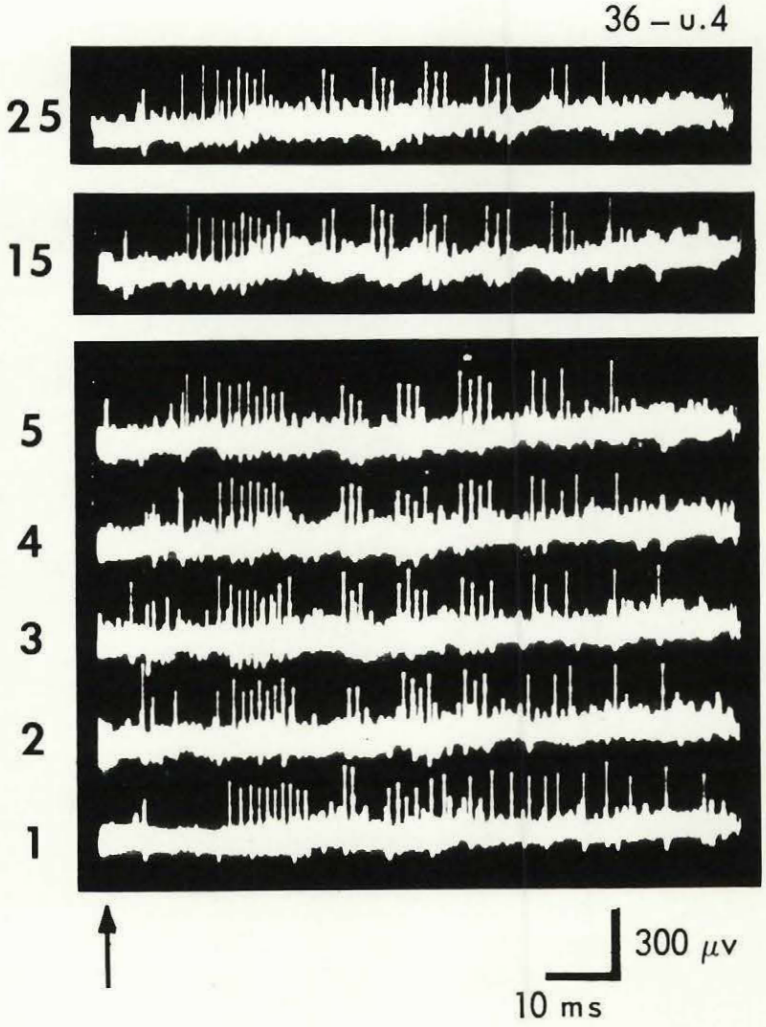


Fig. 10

Grouping of unit discharge during repetitive stimulation. Responses #1-25 (read from bottom to top) of a sample at 2/sec. after 10 min. dark adaptation. Sweep duration: 100 msec. Polarity: positive up.

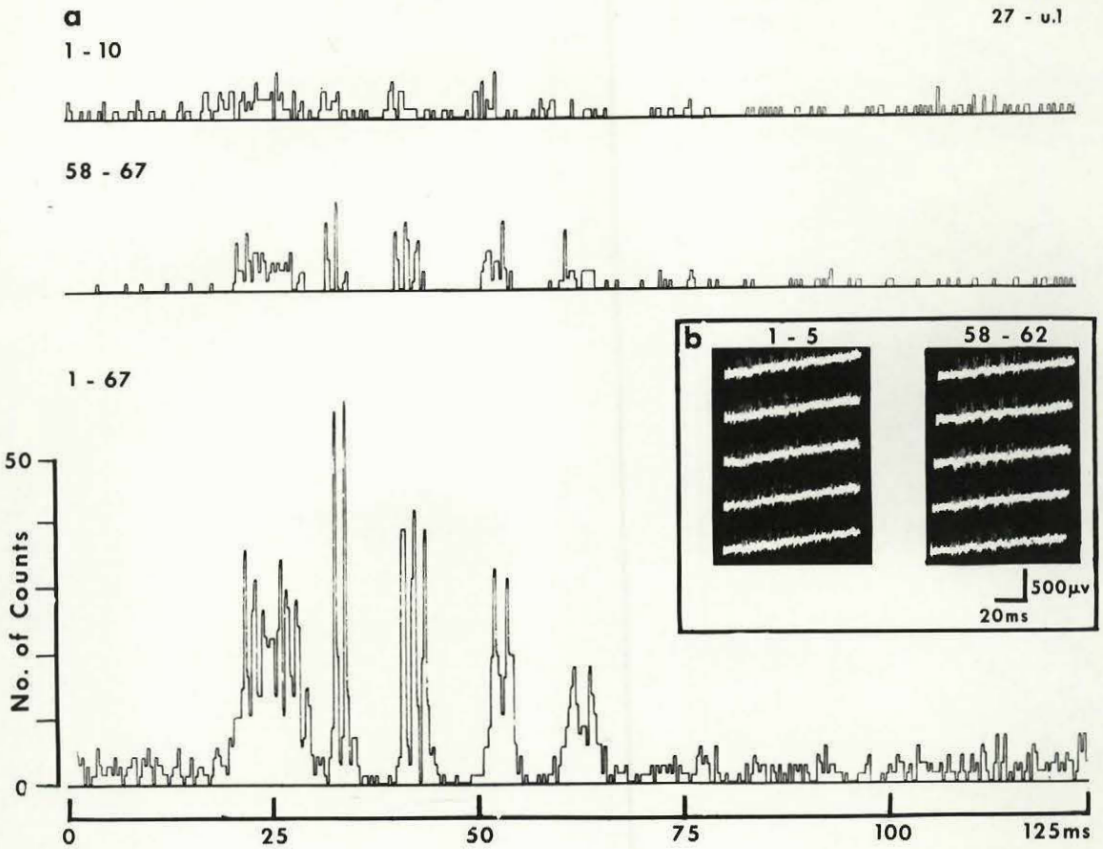


Fig. 11

Grouping of unit discharges during repetitive stimulation; post-stimulus histograms. Histograms were computed in this and all subsequent figures using 400 addresses. The unit discharges had been converted into uniform pulses with an amplitude discriminater. Flashes were presented after 15 min. dark adaptation at a rate of 5/sec.; analysis time was 125 msec. A: Histogram of responses #1-10 (top), #58-67 (middle) and #1-67 (bottom). B: Inset of individual responses #1-15, #58-62, 100 msec. sweep. Polarity: positive up.

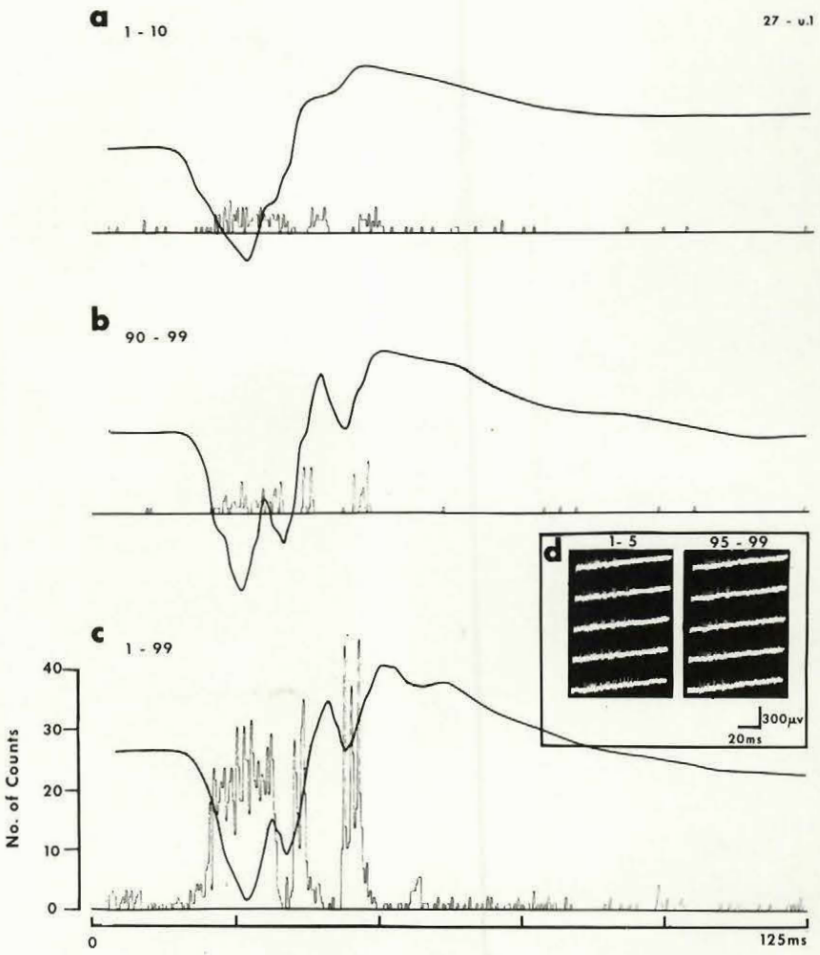


Fig. 12

Grouping of unit discharges (post-stimulus histograms) and oscillatory response change (superimposed averaged responses) during repetitive stimulation. Computation as in Fig. 11. Flashes were presented at 5/sec. after 5 min. dark adaptation. The averaged evoked responses and unit discharges were recorded to separate flash series, but at the same electrode location.

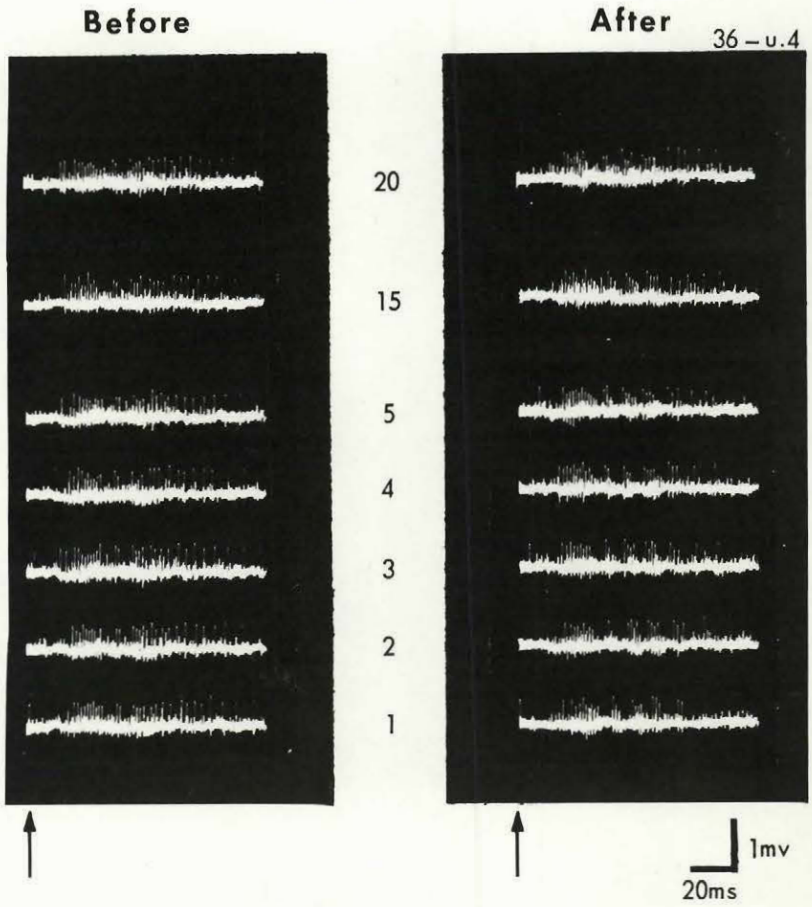


Fig. 13

Grouping of unit discharges after sustained light adaptation. Responses were sampled before and after light adaptation at a flash rate of 1/10 sec.; sweep duration of 100 msec. Before: Flashes were administered after 36 min. of dark adaptation and the scotopic state was maintained during the sample. Responses to flashes #1-5, 15, and 25 are illustrated. After: Responses after 1 min. light adaptation, sampled as above. Polarity: positive up.

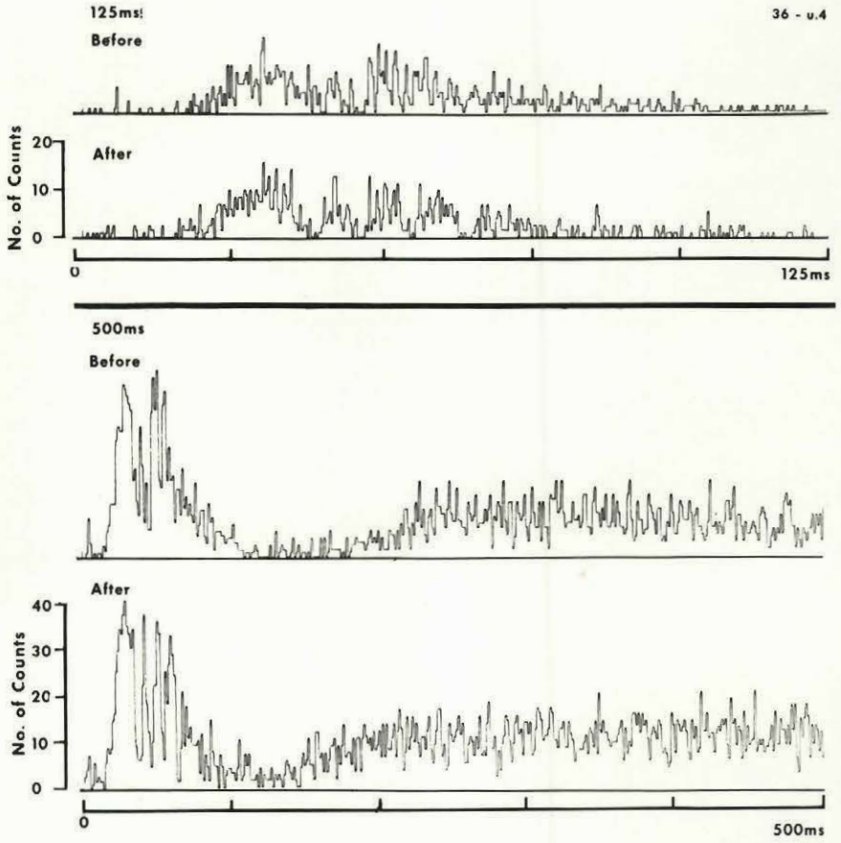


Fig. 14

Post-stimulus histograms computed for the experiment illustrated in Fig. 13, at analysis times of 125 msec. (top) and 500 msec. (bottom). There were 23 responses in the Before sample and 22 in the After.

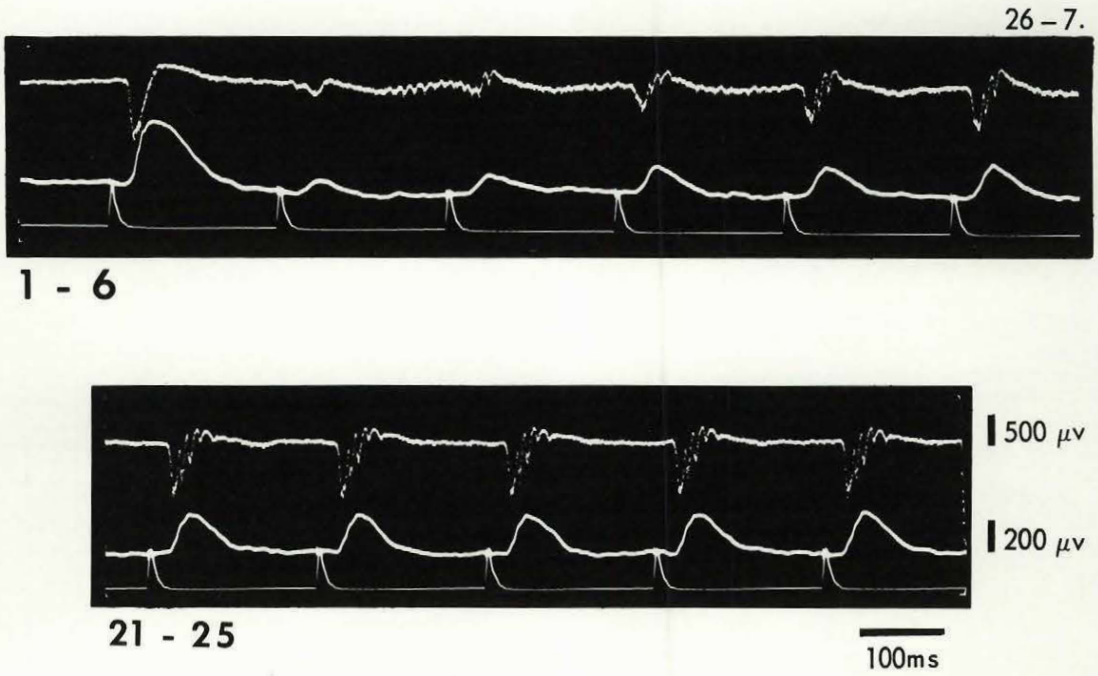


Fig. 15

Oscillatory response evolution in a sample at 5/sec. Responses #1-6 (top) and 21-25 (bottom). Flashes were presented after 1 h. dark adaptation. In each record the order is: OT (top), ERG (middle) and flash monitor (bottom).

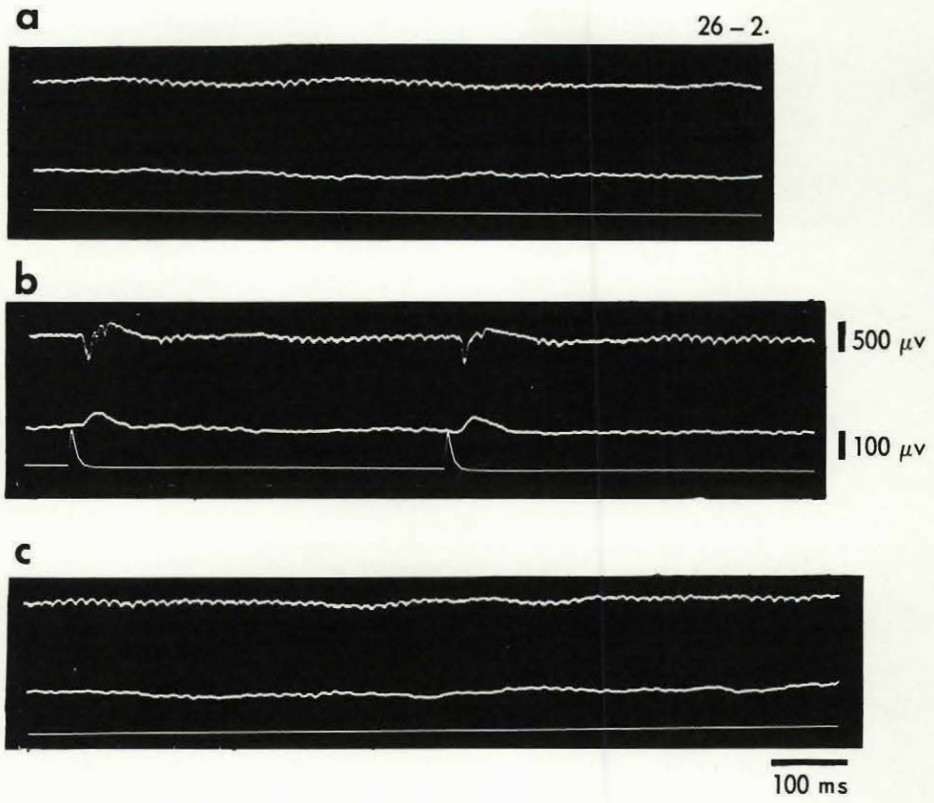


Fig. 16

Spontaneous oscillations following light adaptation (from the experiment of Fig. 4-6; 2' sample). Background record before flash presentation (A). Individual responses to flashes #6, 7 of 2' sample (B). Background record after flash #25 (C).

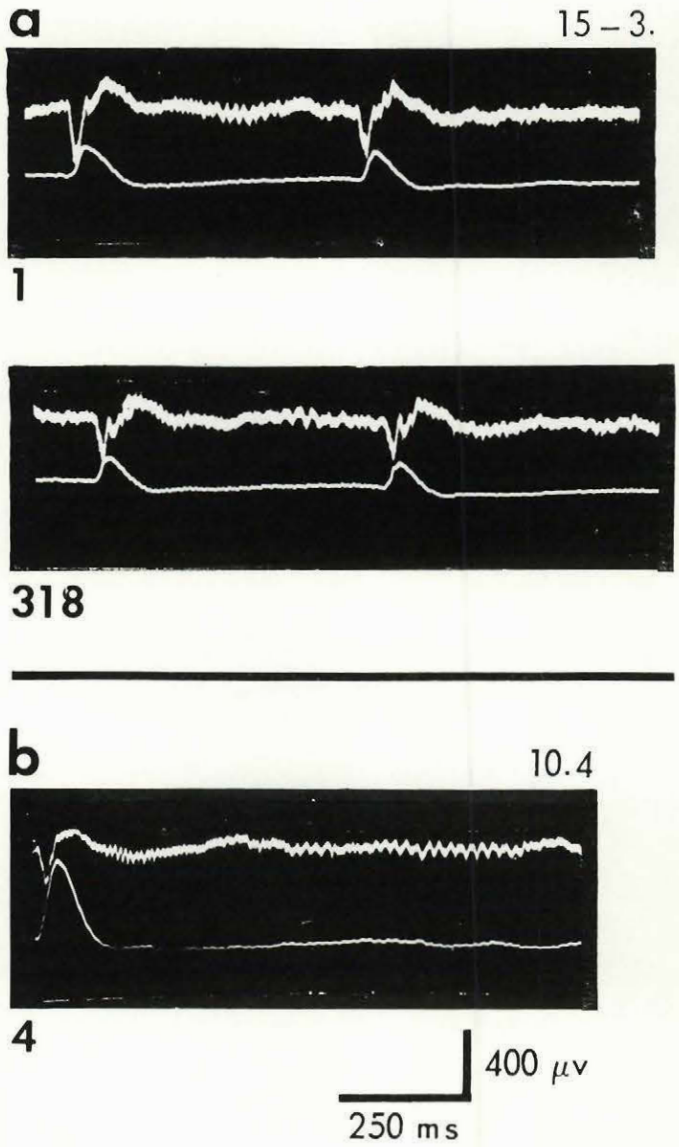


Fig. 17

Long latency oscillations during repetitive stimulation in two preparations (A and B).
A: Response #1, and #318 of a 2/sec. series.
B: Response #4 of a 1/sec. series.

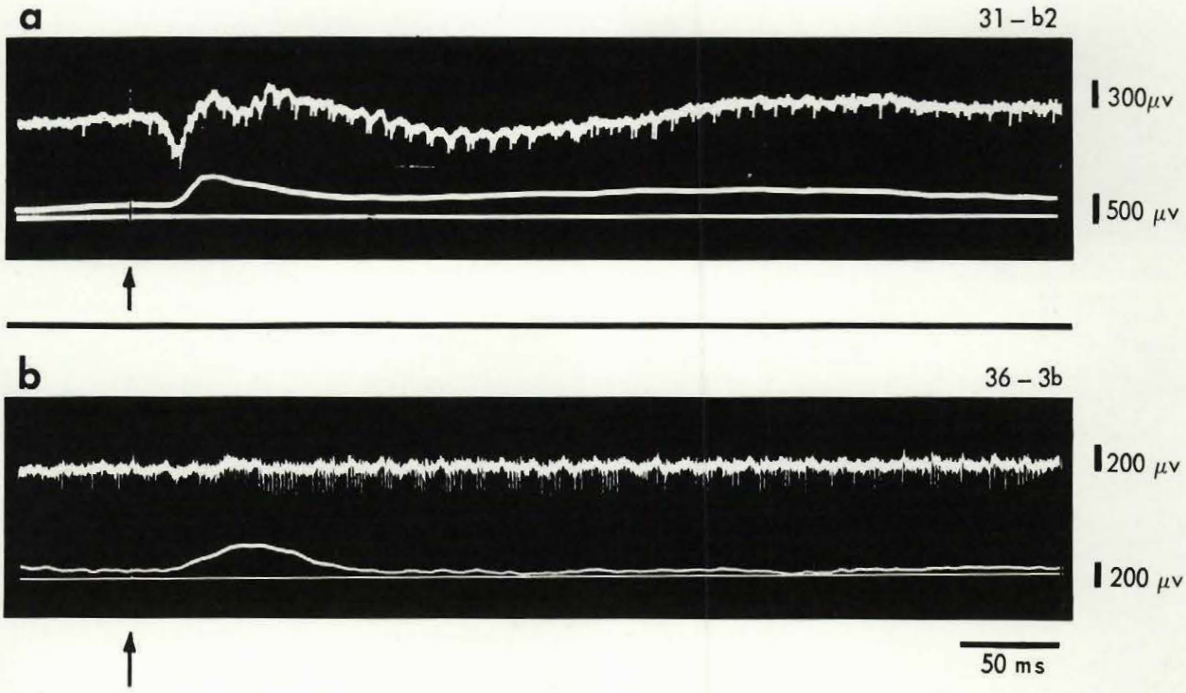


Fig. 18

Grouping of unit discharges at long latencies.
A: Sample of one response at 1/sec. B: Sample of one response at 1/5 sec. in another preparation.

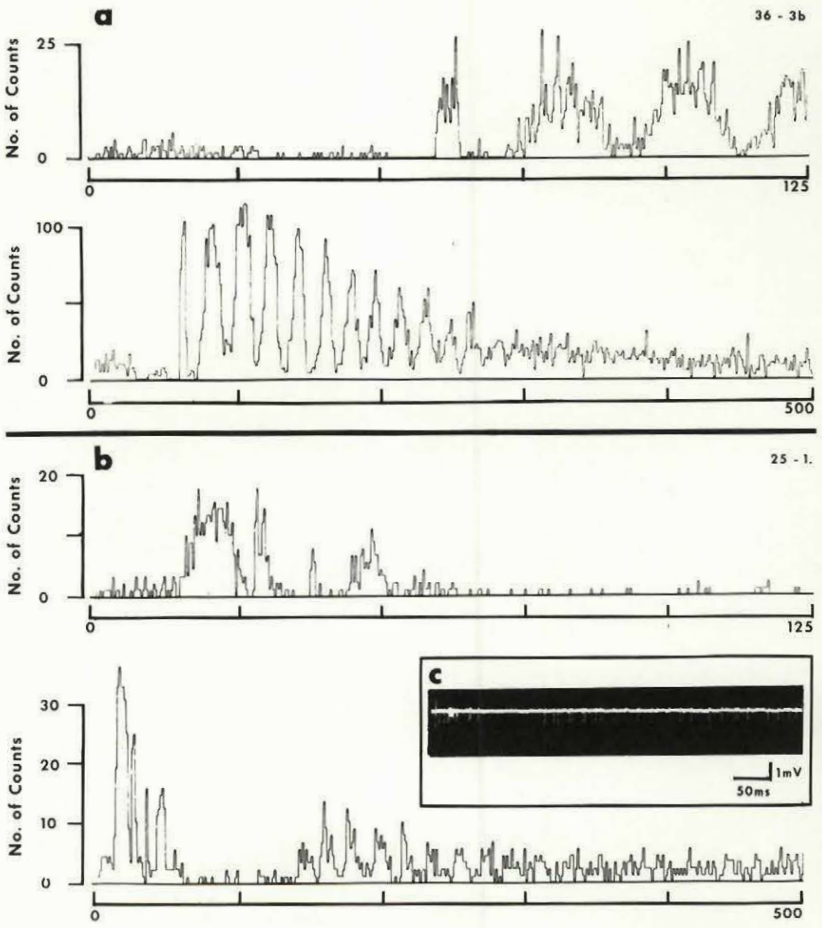


Fig. 19

Grouping of unit discharges at long latencies; post-stimulus histograms. A: Same unit as Fig. 18, B. Post-stimulus histogram of unit response to 100 flashes at 1/5 sec.; analysis time 125 msec. (top) and 500 msec. (bottom). B: Post-stimulus histogram of unit response to 50 flashes at 2/sec.; analysis time 125 msec. (top) and 500 msec. (bottom). Inset (C) the #23 response of this series.

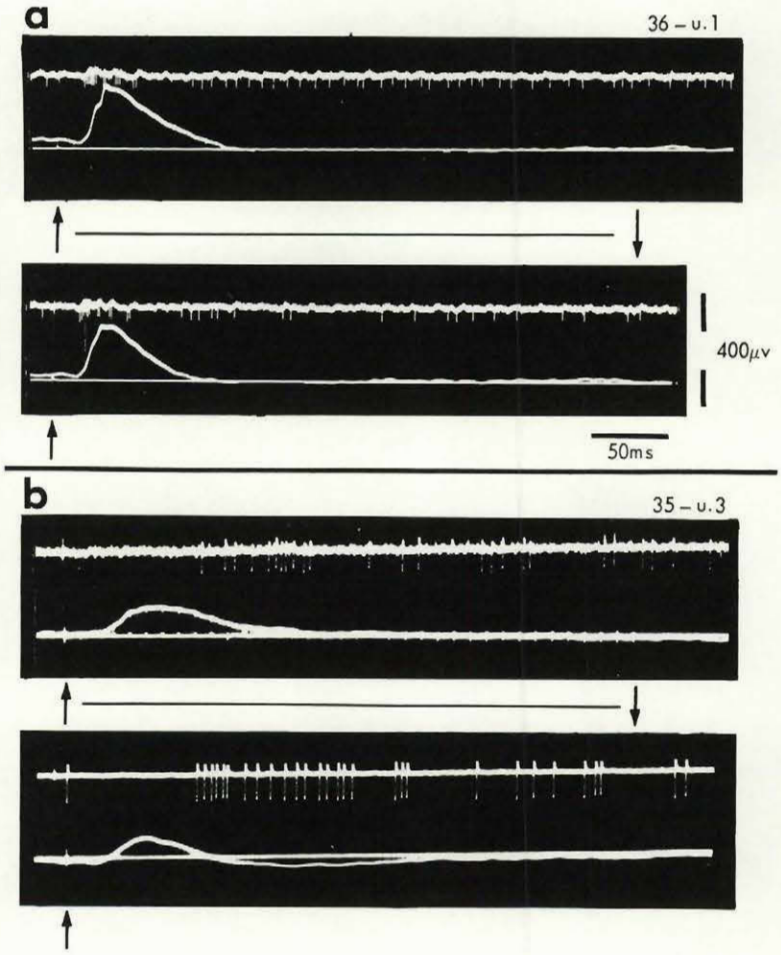


Fig. 20

On-off response pattern (350 msec. flash duration), (top of A and B) compared with response to 10 microsec. flash (bottom of A and B). The 10 microsec. flashes were presented at 2/sec.

III. DISCUSSION

The Oscillatory Response to Flashes

Repetitive stimulation. Oscillatory response enhancement during repetitive stimulation was a function of both the frequency of repetition and duration of the test series. At low repetitive frequencies (1/5 to 1/sec.) there was a steady but slow differentiation of the response to an oscillatory form. Light adaptation, increasing with each flash, paralleled this response evolution. When flash intensity and stimulus frequency were sufficiently low, no response change was recorded as the initial dark adapted state was not altered by the flashes.

At higher repetitive frequencies (2/sec. to 5/sec.) the rapidity of response evolution was striking, i.e., Osc-R's were present to the third and/or fourth flash. In order to adequately relate this phenomenon to light adaptation the parallel retinogram event - b wave suppression - must be considered. Arden et al (1958) discovered that the degree of suppression was independent of quantity of pigment bleached by the flash, but was a function of the duration of the dark interval between flashes. (Bleaching of pigment is a function of duration of exposure and

suppression was not a function of flash duration). Recovery from suppression was exponential, at a time constant of 300 msec. (valid only for the intensity employed which was set below cone threshold). This behavior of the b wave prompted Granit (1962) to refer to it as indicative of "a kind of light adaptation," and its independence from pigment changes demanded an origin in retinal events distal to the receptor element.

Evidence is available for the presence of non-photochemical processes in adaptation, i.e., neural adaptation. This non-photochemical adaptation was postulated in order to account for the 70% reduction of b wave amplitude observed with adaptation to low intensity light when only a negligible quantity of pigment was bleached (Granit et al 1939). Rushton (1959) supported this contention from studies in man where psychophysical sensitivity measurements were correlated with pigment concentrations obtained by reflexion densitometry. Recently, Dowling (1963) identified a non-photochemical adaptive process in the retina of the rat. Employing the increment threshold of the b wave as a sensitivity measure, he observed at adaptive intensities as high as 5 log units above threshold, a unitary - fast recovery

of the b wave threshold. Exposure duration had little effect on the rate of dark adaptation, however, rhodopsin concentration was not significantly decreased at this level of luminance. With more intense stimuli, a significant quantity of rhodopsin bleached and adaptation became a biphasic process. The fast adaptation was followed by a slower, more protracted recovery process. The total rise of threshold was remarkably rapid, a few seconds, and was independent of the quantity of pigment bleached but was a function of light intensity.

The process identified by Dowling in the all-rod retina of rat and that underlying b wave suppression in cat are probably the same. Both were extremely rapid in onset following the on of light, were unrelated to quantity of pigment bleached, and recovered rapidly in the dark. Thus b wave suppression is a function of a neural adaptation. The parallel optic tract event, rapid onset of the Osc-R, must also be related to this process.

Adaptation to sustained light. Osc-R enhancement with exposure to sustained light supports the light adaptation - hypothesis advanced to explain the changes during repetitive stimulation. However, an additional

improvement of the Osc-R was evident during the first minutes in the dark following the off of the adapting light. At the same time rapid recovery of b wave amplitude occurred, suggesting that recovery of cone-system sensitivity resulted in Osc-R facilitation.

A problem of interpretation, however, arises from analysis of the recovery curve. Dowling (1963) pointed to the difficulty when he wrote, "In a typical rod-cone eye the two photochemical phases of dark adaptation make it difficult to distinguish and sort out rapid neural changes in adaptation." That is, in a mixed retina, e.g., cat, what does the rapid phase of b wave recovery represent: (1) neural recovery of the rod system, or (2) neural recovery of both rod and cone systems, or finally (3) neural and pigment recovery of the cone system? The data obtained in the present study did not answer this question but the following related points are important: (1) The short latency and rapid evolution of the 8' response as compared to the 82' response suggest that the "fast" system (Granit 1947) dominates the 8' response. (2) In b wave suppression, rod-system neural-light adaptation paralleled Osc-R enhancement, therefore it is difficult to assign a significant role to rod-system neural-dark

adaptation in the Osc-R enhancement described above. We will hypothesize therefore that cone-system recovery is the factor responsible for the improvement of the Osc-R in the early phase of dark adaptation.

The interaction of light and dark adaptation

The oscillatory response as an event related to light adaptation may serve as an experimental tool by labelling the adaptive process. Therefore, observing the behavior of the Osc-R during dark adaptation could provide information concerning the interaction of these two processes. Granit (1935, 1947) proposed an interaction to account for the competitive relation of these two processes, and some supportive evidence is available. In 1958, Elenius proposed that cones inhibit rods to explain the delayed b wave recovery following adaptation to intense lights in the rabbit. At lower intensities (below cone threshold) only rapid b wave recovery occurred. (At the high intensities cone activation was indicated by the raised threshold for flicker fusion). Further, scotopically-equivalent chromatic stimuli yielded greater retardation of b wave recovery at the longer wavelengths. The finding of only rapid adaptation in the rod-dominant

retina of two color blind human subjects supported the inhibition hypothesis (Elenius and Heck 1958). The differentiation of a rapid and slow recovery process related to adapting intensity raises the possibility of an explanation based on biphasic neural and photochemical recovery (Dowling 1963). Again, the complexity of these events in mixed retinae precludes additional speculation.

Inhibition has also been proposed by Granit (1947) as an aid in understanding the failure of the cone-system to function under scotopic conditions. Here, however, inhibition based on a mechanism of occlusion was proposed. Interaction would not be due to a true inhibition (synaptic mechanism) but a result of competition for the pathways of retinal output. As yet there is no physiological evidence for distinguishing true inhibition from occlusion as the basis for rod-cone interaction.

Waning of the Osc-R during dark adaptation paralleled a late phase of <u>b wave</u> recovery. Completion of this recovery and maximum decrease of Osc-R development were reached simultaneously. Samples taken during the following period exhibited enhancement of the Osc-R relative to the minimum point reached during dark adaptation. If occlusion were the mechanism, i.e., progressive take-over of the outflow

paths by the rod-system, Osc-R diminution should have progressed to a minimum and stabilized at that level. These data suggest that when the eye is dark adapting an active process is involved which suppresses the Osc-R. This activity ceases at the moment when dark adaptation is complete.

Alternatively, however, Osc-R decay during dark adaptation may be completely passive. With removal of light the potential for oscillating (or oscillatory drive) decays passively with time. The return from the minimal point at the end of dark adaptation results simply from a "rebound" to a more stable level.

B wave suppression during high frequency stimulation indicates a decrease in the sensitivity of the rod-system. This probably is a function of slow recovery, characteristic of the rod-system (Granit 1947). While the rod-system is refractory, Osc-R enhancement could result either from cone-system take-over of the outgoing pathways, or release of the cone-system from direct inhibition.

An oscillatory system in the retina

Oscillations were present in the optic tract population response record for several minutes following cessation

of the adapting stimulus. Flash stimulation during this period produced short latency oscillations in the evoked response (Osc-R). Clearly, a single oscillatory mechanism underlies both the flash-related and background oscillations.

Crapper and Noell (1963) described an oscillatory mechanism in the rabbit retina. Ganglion cell grouped discharges at an intergroup frequency of 30-40/sec. were produced by 0.5 msec. (vitreous negative) polarization of the retina. Number of groups and initial latency were functions of stimulus strength. Flash illumination (30 microsecond) also produced grouped discharges. With dual pulse stimulation, a cyclical facilitation and inhibition of ganglion cell activity followed conditioned stimuli which were subthreshold for ganglion cell firing. This cyclical oscillation was at the 30-40/sec. frequency and showed a tendency to damp with time.

The presence of oscillations following the initial flash(es) of a 5/sec. repetitive series, before they are present at a short latency in the evoked response (Osc-R), suggests that the very first flash <u>starts</u> an oscillatory mechanism. Successive flashes add increments of drive to this mechanism. During sustained light adaptation drive is maximal and spontaneous discharge of the ganglion

cells is gated by cycles of inhibition and facilitation which are above threshold for the ganglion cell discharge. The drive for grouping of the discharges was also observed to damp with time.

In this study, although no direct exploration of the structural origin of this mechanism was undertaken, some pertinent findings were obtained. The enhancement of the Osc-R with light adaptation and its further facilitation during the phase of cone-system recovery strongly suggests that the oscillatory mechanism is a part of cone-system activity. The boundaries of the cone-system are wide. They encompass the entire circuit from receptor to ganglion cell which functions under photopic conditions (Polyak 1941).

Oscillation as a property of the ganglion cell membranes was excluded as the primary site of origin by Doty and Kimura (1963) and Crapper and Noell (1963). Doty and Kimura demonstrated that this mechanism can be triggered by antidromic stimulation of the optic nerve and suggested the centrifugal fiber-bipolar cell synapse as one route to the mechanism. (In addition the centrifugal bipolar cell described in primates by Polyak (1941) would, if it exists in cat, provide an alternative path, directed proximally). As the mechanism is also triggered by

polarization, Crapper and Noel suggest that radially oriented structures must be involved.

Loci for inhibition, based on anatomical data, are present in the retina. Crapper and Noell discuss a possible role played by "interreceptor" synapses as inhibitory type synapses in the region of the receptor cells themselves (Sjostrand 1958 - rods of guinea pig retina; Nilsson 1964 - rods and cones of frog retina). However, at the ganglion cell, synaptic terminals occur both on dendrites and cell body, and these terminals correspond, in part, to two different bipolar cell types (mop and brush respectively, Polyak 1941). This differentiation could be a basis for inhibition.

It is possible that a radially oriented circuit, bidirectionally active, between receptor and ganglion cell is involved, feedback from the ganglion cell to the receptor playing an important role. The fact that an initial high frequency burst occurred under all adaptive conditions suggests that excitation of the ganglion cell is always the first transmitted event (for short latency units only). The subsequent gated firing could then be a function of a feedback circuit which operates only under photopic conditions.

Ganglion cell excitability

Ganglion cell discharge also underwent long duration periods of facilitation and inhibition. Discharge completely ceased during the inhibitory periods regardless of the high frequency oscillatory drive which was then gating the cell activity. Therefore two distinct mechanisms controlling ganglion cell excitability can be identified: (1) a mechanism producing long duration periods of inhibition and facilitation and (2) the oscillatory mechanism which consists of shorter periods (10 msec.) of inhibition and facilitation. The former was identified by Grüsser and Rabelo with the mechanism which determines the on-off patterning of ganglion cell discharge. On elements responded to brief flashes (time constant of 0.3 msec.) with a short latency discharge, followed by an inhibitory pause, a secondary discharge and sometimes secondary inhibition and tertiary excitation. However, Off elements responded with a primary inhibition (50-350 msec. duration).[5] Therefore the synapses and conduction

5. On-off units were mainly distinguished by the occurrence of grouping (Grüsser and Rabelo 1958). This conflicts with the more widespread presence of this pattern in all units observed in the present study. These investigators noted, however, that simultaneous background illumination did alter the grouped pattern.

pathways which operate to produce the post-excitatory and pre-excitatory inhibition (Granit 1947) upon which the On-Off categorization has been based are also revealed by facilitatory and inhibitory periods which follow a flash of only 10 microseconds duration.

The rapid oscillation of excitation and inhibition represents a finer control superimposed on this pattern. It is revealed whenever the cell discharges during the long excitatory periods, e.g., a long latency unit exhibited a grouped pattern when it discharged following the initial long inhibitory period.

With total-field illumination as used in the present study,[6] the receptive field organization must play an important role in the discharge of every ganglion cell. Barlow et al (1957) demonstrated that this organization is expressed in its complex form only under photopic conditions. Under scotopic conditions only simple unicentered fields were observed while the annulus of opposite sign appeared under photopic conditions.

In the present work the long duration inhibitory-facilitatory periods were sharpened and enhanced by

6. In fact, total-field illumination may be essential. The intraretinal oscillations described by Brindley (1956) in the excised frog eye were well developed only if the whole retina was illuminated.

light adaptation. Thus both mechanisms controlling ganglion cell excitability are enhanced by light adaptation, indicating the activity of more complex neural circuitry in the photopic state.

CHAPTER IV

REPETITIVE STIMULATION AND STATE OF AROUSAL

> ...there really is a rational basis for postulating a central neural factor that modifies the action of a stimulus...At first glance this is a problem for the neurophysiologist only...The problem is after all the problem of attention, and seen best in the activity of the whole animal. It is in the highest degree unlikely that it can be solved either from the physiological alone or from the behavioral evidence alone...
> (Hebb 1949)

I. INTRODUCTION

The relation of reticular formation function (formatio reticularis of the brain stem; RF) to wakefulness was physiologically established when its electrical excitation activated the electrocorticogram (Moruzzi and Magoun 1949). As intake and integration of sense data are fundamental properties of the waking state the question of sensory-reticular relationships immediately arose. One could examine either properties of the input to the reticular formation or the role played by reticular formation output in the operation of sensory channels. The latter, effector role, and its relation to visual system function was the subject of this inquiry.

Reticular activation as inhibiting sensory transmission

Initial observations disclosed a reticular inhibition of sensory transmission. Bremer (1951) demonstrated that cortical evoked potential amplitudes (auditory cortex) decreased during arousal. He explained this apparent inhibition on the basis of occlusion. Sensory impulses were "masked" by the simultaneous arrival of a strong reticular input which dominated cortical activity. However, Hernández-Péon et al (1955, 1956) assigned a true inhibitory role to the reticular formation in relation to subcortical pathways. This hypothesis evolved from studies of habituation and attention as well as physiologic investigation of reticular function. Electrical stimulation of the reticular formation decreased evoked potential amplitudes at subcortical stations (nucleus gracilis and lateral geniculate nucleus) to stimulation of the corresponding peripheral sense. Barbiturates, known to depress the reticular formation, enhanced these amplitudes. Long-term peripheral stimulation (flashes) resulted in the reduction and disappearance of evoked potentials at both lateral geniculate nucleus and visual cortex. This habituation of evoked potentials was prevented by barbiturate narcosis, while arousal led to a recovery of habituated responses.

More recently, an alternative explanation was offered for these early findings. Naquet et al (1960) demonstrated that pupillary diameter played an important part in determining evoked potential amplitude along the primary visual pathway. In normal preparations, reticular stimulation aroused the cortex, increased the diameter of the pupil (mydriasis) and augmented the amplitudes of evoked potentials at optic tract and lateral geniculate nucleus. With sleep, and its related pupillary constriction (miosis), amplitude diminution occurred. However, permanent dilatation of the pupil (atropinization) prevented these amplitude changes. Still, at the visual cortex, arousal reduced evoked response amplitude regardless of pupillary size.[1] These data explained habituation on the basis of a reduction of stimulus input unrelated to central mechanisms of inhibition. Fernández-Guardiola et al (1961) confirmed this hypothesis in <u>chronic</u> preparations where habituation of evoked potentials at LGN did not occur with atropinization of the pupils (at cortex, diminution but never disappearance was occasionally observed). Additional corroborative

1. Fernández-Guardiola et al (1964) observed this relationship of evoked response to pupil diameter for the latency of the response at optic chiasm, but amplitude diminution during arousal was still observed at visual cortex and in addition at lateral geniculate nucleus.

evidence was offered by Affani et al (1962) and Gallardo et al (1962) while exercising a variety of methods for peripheral control (fissurated artificial pupil; fixation of the head in relation to the stimulus, and mydriasis).

Reticular activation as facilitating sensory transmission

Other investigators simultaneously produced evidence justifying an opposite process, i.e. facilitation. Gauthier et al (1956) observed that if somatosensory cortical responses were evoked by an electric shock to the thalamic relay instead of peripheral sensory stimulation, amplitude diminution did not occur during reticular activation. A more positive role for reticular activation was demonstrated by King et al (1957) in recording evoked responses from the internal capsule to electrical stimulation of the peripheral nerve. Arousal was associated with a decreased latency and shortened duration of the capsular response. These effects were absent in the medial lemniscus but were still observed when the locus of stimulation was moved from the peripheral nerve more centrally, i.e., to the lemniscus itself. Therefore, the physiological activity responsible for facilitation must have occurred

at the thalamic relay nucleus (ventralis posterior). These initial findings were soon solidified and expanded in the investigations of Bremer and Stoupel (1958, 1959) and Dumont and Dell (1958). Visual cortical potentials, evoked by electrical stimulation of optic nerve or lateral geniculate nucleus, were markedly enhanced during arousal. This facilitation was expressed both in the amplitude (increased) and latency (shortened) of the response. Further investigations extended the analysis of this facilitatory effect by attempting to answer the following questions: (1) Where are the anatomical loci for these effects, i.e., lateral geniculate nucleus, visual cortex (area striata), or both? (2) Why are responses evoked by peripheral sensory stimulation (e.g., light) diminished in amplitude while electrically evoked responses (e.g., optic nerve stimulation) are facilitated? (3) What are the significant events at the unitary level which correspond to the observations from population response data?

Lateral geniculate nucleus. Dumont and Dell (1960) had observed an augmentation of the initial positive deflection of the cortical response to optic nerve stimulation during reticular formation activation. This

finding pointed to the presence of facilitation at the LGN, for the initial positive cortical deflection is an electrophysiological representation of the input from the optic radiation. Microelectrode recordings from this nucleus offered more direct support for this finding. Arden and Söderburg (1959) reported variations in the discharge rate of geniculate units which were related to the state of wakefulness, particularly episodes of arousal (rabbit, encephalé isolé). Recordings from unrestrained, chronic preparations also indicated modification of discharge patterns during arousal and sleep (Hubel 1960).

Additional direct evidence was obtained by Suzuki and Taira (1961) in recording the population response at the LGN to OT stimulation in the unanesthetized preparation. Single conditioning stimuli to the midbrain tegmentum enhanced the post-synaptic component of the geniculate response to OT shocks. Maximal amplitude enhancement occurred at CS-TS intervals of 100 msec., however, facilitatory effects at separations as long as 500 msec. and 1000 msec. were reported (Okuda 1962). Recordings from individual radiation fibers supported their findings, as reticular stimulation increased the probability of unit

responses to threshold electrical stimulation of optic tract.

These positive findings demanded a re-examination of reticular-sensory relations when the sensory receptor itself is stimulated. Steriade and Demetrescu (1960) examined flash-evoked geniculate responses in the encephalé isolé preparation. They noted amplitude enhancement at flash rates of 1/sec. during reticular activation. Although in this investigation pupillary diameter was not controlled, confirmation was obtained by Taira and Okuda (1962) with mydriatic pupils. The population response change (Flash - 0.5 sec., every 7-8 sec.) was more subtle, however, consisting of a sharpened wave form and reduced response variability ("response stabilization"). Similarly, radiation unit responses exhibited a reduction in variability of discharge rate to flashes during activation periods. More definitive evidence for enhanced unit responsiveness was reported by Ogawa (1963) and Hotta and Kameda (1964). The former demonstrated that conditioning stimuli to the RF enhanced the temporal resolution of geniculate unit discharge to intermittent flashes. Hotta and Kameda (1964) used high frequency RF stimulation and observed a lowering of unit

response threshold and an increase in discharge rate to flashes.

Visual cortex. The initial observations of cortical evoked response facilitation were made by Bremer and Stoupel (1958, 1959), Dumont and Dell (1958, 1960) and Long (1959) (vida supra). Recordings at the cellular level confirmed these findings (Creutzfeldt et al 1960). Unit responsiveness to optic nerve shocks was enhanced by both natural arousal (acoustic stimulation) and RF stimulation. Facilitation consisted of increased discharge rate, increased discharge probability, reduced response threshold, and shortened response latency.

The problem of flash-related effects was also investigated with the microelectrode technique. In general, waking was found to be accompanied by an increase in the ratio of evoked to spontaneous activity, although both facilitatory and inhibitory effects were demonstrated (Jung 1958; Evarts 1960; Akimoto et al 1961). Jung and co-workers (1958) identified convergence of primary sensory and "non-specific" influences on single cortical cells. Thus visual cortical units actually followed high frequency stimulation of intralaminar thalamic nuclei and flash evoked discharge was facilitated during

this period. Akimoto et al (1961) extended this observation to include arousal evoked by midbrain RF or peripheral nerve (sciatic) stimulation. Facilitation was the most common consequence in the form of increased rate and shortened latency.

More recently, Evarts (1963) studied unit responsiveness from visual cortex in chronic preparations during spontaneous variations of the sleep-wakefulness cycle. Waking was accompanied by enhanced responsiveness, as a significant number of units responded during waking that had failed to respond during sleep while the reverse was rare.

On the other hand, observations of alterations of the complex flash-evoked population response have been few and relatively unrewarding. Steriade and Demetrescu (1960) reported amplitude augmentation of the cortical response as a function of flash rate, i.e., facilitatory changes were observed at flash rates of 5/sec. and above, but not at lower rates. At rates below 5/sec., amplitude enhancement at LGN was observed (vide supra). The rate related enhancement of the cortical flash-evoked response was confirmed by Narikashvilli (1963), however, geniculate facilitation was not observed. In these studies the data were obtained from electroencephalograph

tracings and response details apart from gross amplitude changes could not be analysed. Akimoto et al (1961) was able to observe that the cortical evoked potential, although depressed in amplitude during arousal, appeared at a shorter latency (peak of the initial positive deflection).

It is clear that arousal enhances transmission in the primary visual pathway. Facilitation has been observed at both the lateral geniculate nucleus and visual cortex in response to electrical stimulation and photic stimulation. The purpose of this investigation was to determine the nature of the response change at each level of the primary visual pathway and the interrelation of activity at these levels during repetitive photic stimulation and alterations in reticular activation. Average response analysis (CAT) provided reliable response definition at four levels--VC, OR-LGN, OT and ERG in acute unanesthetized preparations, and at the VC alone in chronic freely-moving preparations.

II. RESULTS

Optic Radiation - Lateral Geniculate Nucleus

Electrode localization. The dorsal portion of the lateral geniculate nucleus (LGN) is an S shaped structure in parasagittal section. It contains three cellular layers (A, A_1 and B of Thuma 1928) of which the outer two (A and B) receive optic tract (OT) fibers from the contralateral eye and the middle layer (A_1), homolateral fibers. Optic tract fibers enter the ventral and posterior aspects of the S and the optic radiation fibers (OR) leave at the anterior and dorsal surfaces.

In order to study the effect of midbrain tegmental stimulation on LGN transmission, it was necessary to place the recording electrode at a location optimal for recording the output of the nucleus. This region must be readily identifiable by electrophysiologic techniques. The optic radiation at its exit points from the LGN fulfilled these requirements and was selected as the recording site.

The optic tract electrode was first placed (see Chapter II) and then the OR electrode lowered through the surface of the suprasylvian gyrus at Horsley-Clarke

coordinates Fr 7, L 9. The dorsal and/or anterior border(s) of the LGN were located by identifying alterations in the population response to homolateral OT stimulation while the OR electrode was lowered in .1 mm steps. The alterations in form of the response described by Bishop and O'Leary (1942) and Bishop and McLeod (1954) were useful guides. In the radiation, low amplitude and/or mainly positive potentials were recorded (Figures 21, 22). As the LGN border was crossed the potentials increased in amplitude and became mainly negative in sign (Figure 21). Supplementally, identification of the border between LGN and OR (LGN/OR) was aided by recording the response to photic stimuli. When the border was crossed the background spike activity heard on the speaker became more intense and the spikes were of longer duration. Visualization of the response to flash was occasionally helpful. In Figure 22, responses to OT stimulation and to photic stimulation are illustrated for one experiment. A portion of the electrode tract and the lesion at the recording area can be seen in this coronal section taken at the rostral tip of the LGN. When the electrode entered the body of the nucleus the population response to flash reversed in polarity and unit activity increased (Figure 22, photic stim. -3).

The responses to OT stimulation increased in amplitude but reversal of sign was not observed. (The photic and electrical stimuli were actually not equivalent since the contralateral flash excited only fibers which crossed at the optic chiasm and the optic tract shock excited the entire input of the right LGN in a proportion dependent upon the electrode placement).

In all experiments the electrode location was identified histologically. From these sections the area recorded from during the experiment was located and designated as either optic radiation (OR), lateral geniculate nucleus (LGN), or border (LGN/OR). The approach to the nucleus from its dorso-anterior aspect offered the least chance for recording directly from the optic tract. The electrode locations in two additional experiments (Figure 23, upper) illustrate two LGN/OR placements, one in coronal section (upper left) and the other in sagittal section (upper right).

Response form. In different preparations a variety of responses were recorded. Several factors were responsible for this variation and of these the most significant were the size of the exposed tip, and presumably the amount of tissue damage at the tip, and electrode location. On the

other hand constant features of the response to flash could also be described: (1) an initial positive deflection, (2) a long duration, slow, negative deflection, (3) multiple rapid waves at frequencies of about 100/sec. Flash related components were reliably identified at latencies of 150 msec. and occasionally at 250 msec. Forms of the response in four preparations are illustrated in Figures 24, 25, 27, 28. Multiple deflections were prominent in the records illustrated in Figures 24 and 27. Despite the polarity reversal observed at the LGN/OR (border) in Figure 22, it was impossible to classify the responses of the experimental group on the basis of electrode location.

Repetitive stimulation. In twenty-two acute experiments a minimum of 300 repetitive flash series at flash frequencies of 1/10 sec. to 5/sec., and of 1-30 minute series duration were administered. No significant reduction of the amplitude of the response during a series was noted when stimulation and recording conditions were constant. The response was constant from the beginning to the end of a series except when 100/sec. deflections (oscillations) were recorded. Oscillations were recorded, therefore, both at OR-LGN

and OT sites and the oscillations at the two levels (OT and OR-LGN) evolved in parallel (see Chapter III for the evolution of the OT oscillations).

Stimulation of the reticular formation. Responses along the primary visual pathway were examined during and after stimulation of the reticular formation only when definite signs of the effectiveness of the stimulus were recognized. A complete response to RF stim. consisted of the following: (1) A prompt onset of low voltage fast activity in the background electrocorticogram (ECoG) which outlasted the period of stimulation. (2) Dilatation of the non-atropinized pupil. (3) Retraction of the nictitating membrane. (4) An increase in the level of background spike discharges recorded from the LGN-OR electrode. (2), (3), and (4) reliably occurred at a lower threshold than (1). Often when only (2) and (3) were produced, a small change in electrode position without any change in stimulus intensity was followed by arousal of the electrocorticogram.

Alterations of the responses recorded from the optic tract and cornea (ERG) were never observed to occur during and/or following tegmental stimulation. This consistency allowed these responses to serve as a partial

control of peripheral illumination factors. Optic tract amplitude and latency were far more sensitive to alterations in peripheral illumination than was b wave amplitude of the ERG.[2]

Changes related to tegmental stimulation did occur at the geniculate relay-radiation level. However, every stimulation period did not result in response alterations even when all other signs of stimulus effectiveness were observed (vide supra). In general, effects at this level were more difficult to produce than at the cortex. In all cases the changes observed could be described as facilitatory. The most frequently observed changes were the augmentation in amplitude of the long duration negative deflection and an increase in amplitude and number of the oscillatory components.

In the majority of cases responses were studied before and after the period of tegmental stimulation. (A procedure which in one sense raised the threshold for response change by requiring that changes be present in the period after stimulation). An increased amplitude of the slow negative component is illustrated in Figure 24.

2. B wave amplitude is linearly related to log intensity of illumination and therefore small changes in illumination would not be measurable in the electroretinogram (Rushton 1962).

The first averaged response following the stimulation period exhibited the amplitude change in the negative deflection at a peak latency of 65 msec. An increase in the amplitude of the initial positive component (Latency about 18 msec.) also occurred. These alterations were still clearly present 30 sec. after stimulation (#5, although not as obviously in #4). In this series the stimulation did not alter the background electrocorticogram, i.e. the slow, high-amplitude resting activity did not convert to a pattern of low voltage fast activity. The recording electrode was located on the border (LGN/OR). (See histological section in Figure 23, upper left, right LGN).

In another preparation RF stim. (13 sec.) produced ECoG arousal visible for 30 sec. post-stimulation (Figure 26). The response recorded from LGN/OR (histological section of Figure 21) underwent an increase in the amplitude of the initial positive deflection (latency 25 msec.) and of a later sharp negative deflection (latency about 45 msec.) (Figure 25). Facilitatory effects were still observed 30 sec. (#5) after the end of the stimulation period.

Occasionally, more striking effects were observed (Figures 27, 28). In Figure 27, the OR response consisted of an initial positive deflection (peak latency about 25 msec.) followed by a series of rapid pos.-neg. deflections (interpeak period about 10 msec.) or oscillations. The first average following RF stim. (15 sec. duration) exhibited a facilitation characterized by an increase in the amplitude of the initial deflections and the sudden appearance of longer latency deflections. In addition, a marked increase in the amplitude of a long latency slow negative deflection was observed in the next average (#5). In average #7 the late rapid deflections were no longer visible and in #8 the slow negative wave had diminished considerably. In this trial the ECoG exhibited "spindle blocking," with return of spindles by average #5.

Rarely (2 preparations) definite shifts in latency were noted (Figure 28).[3] Following the RF stim. (15 sec. duration) the initial components (latency 35-37 msec.) of the LGN evoked response increased in amplitude and underwent a latency shift of 4-5 msec. (#2). In #4 the

3. The long latency of the response is related to the lower flash intensity in this experiment (with tungsten bulb).

response had returned to its pre-stimulus condition. In this trial evidence of arousal was not present in the ECoG. However, during and following the period of RF stim., a marked increase in background spike discharge was heard at the LGN electrode.

Visual Cortex - Acute Experiments

Response form. The cortical evoked responses were monopolarly recorded from gyrus lateralis within the area striata (as defined by Otsuka and Hassler 1962). In all experiments the electrode location was the same as that which yielded optimal evoked responses to electrical stimulation of the optic tract. As the gyrus lateralis was not explored for the optimal response to photic stimulation or even for uniform responses between preparations, a great variety of responses were seen. In addition, the form of the response altered with both the frequency and intensity of stimulation. Therefore, a definitive response form cannot be presented but certain frequently observed features will be enumerated.

The evoked response to a monocular flash usually began with a pos.-neg. deflection at a latency of 18-40 msec. This initial response was then followed by one, several

or many additional deflections. In Figure 24, a simple pos.-neg. deflection is illustrated, while in another preparation the initial response was followed by 3-4 additional deflections within the first 125 msec. after the flash (Figure 25). This afterdischarge was sometimes further developed as 8-10 deflections within the first 250 msec. after the flash (Figure 32). Rarely, a remarkably well developed long duration (500 msec. to 1 sec. or longer) repetitive afterdischarge was observed (Figure 29). Low amplitude rapid deflections at high frequencies were sometimes seen superimposed on the larger deflections as in Figure 37 (B, 1) at 90-100/sec. or in Figure 39 (9, 10) at 40-50/sec.

Repetitive stimulation. The averaged response, once identified in each preparation for a particular set of experimental conditions, varied little throughout the experiment. Major response components of the initial 250 msec. following the stimulus did not decrease in amplitude or disappear during the repetitive series.

A striking alteration was seen with the very first few stimuli in some experiments (4 preparations). This change concerned a long duration rapid afterdischarge which disappeared during the repetitive series (for

this reason these events were not observed in the average response records but were detected only on the film records of the individual responses). This afterdischarge was not related to stimulus frequency as it was present at different frequencies. In Figure 29 the afterdischarge is illustrated in one preparation at both 1/sec. and 5/sec. flash rates. At 1/sec. a high amplitude rhythmic response followed the first stimulus and was prominent at 200-800 msec. Although afterdischarges were present to the second and third stimulus they were not nearly as rhythmic nor as prominent. At 5/sec. the rhythmic response was marked in responses #2-11. At both frequencies the presence of the cortical rhythmic afterdischarge paralleled the appearance of oscillations in the OT and OR. These later oscillations were at a frequency of about 100/sec. In the cortical response, rhythmic activity at this frequency could be identified as well as components at slower frequencies (particularly at about 50/sec.). The diminution of the cortical rhythmic response occurred simultaneously at both frequencies with loss of the oscillations at OT and OR (i.e., note at 5/sec. that after the eleventh response a decrease in late rhythmic activity occurred simultaneously at VC,

OR, and OT). However, this parallel behavior at subcortical and cortical sites was not as clearcut in all preparations. In Figure 30, part of a 1/sec. series is illustrated. The cortical response consisted of 3-5 repetitive pos.-neg. deflections at intervals of 50-100 msec. Yet striking oscillatory activity present at OT and OR did not appear to be reflected in the cortical response.

Stimulation of the reticular formation. Analysis at the cortical level was identical to that described for the OR-LGN response. For the cortical response it was particularly important to identify stable pre-arousal response patterns with which later responses were compared.

Alterations of the response, interpreted as facilitatory, were observed. When fully developed the most reliable change was a "sharpening" of the short latency deflections and a shortening of latency. The sharpening was further identified as a decrease in the rise time (or faster rate of change) to the peak and a decrease in the peak-to-peak duration. This also contributed to the shorter peak latencies. Arousal related changes of this type are illustrated in Figure 31. Following a 10 sec. period of RF stim., a marked alteration of the cortical response occurred (Figure 31, #5), and

in the ECoG record from visual cortex low voltage fast activity had replaced slower higher amplitude waves. The initial positive deflection, although of lower amplitude, appeared at a latency 3-4 msec. shorter than in the previous responses. The ascending slope of the negative deflection had a steeper rate of rise and fall, which resulted in a sharper peak and decreased duration of the deflection. The waves which followed were more prominent and of sharper definition than in the pre-arousal responses. In #6-11, the response tended to assume its pre-RF stim. form. However, response alterations were still present despite the return of the ECoG to slow wave activity. In these preparations amplitude changes of the initial components of the evoked responses were usually not reliable indicators of facilitation as amplitude decreases were more often observed. Amplitude diminutions occurred more often at flash rates below 5/sec. Facilitatory changes were usually more prominent at higher stimulus rates but were also observed at all flash rates (e.g., Figure 25 at 2/sec. is from the same preparation as Figure 31 at 5/sec.).

In addition to alterations of the initial deflections facilitation of the afterdischarge occurred. In Figure 32,

the first averaged response to follow RF stim. (#5) demonstrated a marked enhancement of the repetitive discharge at a 125-250 msec. latency. The frequency of the after-discharge was about 40/sec. These effects also outlasted the period of ECoG change. Note, however, that oscillations at 100/sec. in OT were at the same latency as the cortical afterdischarge and were prominent in responses #4-11. There was also, in OT, a later rhythmic discharge beginning at 350 msec. at a frequency of approximately 40/sec. This component was prominent in #5-11 and a corresponding low amplitude rhythmicity at this frequency could also be seen in the cortical response.

Relation to response changes at OR-LGN. The after-discharge just described was related to the late oscillations at subcortical levels of the primary visual pathway. However, in Figure 33, a striking enhancement of the cortical afterdischarge had no correlate at either OR or OT. The facilitation observed in #3 receded in #4-6, whereas the late oscillations of the optic tract were enhanced in responses #1-4 but were unchanged in #4-6 (in this preparation the late oscillations were not seen at the LGN/OR electrode).

Regarding the initial deflections of the evoked response, facilitatory changes were observed simultaneously at OR and cortical levels (Figure 25). A sharpening and faster rise time (#3) accompanied the appearance of low voltage fast activity in the electrocorticogram from visual cortex. At the OR a facilitatory change in the form of increased amplitude (vide supra) was seen. These alterations at both levels were clearly related to the period of RF stim. However, on the basis of this experiment we cannot implicate the OR facilitation as causally related to the VC change. In support of this analysis is the finding that cortical facilitation was observed independent of changes at the subcortical stations (Figure 34). In this experiment, RF stim. was followed by spindle blocking in the ECoG. The amplitude of the negative deflection of the cortical evoked response decreased (#3), the initial positive deflection increased and a 5 msec. shortening of latency occurred. Recovery to the pre-activation response was observed in averages #4-6, accompanying the return of spindle activity. However, no alteration in the response at LGN occurred.

On the other hand, subcortical responses showed signs of facilitation without any concomitant effects in the

cortical responses (Figure 27). The striking alterations at the geniculate level have already been described (Vide supra) but the cortical response was only characterized by a decrease in amplitude. Again, in the experiment of Figure 24, the amplitude increase at the LGN/OR was correlated with a slight amplitude decrease at the cortex (#3, 4). In these experiments the RF stim. did not alter the background ECoG at the visual cortex, i.e., there were no signs of arousal. It was clear, then, that facilitatory effects at the cortical level were most readily observed when a definite change in the ECoG resulted from the RF stim. This was optimally a conversion from spindling and high amplitude slow activity to a low voltage fast pattern, although spindle blocking by itself was accompanied by cortical response facilitation (Figure 34). In Figure 28, therefore, latency shifts occurred simultaneously at both cortex and LGN despite the absence of any cortical sign of arousal. The shifts were strictly parallel and evolution to the pre-stimulation form was simultaneous. It must be concluded here that the primary shift was at the geniculate and the change was transmitted to the cortex.

Similarly, a few preparations had a "resting" record of low voltage fast activity.[4] Stimulation of the R.F. produced additional flattening and increased frequency but never resulted in facilitation of the cortical evoked response. In some experiments small quantities of thiopental (Pentothal) were administered i.v. in order to convert this low voltage fast pattern to a sleep record. This manoeuver was unexpectedly rewarding and an experiment is illustrated in Figure 35, A and B, and 36. Following the rapid i.v. injection (Pentothal 5 mg/kg), the surface activity became slower and of higher amplitude (suprasylvian gyrus, Figure 36, #4). Changes in the evoked responses occurred at all levels. When the ERG had adequately regained its pre-Pentothal amplitude, the reticular formation was stimulated for 10 sec. Here, then, about 70 sec. after the injection, while the animal still exhibited Pentothal effects, a striking enhancement of the cortical evoked response was produced. The response recorded during the RF stim. (Figure 35, A #10) underwent a 40% increase in amplitude of the initial positive deflection and corresponding enhancement of the succeeding

4. This condition could not be differentiated from fast wave sleep since the animal was curarized.

negative wave. The deflection was shorter in duration and the peak sharper at a slightly shorter latency. This change was clearly independent of all events which were recorded at subcortical levels (progressive alterations at the OR were related to recovery from Pentothal). However, this cortical facilitation was not associated with any observable change in the ECoG. At these stimulus parameters "arousal" was still prevented by the residual effects of Pentothal.

In order to insure that this striking effect was not artificial, an identical period of RF stim. was repeated 70 sec. later (B, #18). Recovery from Pentothal had proceeded further and a distinct alteration in the ECoG occurred in the form of photic "driving." Facilitatory changes similar to those which followed the first RF stim. occurred, again unaccompanied by subcortical enhancement.

In sum, this experiment provided additional evidence related to two distinct problems: (1) the separation of facilitatory influences on cortex and LGN-OR, (2) the occurrence of cortical facilitation without ECoG arousal.

Circulatory factors. When during these experiments systemic blood pressure (femoral artery) was monitored, hypertensive changes were observed to follow RF stim.

Also, the rapid i.v. injection of Pentothal produced a hypotensive phase immediately after the dose was given. These observations led us to question if the facilitatory effects of RF stim. were not actually a result of circulatory changes. The response enhancement would result from a sudden increase in the local supply of metabolites to the neural tissue.

In order to further investigate this question a group of preparations were studied while monitoring femoral artery pressure (6 cats) and cortical temperature (2 cats). The thermocouple probe was placed on the surface of gyrus lateralis, 1 mm distant from the surface electrodes. Figure 37 illustrates the association of alterations in systemic blood pressure with average responses of the visual cortex. Intravenous Pentothal produced a depression of the evoked responses along the entire primary visual pathway (Figure 37, A). (Effect was maximal at 30 sec., as cortical latency was prolonged 5 msec.). The ERG recovery was essentially complete at 60 sec. (#3 post-injection). At this time RF stim. resulted in facilitation of the cortical evoked response (shortened latency). A second episode of RF stim., 60 sec. later, also was facilitatory (decrease in rise

time, increase in amplitude of initial positive deflection). The blood pressure underwent a minimal decrease following Pentothal but had recovered by the time of the first RF stim. Both periods of RF stim. were accompanied by sharp increases in systolic pressure (#3, 110-170; #8, 90-200).

However, a rise in pressure per se was not a sufficient condition for evoked response facilitation (Figure 37, B). The experiment illustrated in B was performed three hours later in the same preparation. Conditions were identical except that the hypertensive episode was induced by a small i.v. dose of adrenaline hydrochloride (30 micrograms) 60 sec. after the Pentothal injection. The adrenaline did not produce evidence of arousal, no change in ECoG, but was followed by a steep rise in systemic pressure (80-200). Evoked response facilitation did not accompany this hypertensive episode.

That adrenaline induced hypertension was accompanied by cortical temperature change is illustrated in Figure 38. Here, the i.v. injection of adrenaline (50 micrograms), in another preparation, was followed by a sharp 80 mm rise in systolic pressure (140-220). Cortical temperature began its ascent within 10 sec., climbed at a much slower

rate and reached a total elevation of 0.6° - 0.7°C. Again, there was no arousal, only circulatory changes which were not paralleled by evoked response enhancement. However, RF stim. (#6) at the peak of the cortical temperature rise and pressure elevation still produced some evidence of response facilitation. Associated with the onset of low voltage fast activity in the ECoG was the shorter rise time and increased amplitude of the initial positive deflection.

The increase in cortical temperature was related to the systemic hypertension as a passive dilatation of cerebral vessels in response to the increased head of pressure. However, RF stim. produces cortical temperature elevations which do not result from passive changes but are due to direct effects on local cerebral vessels associated with the increased tissue metabolism (Ingvar 1958). Active dilatation can also be produced by hypercapnia. Carbon dioxide inhalation experiments were performed in two preparations. In one, (not illustrated) facilitation of the cortical evoked response in the form of an amplitude increase of the initial pos. and neg. deflections did occur. It was transient and was not accompanied by arousal. A depression of

response amplitude followed. In the second preparation, inhalation of a mixture of 20% CO_2, 20% O_2, and 60% N for 70 sec. produced a 25% decrease in response amplitude (Figure 39, peak effect, #6, 75 sec. after start of inhalation). There was a moderate blood pressure rise (30 mm, 130-160) and a large increase in temperature (.65°C). When these circulatory effects were still near peak, RF stim. produced ECoG arousal and response enhancement in the form of facilitation of the late afterdischarge (#9, 10).

Visual Cortex - Chronic Experiments

Corroborative findings were obtained in a separate group of experiments performed on cats with implanted electrodes. Only the evoked response from the visual cortex was recorded.

Repetitive stimulation. Periods of repetitive stimulation varied from two to nine hours. Stimuli at intensities of 20 - 40 mL and at frequencies of 1/sec. and 1/4 sec. were employed. A significant and progressive diminution in amplitude or disappearance of the evoked potential, early and late components, was not observed under these conditions (Figure 40). This was true for

all frequencies and intensities of stimulation.

It was also consistently noted that the averaged evoked potential continuously evolved in form and that successive averages in time were more alike than averages which were temporally further apart. This is illustrated in Figure 40 (compare responses at 2-5; 23-24; 30 and 31).

Changes during spontaneous variations in level of arousal. An attempt was then made to compare the amplitude and latency alterations with the changes in the arousal state of the animal as monitored in the ECoG. Arbitrarily, as a measure of the depth of sleep, the frequency of appearance of sleep spindles was employed.[5] In the typical experiment, the animal would show an ECoG sleep picture (spindles and slow waves) within 10 sec. after being placed in the testing room and would remain asleep for 80-90% of the trial.

The amplitudes of the major slow deflections of a typical response (Figure 41, deflections α, β, γ) were positively correlated with the SI. The amplitude of the early diphasic multiple deflections, exclusive of the very

5. The interval of time occupied by the responses in each average was quite long (200 sec. for stimuli at 1/4 sec.), and it was possible to count the number of distinct spindles (minimum duration 0.5 sec.) occurring during this period. This figure was converted to a per cent and a "spindle index" (SI) was obtained.

first deflection, showed a suggestive positive correlation with SI, valid for both positive and negative peaks except when adjacent peaks fluctuated reciprocally.

The latency of the initial deflection increased during higher levels of spindling and decreased during lower levels. These changes were statistically significant only when a sufficiently wide variation in the SI occurred during an experiment (Figure 42).

Changes during induced arousal. Evoked potentials recorded during well defined periods of spindle and slow activity were compared with those recorded during well defined periods of low voltage fast activity produced by intentionally arousing the animal (presentation of auditory stimuli or opening the door of the experimental room). Frequencies of photic stimulation at 1/2 sec. and 5/sec. were used. The number of evoked potentials forming an average was dependent on the duration of the arousal period. With this procedure the above observations were confirmed. An abrupt alteration of the evoked response characterized by shortening of the latency and decrease in duration of the deflections occurred during the arousal period (Figures 43 and 44). The response gradually

returned to its resting form in the period which followed. The initial positive deflection was observed to increase in amplitude in some experiments and to decrease in others (Figure 44). The facilitatory effects were present at both slow (Figure 44) and rapid repetitive frequencies (Figure 43).

Simultaneous Effects at Four Levels of the Primary Visual Pathway - Intravenous Pentothal

The value of simultaneously recording responses from multiple levels of the visual pathway was also demonstrated in the Pentothal experiments. Intravenous injection was followed by alterations in the electrical activity at each level (Figures 35, 36). Figure 36 illustrates the continuous record of spontaneous activity. The ERG was markedly flattened and the b wave disappeared (#4-8). At the same time a severe reduction in amplitude of the OT response was observed while high amplitude slow activity appeared in the OR. The surface activity of the visual cortex decreased in amplitude.

Analysis of the averaged evoked responses corroborates the observation of effects at all levels (Figure 35, A and B). The OT response was not only depressed in amplitude

but increased in latency. The superimposed oscillatory deflections disappeared (Figure 35, A, #4-10). Note in the ERG that the flattened b wave was visible at a long latency (#5-8). Similarly, OR depression was indicated by the diminished amplitude of the initial positive deflection and the multiple deflections, and a prolonged latency (#4-9). The high amplitude slow wave observed in the ECoG was present in the evoked response as an enormous slow negative, long duration deflection. This event was not observed in the cortical response. Here, depression of the afterdischarge, diminution in amplitude, and increase in latency were the changes observed.

Examination of the recovery phase also revealed similarities and differences at the different recording areas. The b wave of the ERG which had been so markedly depressed was equally notable for its rapid recovery of both amplitude and latency (Figure 35, A, #9). At this time equivalent recovery had not occurred at any other level. Return of the oscillatory deflection of the OT was directly paralleled by the appearance of multiple deflections in the OR response (#6-12). Cortical recovery also paralleled the recovery of these lower centers (#6-9) but was interfered with (accelerated) by RF stim.

At the point when recording was terminated (Figure 35, B, #24) all responses had practically assumed their pre-injection form (#1). This was especially true of the ERG and cortical response.

Figures 21-44

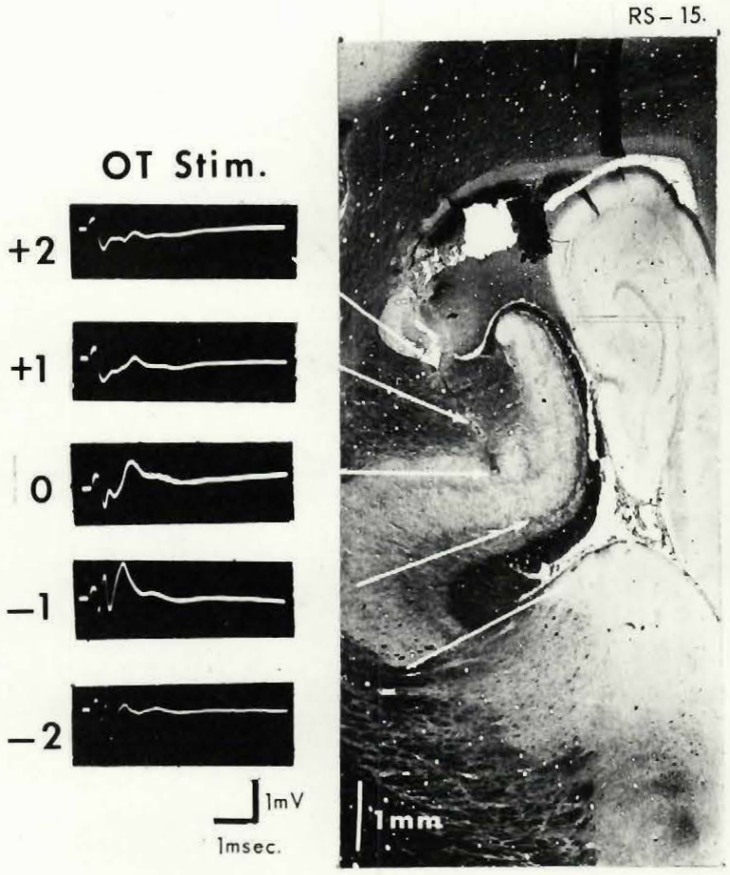


Fig. 21

Evoked responses to OT shocks recorded from the LGN-OR region in one preparation. Parasagittal section through right LGN with electrode tract and lesion at recording site near LGN/OR (border). Evoked responses consist of 10 superimposed responses to suprathreshold shock, right OT, 0.2 msec. duration. Responses at the recording site (0) and at 1 mm steps, above and below, are shown (arrows).

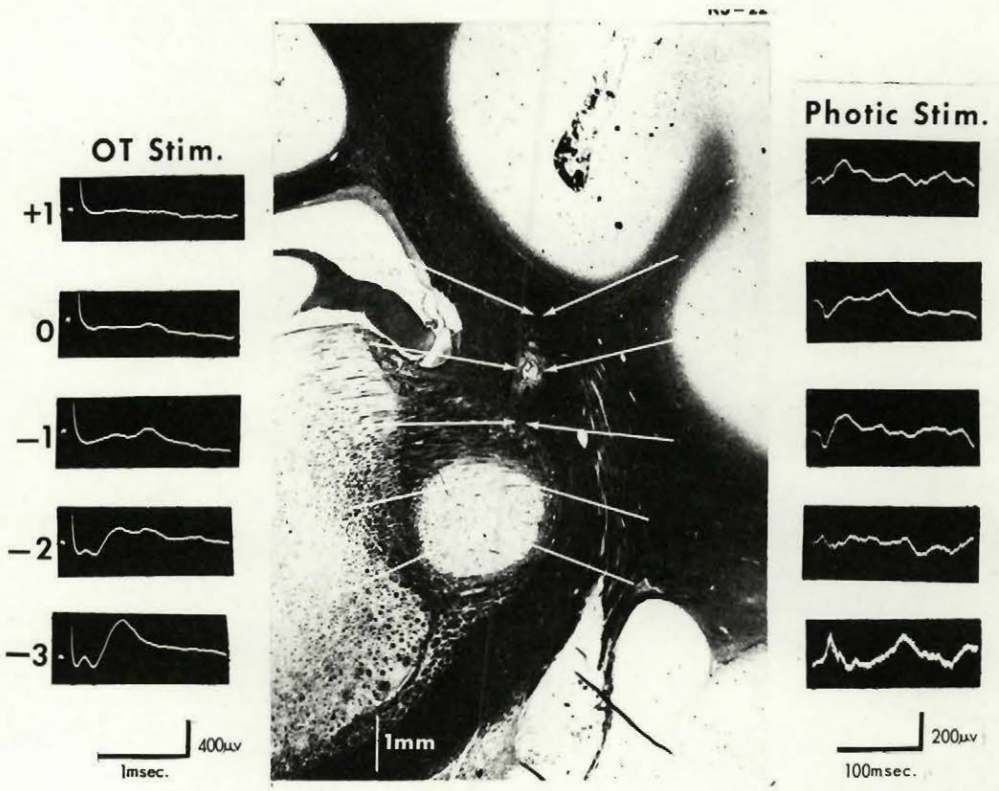
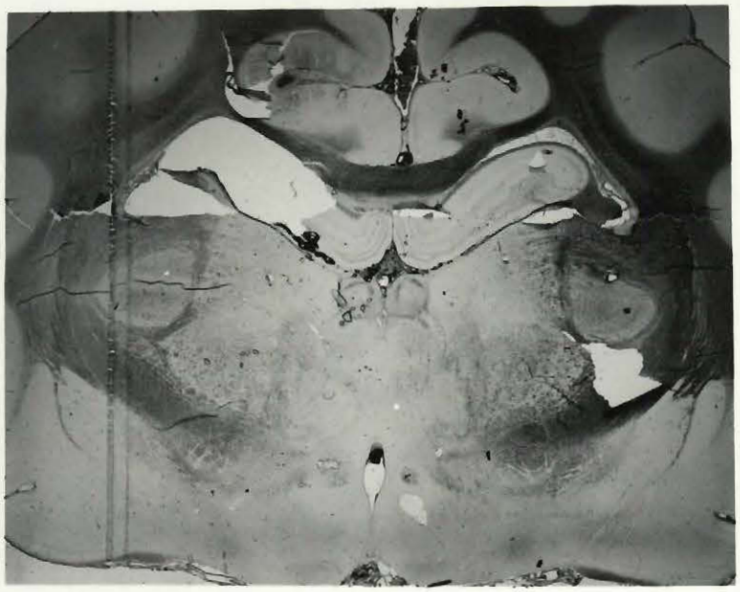


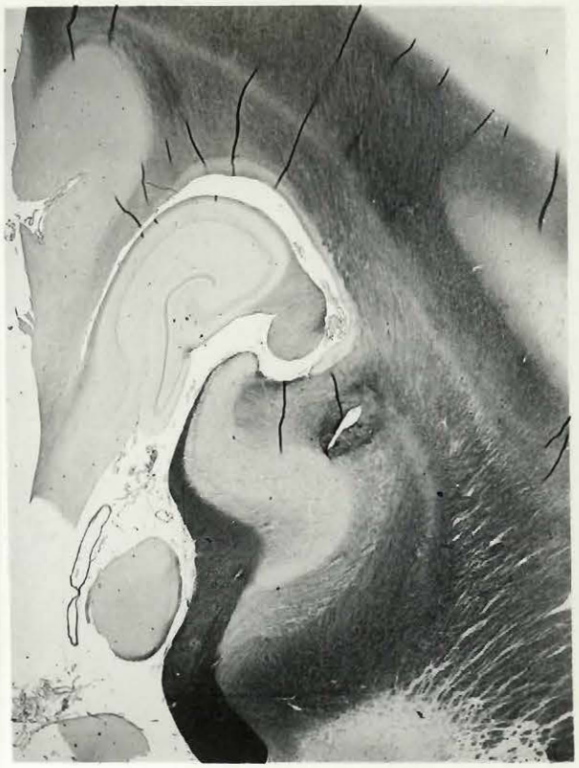
Fig. 22

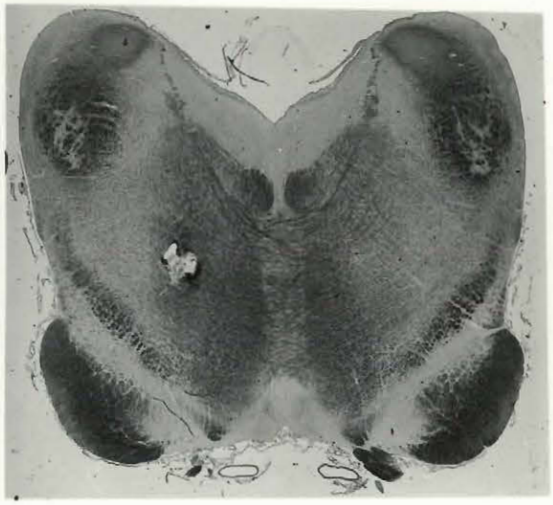
Evoked responses to OT shocks and to flashes (left eye) recorded from LGN-OR region in one preparation. Coronal section through rostral tip of right LGN with a portion of the electrode tract and lesion at recording site in OR. Single evoked responses to suprathreshold right OT shocks, 0.2 msec. duration, and to flash illumination of left eye are shown for the recording site (0) and at 1 mm steps above and below (arrows). The flash was administered at the onset of each sweep.

Fig. 23 (cont'd).

Lower Left: Coronal section through midbrain. Lesion at stimulation site in left RF.
Lower Right: Coronal section through right OT. Lesion at recording site near the midline in right OT (faint).
Magnification: Upper left X 3.5, all others X 6.







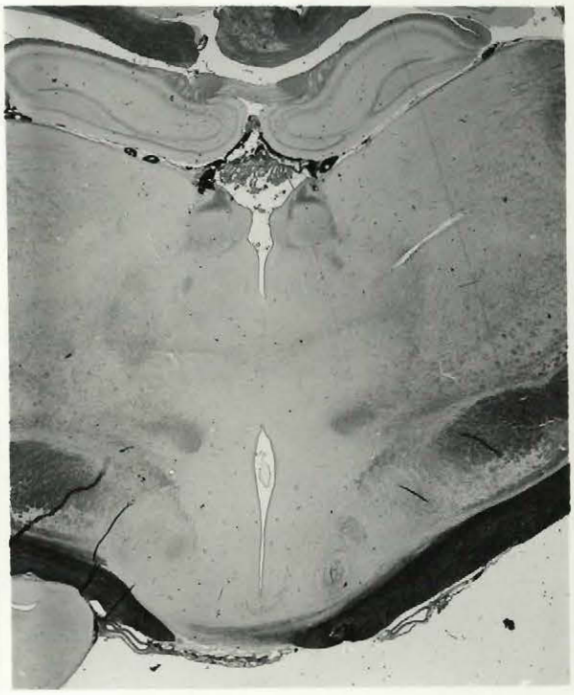


Fig. 23

Histological Sections.

Upper Left: Coronal section through rostral portion of right LGN. Lesion at recording site, LGN/OR (border).

Upper Right: Sagittal section through right LGN. Lesion in OR and at LGN/OR (border).

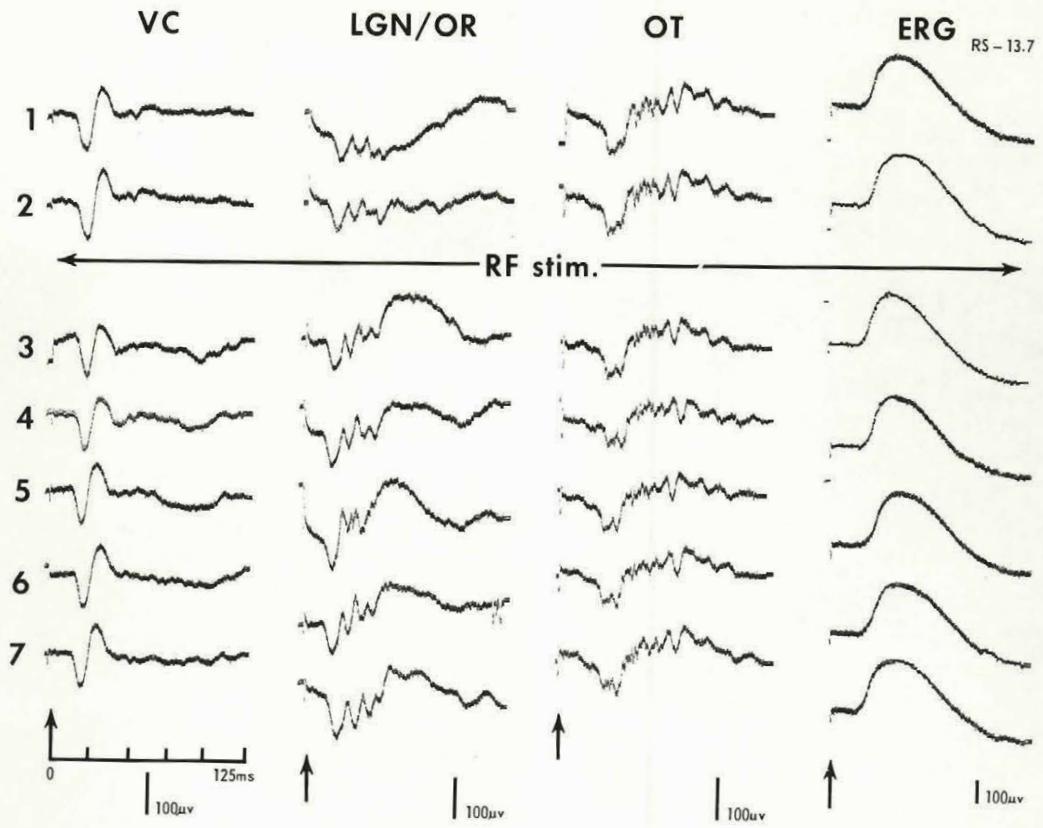


Fig. 24

Consecutive averaged responses before (1-2) and after (3-7) RF stimulation. Each average has been computed from 20 individual responses (N-20) at an analysis time of 125 msec. The RF was stimulated with a train of pulses at 150/sec., .2 msec., 6V, for 10 sec. Photic stimulation consisted of 10 microsec. flashes at 2/sec. to the left eye. Recording in this and all subsequent figures was from the right side at all levels except for the left ERG. The flash occurred at the onset of each trace (arrows). Deflection in this and all subsequent figures was negative up at the active electrode for all responses except ERG, which was positive up.

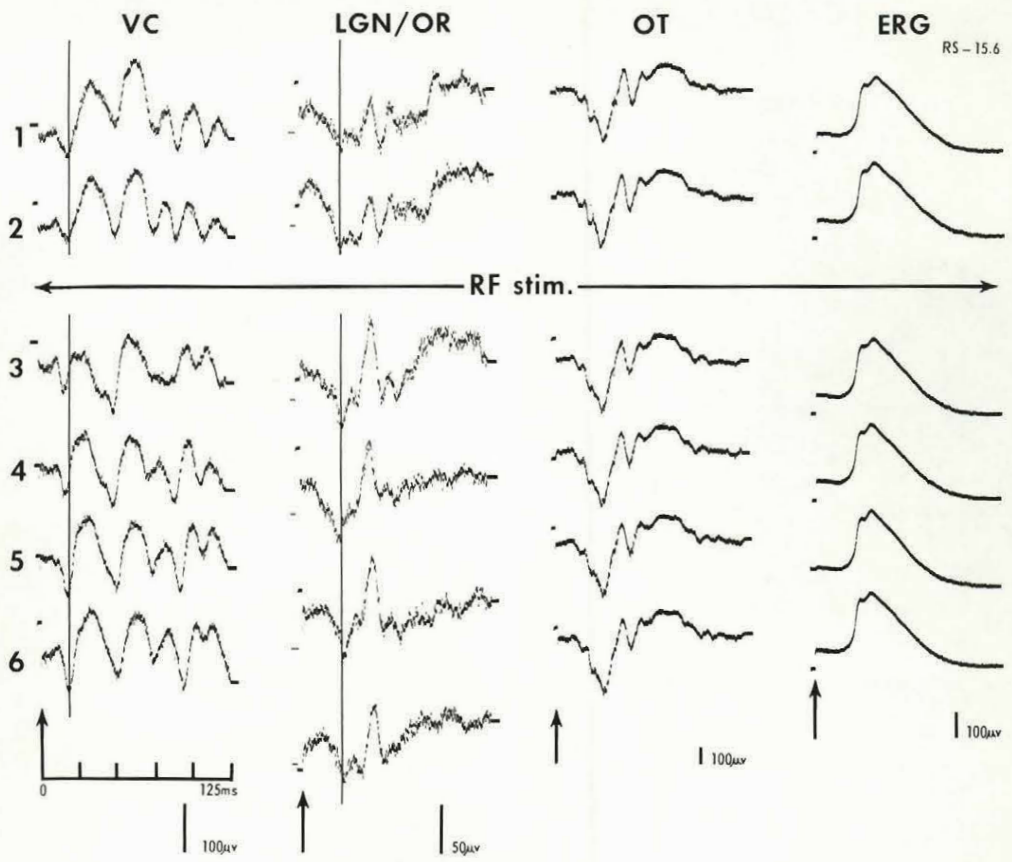


Fig. 25

Consecutive averaged responses before (1-2) and after (3-6) RF stim., N-20, analysis time 125 msec. RF stim: 150/sec., 1 msec., 6V, 13 sec. Photic stim.: 10 microsec., 2/sec. (See Fig. 26 for ECoG and photographs of the pupil).

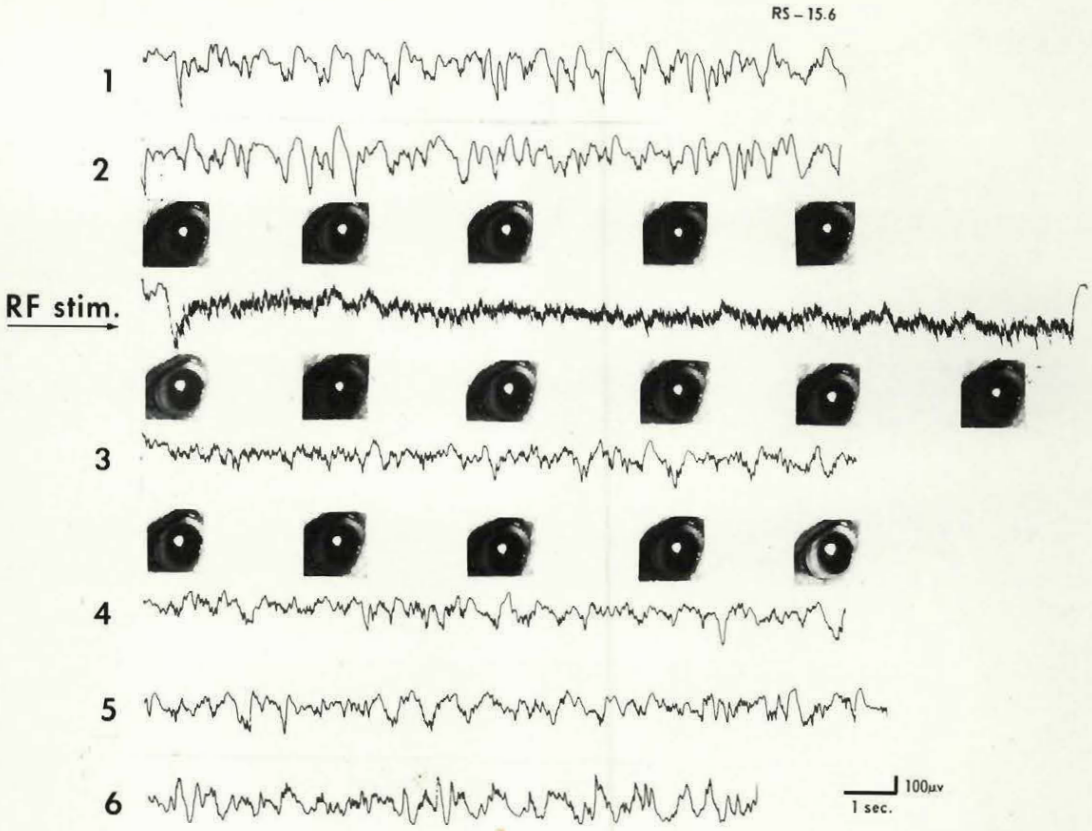


Fig. 26

Electrocorticogram of visual cortex and pupil photographs, before (2), during and after (3) RF stim. The pupil was photographed under infrared illumination at 1 frame/sec. Every other frame (1/2 sec.) is shown. (The image reflected on the pupil was from the infrared beam and not the flash stimulus).

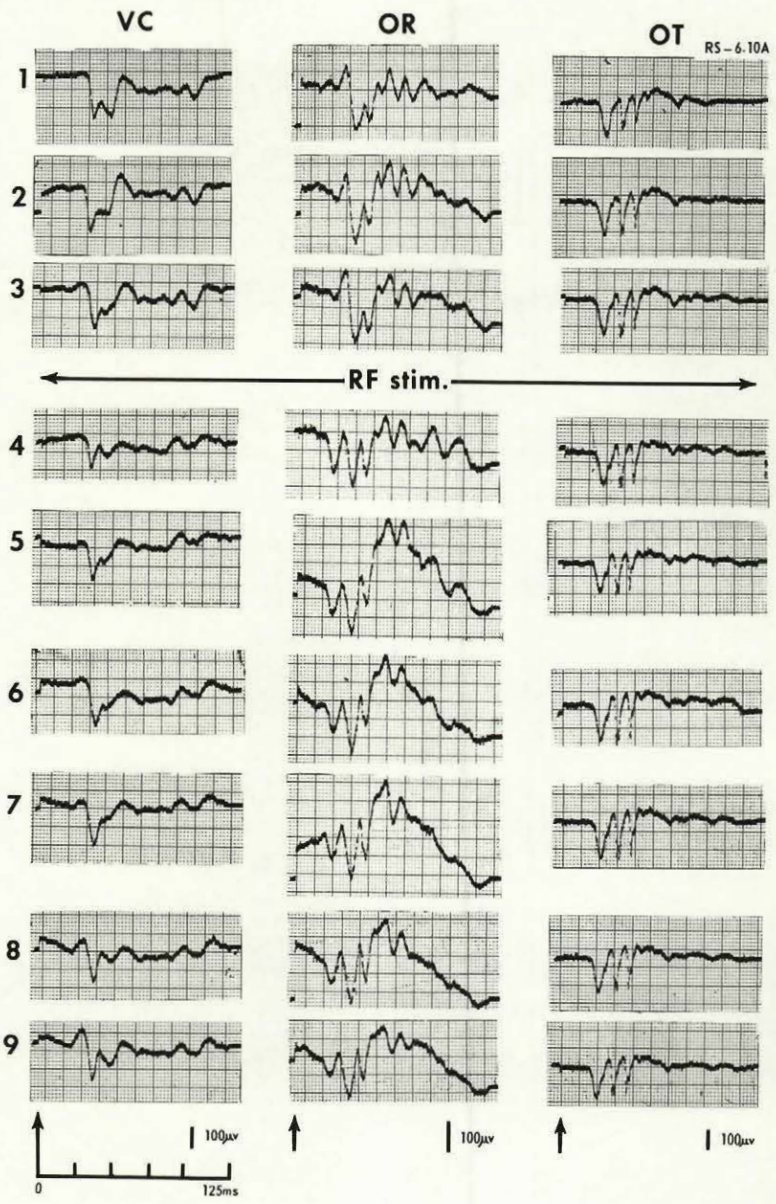


Fig. 27

Consecutive averaged responses before (1-3) and after (4-9) RF stim., N-20, analysis time 125 msec. RF stim.: 150/sec., .2 msec., 8V, 15 sec. Photic stim.: Contact occluder, 10 msec. flash, 40 mL peak intensity, 2/sec.

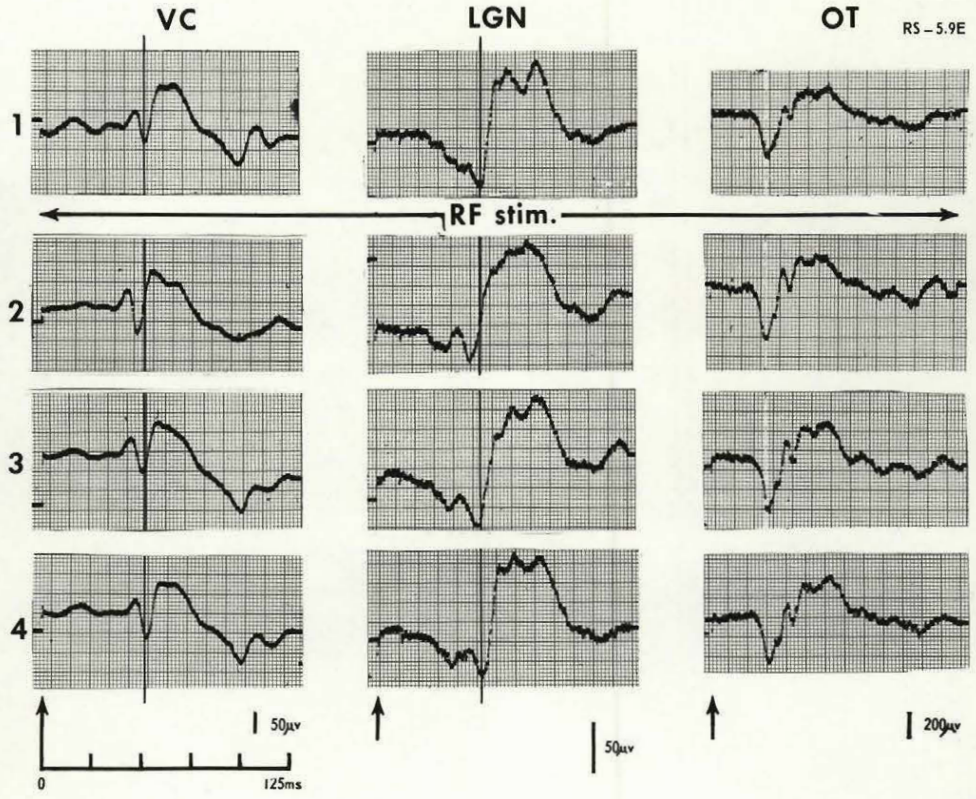


Fig. 28

Consecutive averaged responses before (1) and after (2-4) RF stim., N-50, analysis time 125 msec. RF stim.: 150/sec., .1 msec., 6V, 15 sec. Photic stim.: Contact occluder, 10 msec. flash, 35 mL, 5/sec.

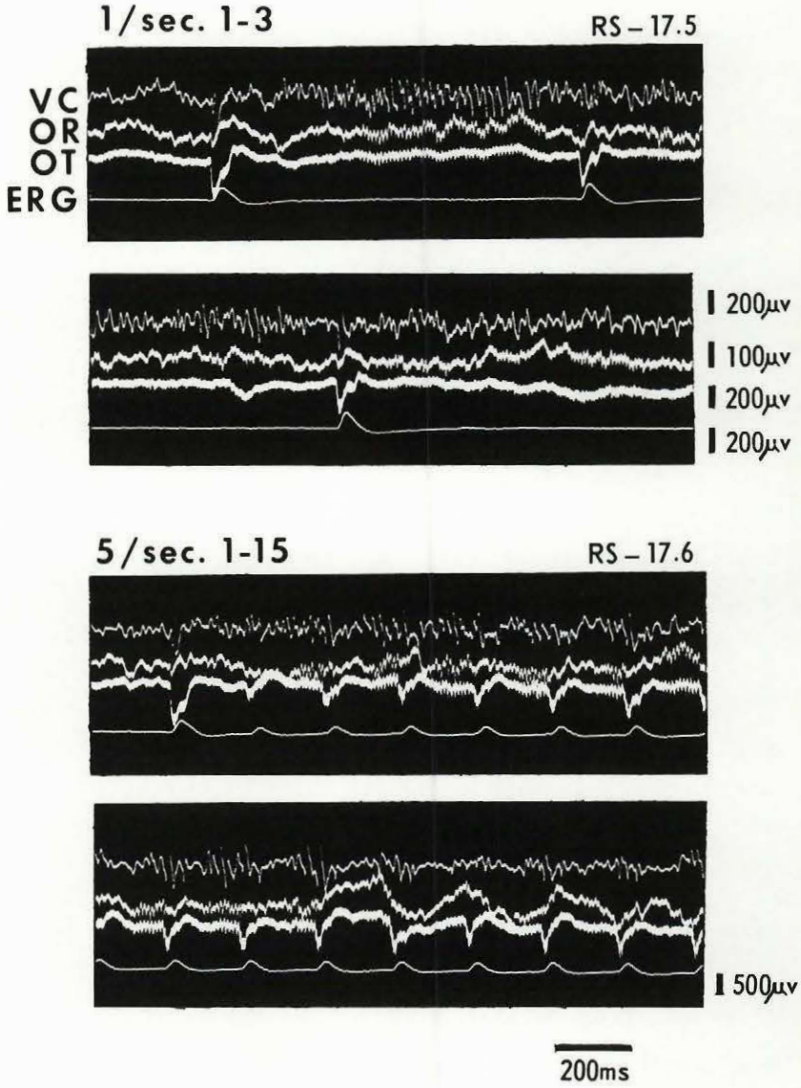


Fig. 29

Cortical afterdischarge and subcortical oscillations. Responses recorded simultaneously from VC, OR, OT, ERG. Photic stim.: 10 microsec., 1/sec. (top) and 5/sec. (bottom).

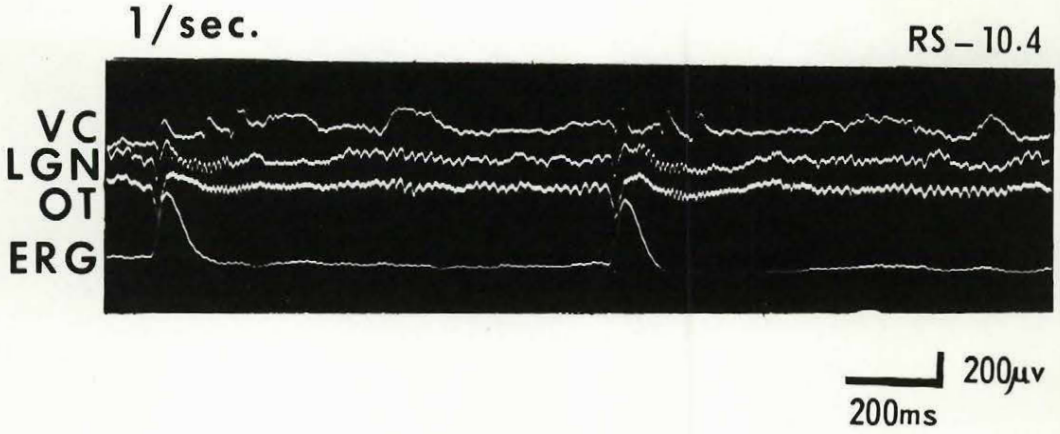


Fig. 30

Cortical afterdischarge and subcortical oscillations. Responses recorded simultaneously from VC, LGN, OT, ERG. Photic stim.: 10 microsec. flash, 1/sec.

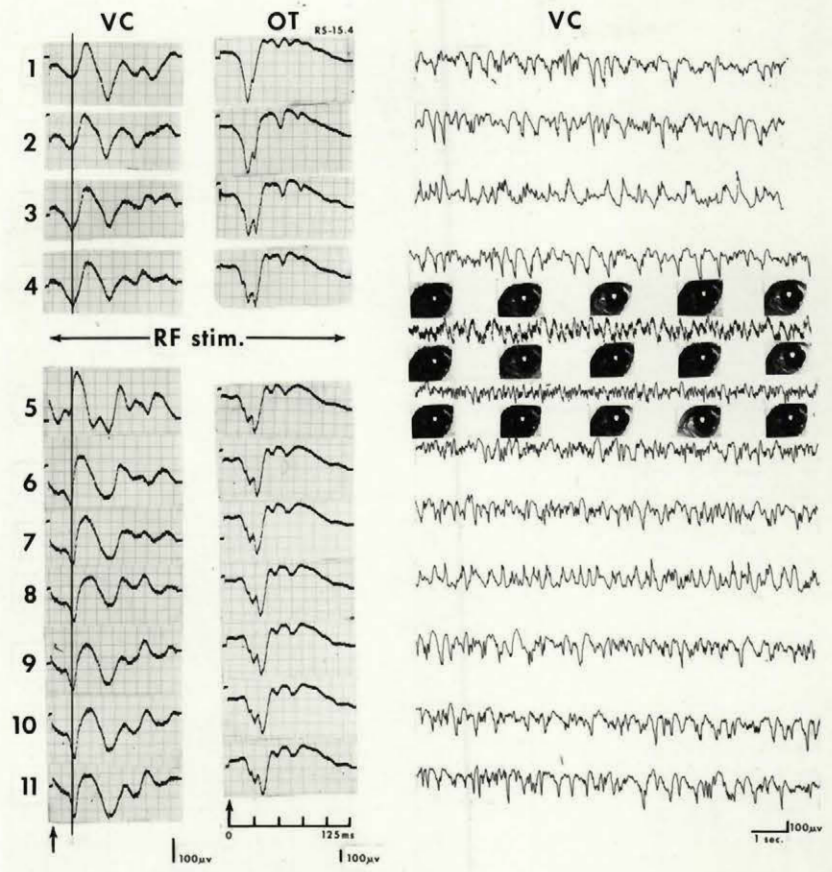


Fig. 31

Consecutive averaged responses before (1-4) and after (5-11) RF stim., and ECoG from VC with photographs of pupil before (4), during, and after (5), N-50, analysis time 125 msec. RF stim.: 150/sec., 1 msec., 5V, 10 sec. Photic stim. 10 microsec., 5/sec. Pupil photography as in Fig. 26.

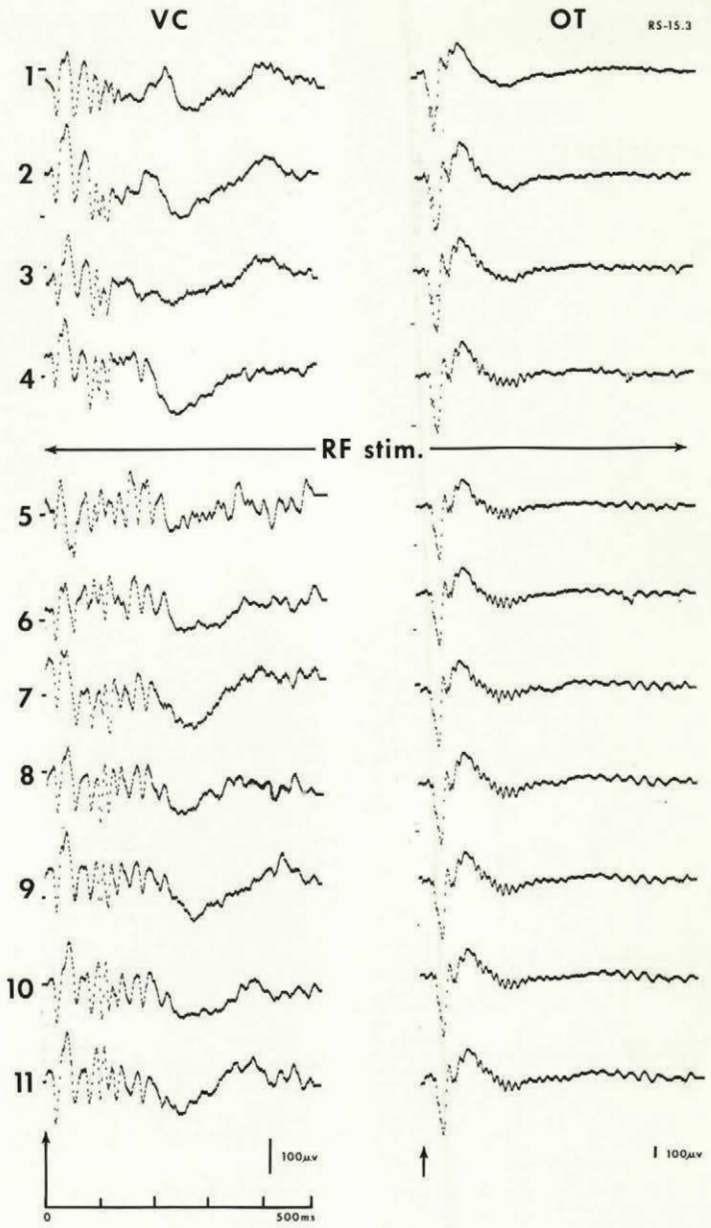


Fig. 32

Consecutive averaged responses before (1-4) and after (5-11) RF stim., N-20, analysis time 500 msec. RF stim.: 150/sec., 0.6 msec., 5V, 15 sec. Photic stim.: 10 microsec., 2/sec.

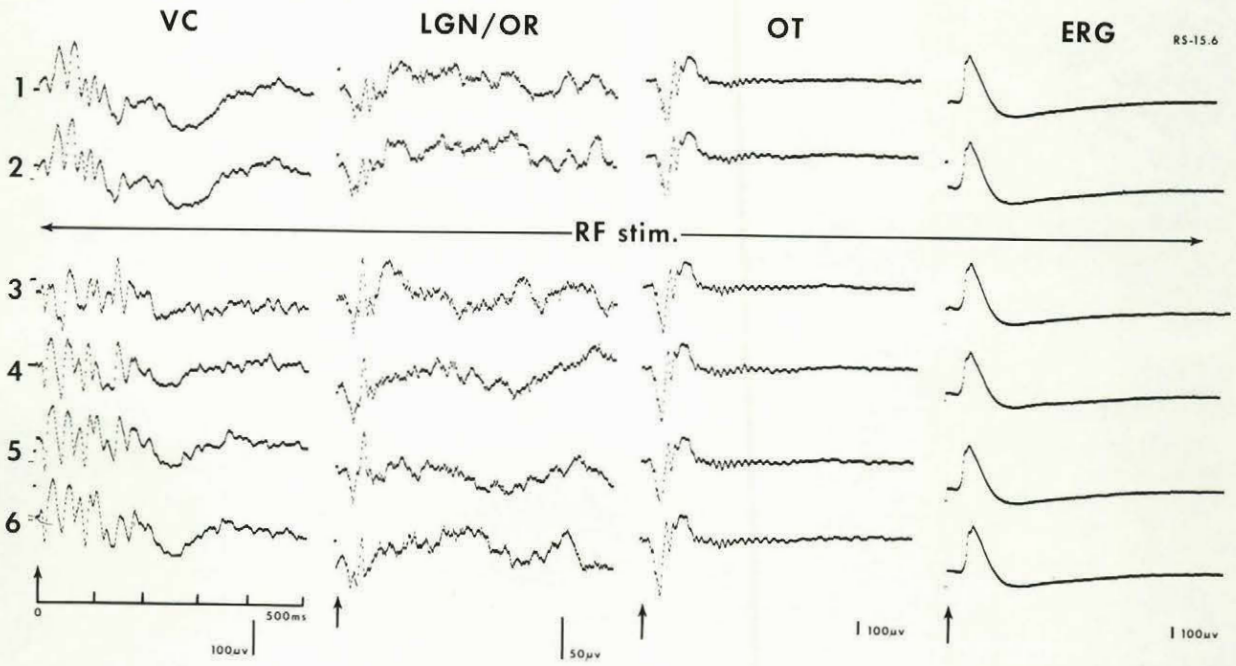


Fig. 33

Consecutive averaged responses before (1-2) and after (3-6) RF stim. The same experiment as Fig. 25 but analysis time of 500 msec.

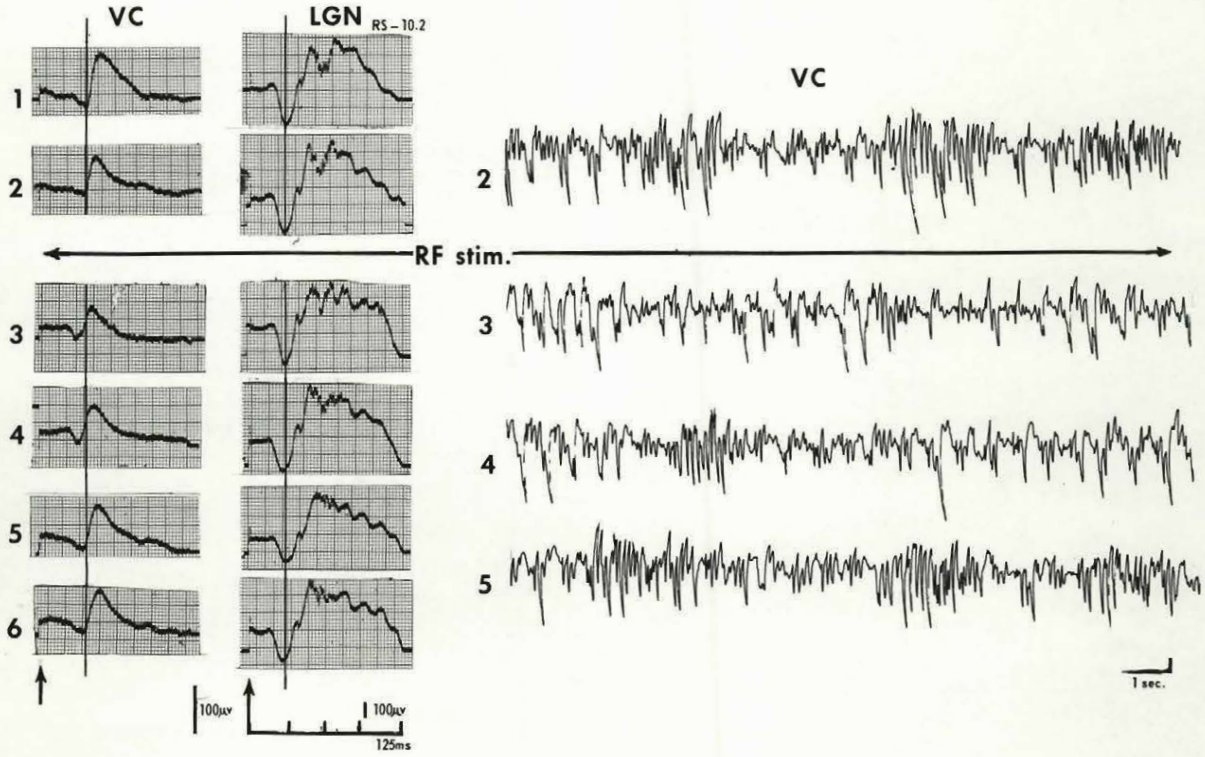


Fig. 34

Consecutive averaged responses before (1-2) and after (3-6) RF stim., and ECoG of VC before (2) and after (3-5), N-25, analysis time 125 msec. RF stim.: 150/sec., 1 msec., 7V, 15 sec. Photic stim.: 10 microsec., 2/sec.

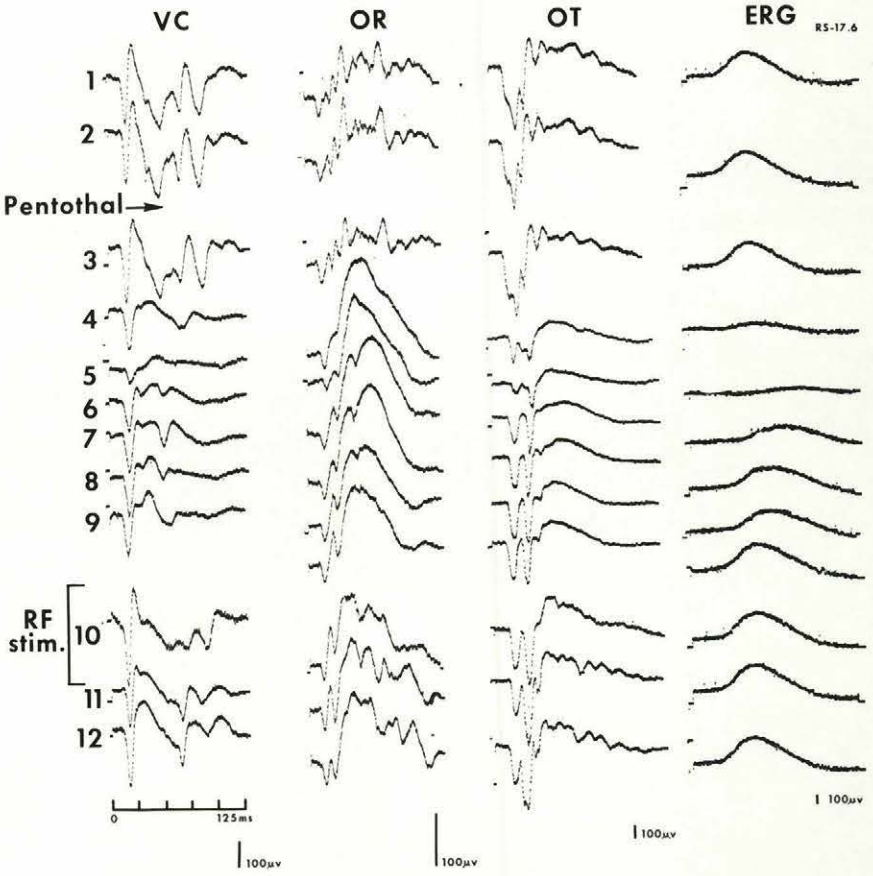


Fig. 35A

Consecutive averaged responses (see also Fig. 35B, a separate illustration) before (1-2) and after (3-24) i.v. Pentothal, and before, during and after periods of RF stim. (10, 18), N-50, analysis time 125 msec.
RF stim.: 150/sec., .2 msec., 5V, 10 sec.
Photic stim.: 10 microsec., 5/sec.
Pentothal: Rapid i.v. injection of 5 mg/kg.

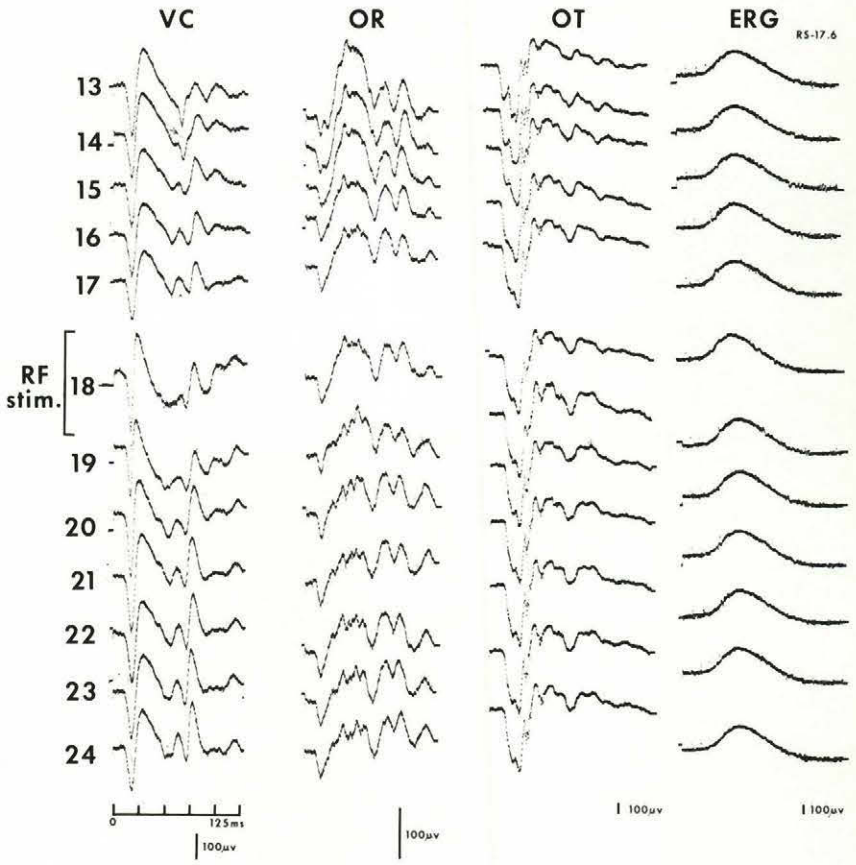


Fig. 35B

See Fig. 35A.

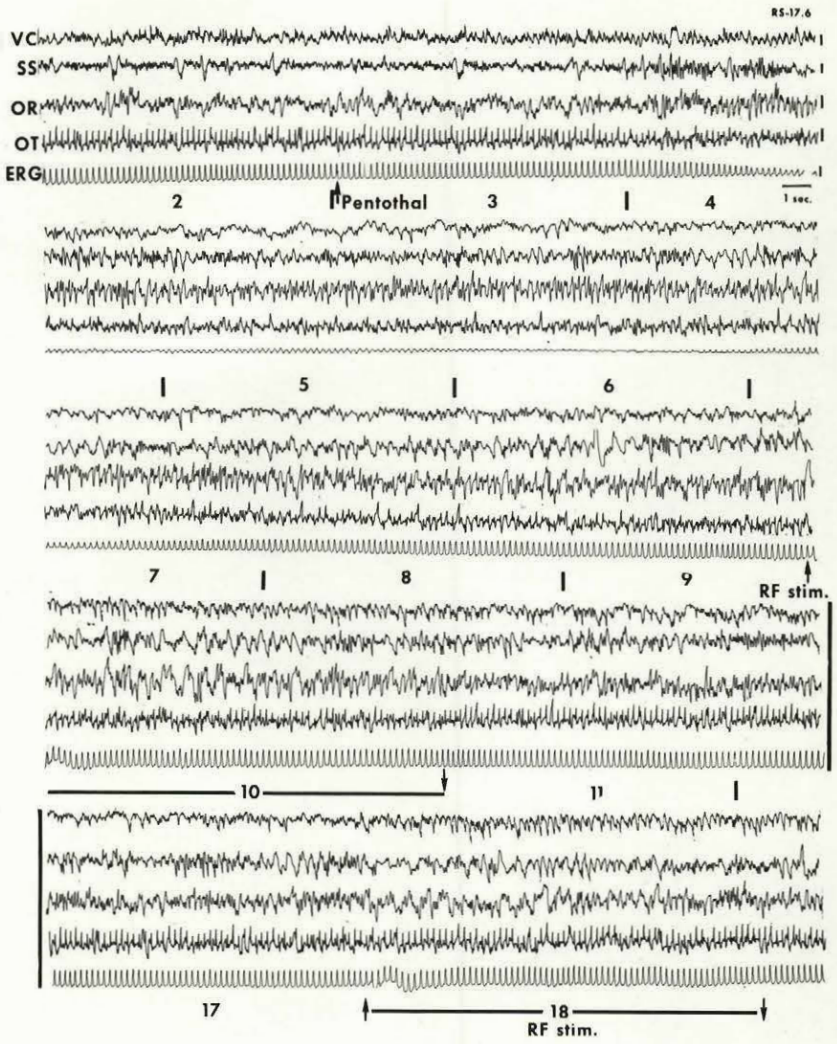


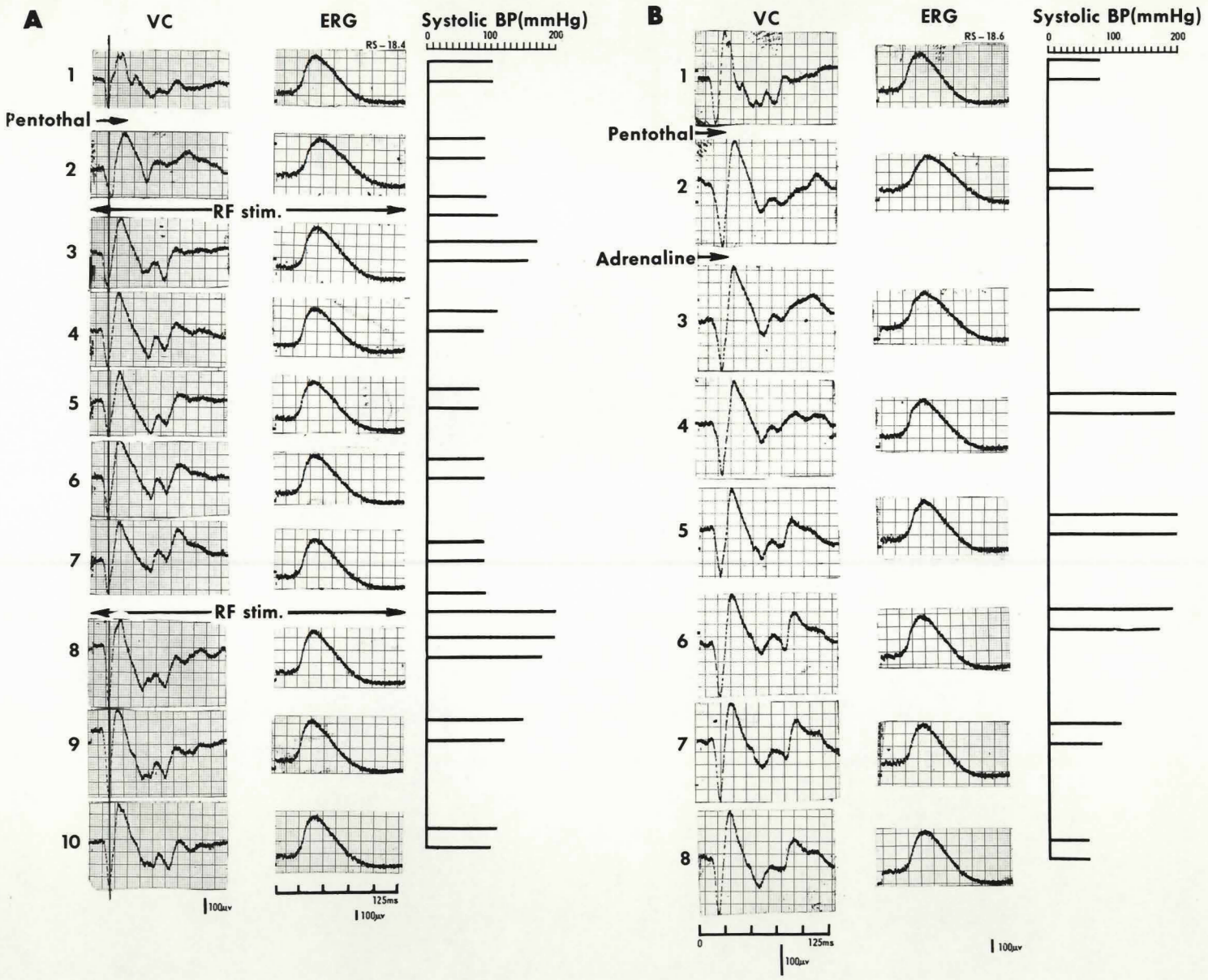
Fig. 36

Electrocorticogram of the experiment illustrated in Fig. 35A and B. Record included recording from suprasylvian gyrus (SS). Numbers indicate the periods during which the averages were computed (12-16 are excluded).

Fig. 37

A: Averaged responses before (1) and after (2-10) i.v. Pentothal, and before and after RF stim., with monitoring of systolic blood pressure, N-50, analysis time 125 msec. RF stim.: 5/sec., 2.0 msec., 6V, 10 sec. Photic stim.: 10 microsec. flash, 5/sec. Pentothal: 4 mg/kg rapid i.v. injection. Average #2 computed from responses in the 50-60 sec. period after Pentothal injection, subsequent averages are consecutive. BP was recorded continuously from the femoral artery, readings at 5 sec. intervals are shown (2 readings per average).

B: The format of (A) was repeated 3 hours later, and all parameters were the same, but RF stim. was replaced by the rapid i.v. injection of adrenaline (30 micrograms).


A
VC
ERG
Systolic BP(mmHg)
0
100
200
RS – 18.4
1
Pentothal
2
RF stim.
3
4
5
6
7
RF stim.
8
9
10
100μv
125ms
100μv
B
VC
ERG
Systolic BP(mmHg)
0
100
200
RS – 18.6
1
Pentothal
2
Adrenaline
3
4
5
6
7
8
0
125ms
100μv
100μv

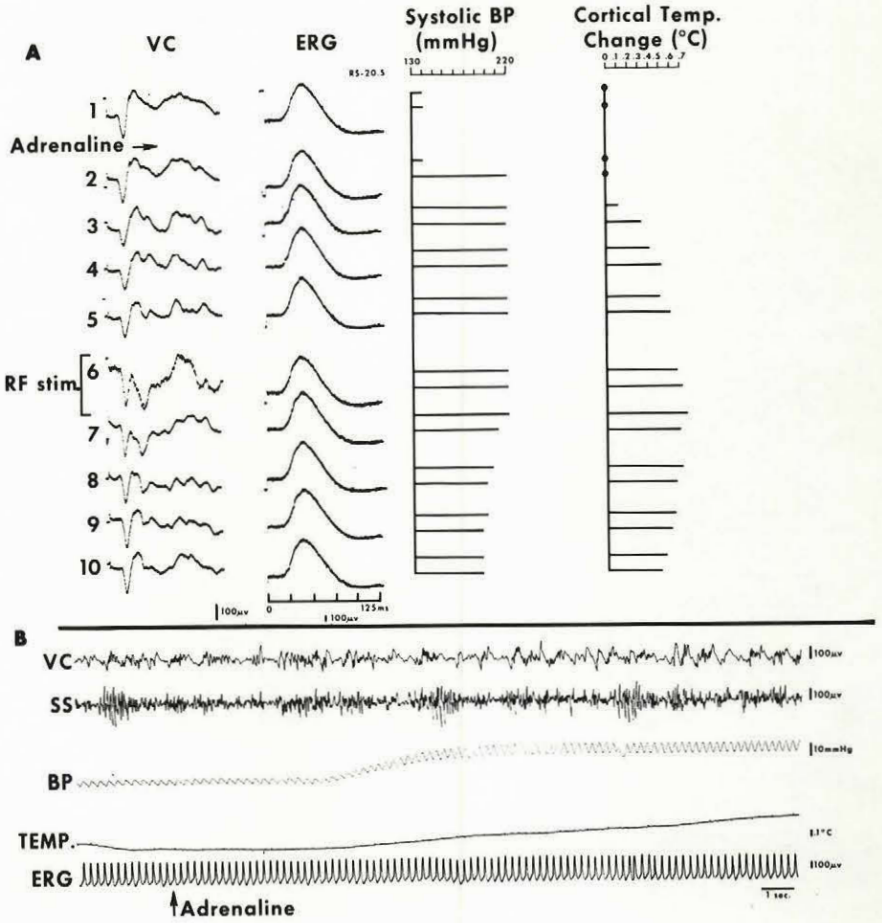


Fig. 38

A: Consecutive averaged responses before (1) and after (2-10) i.v. adrenaline, and before, during and after RF stim., with monitoring of systolic BP and cortical temperature, N-50, analysis time 125 msec. RF stim.: 150/sec., .3 msec., 5V, 10 sec. Photic stim.: 10 microsec., 5/sec. Rapid injection of adrenaline (50 micrograms). BP recorded as in Fig. 37. Cortical temperature recorded from right VC.

B: Sample of ECoG, with BP and Temp. recording, at the moment of adrenaline administration.

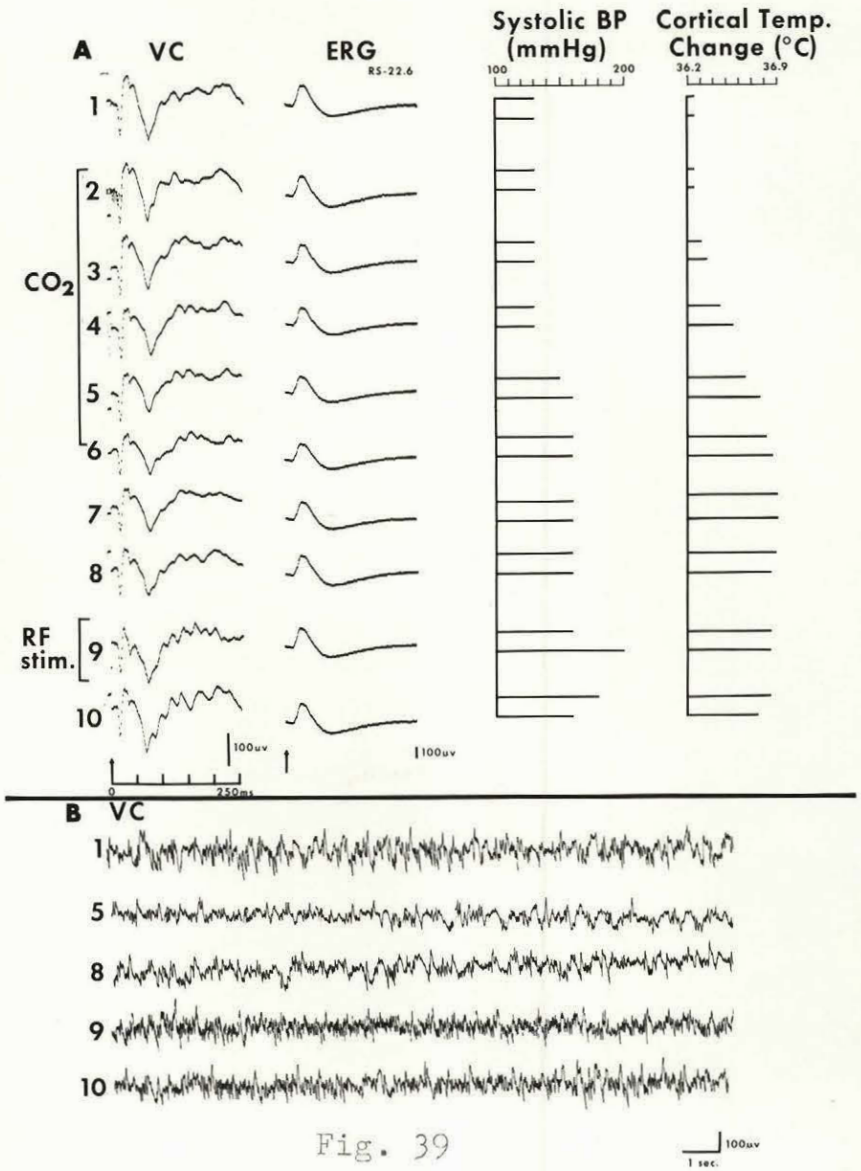


Fig. 39

A: Consecutive averaged responses before (1), during (2-6) and after (7-10) CO_2 inhalation, and before, during and after RF stim., with monitoring of BP and cortical temp., N-30, analysis time 250 msec. RF stim.: 150/sec., .2 msec., 5V, 15 sec. Photic stim.: 10 microsec., 2/sec. Carbon dioxide was administered via the respirator as a mixture of 20% CO_2, 20% O_2, 60% N, for 70 sec. BP and Temp. as Fig. 38.

B: Electrocorticogram from VC before (1), during (5) and after CO_2 (8), and before (8), during (9) and after (10) RF stim.

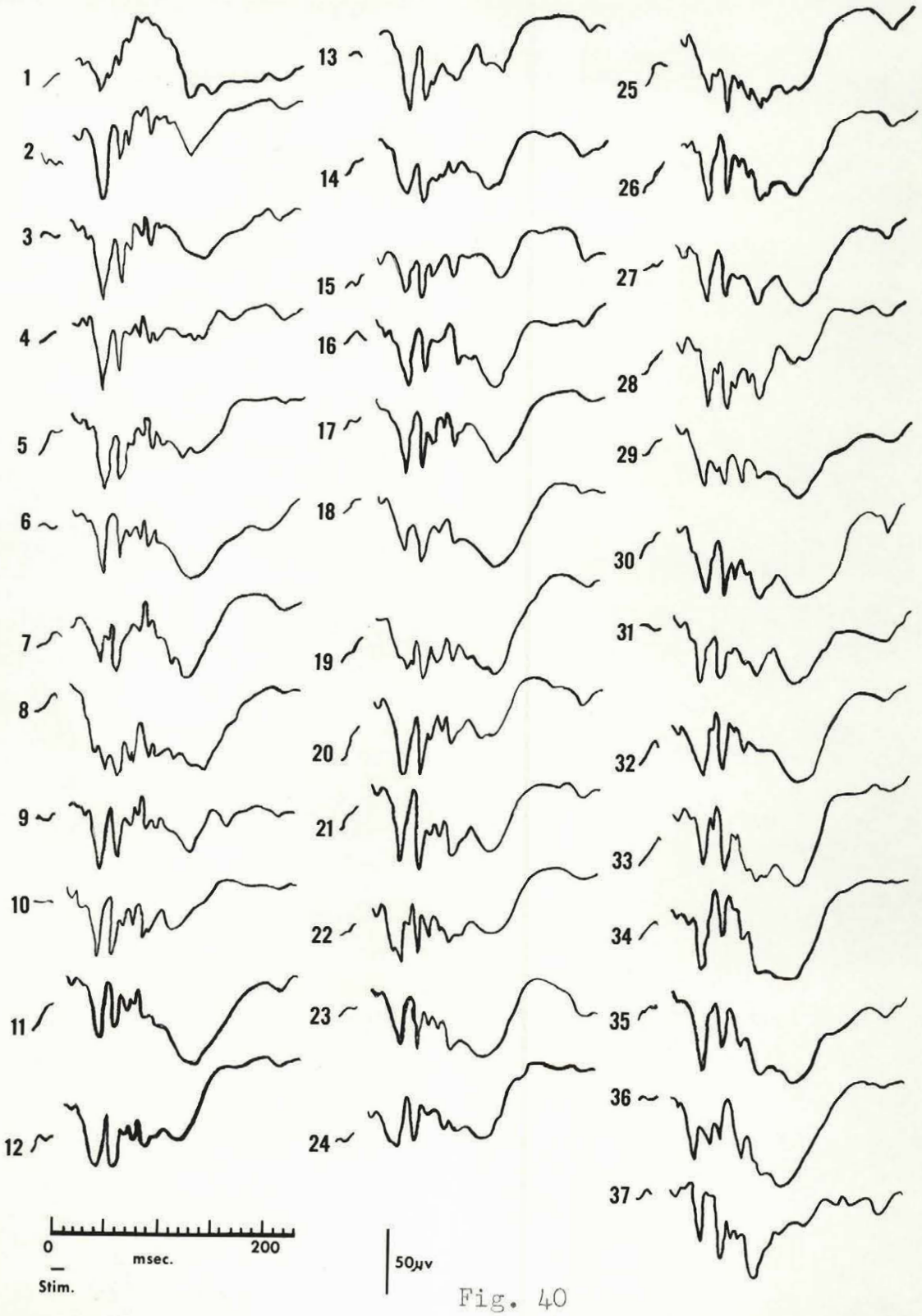


Fig. 40

Average evoked responses during 6 h. of repetitive stimulation. N-50, analysis time 250 msec. Photic stim.: Contact occluder, 10 msec. flash, 40 mL, right eye, 1/sec. The responses were sampled at a mean interval of 5 min., and only alternate averages are shown (10 min. interval). (Due to the faintness of the original tracings, these have been re-traced by hand for reproduction).

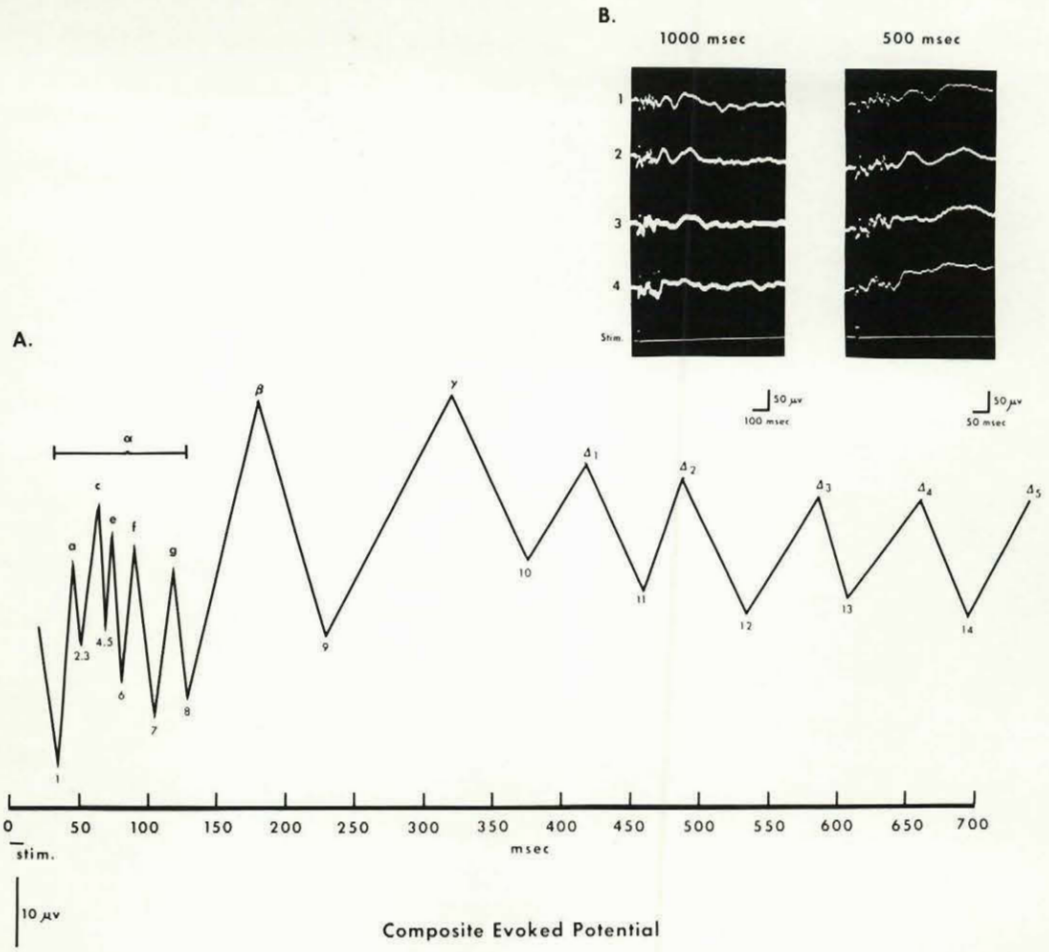


Fig. 41

Composite evoked response (A) and sample of individual averaged evoked responses (B). The composite was drawn from measured latencies and amplitudes of 16 averages, sampled at 15 min. intervals, during 4 h. 10 min. of repetitive stimulation, N-50, analysis time 1000 msec. Photic stim.: Contact occluder, 10 msec. flash, 40 mL, right eye, 1/4 sec. The composite is of the initial 750 msec. Sample averages at 1000 msec. with 500 msec. detail (B).

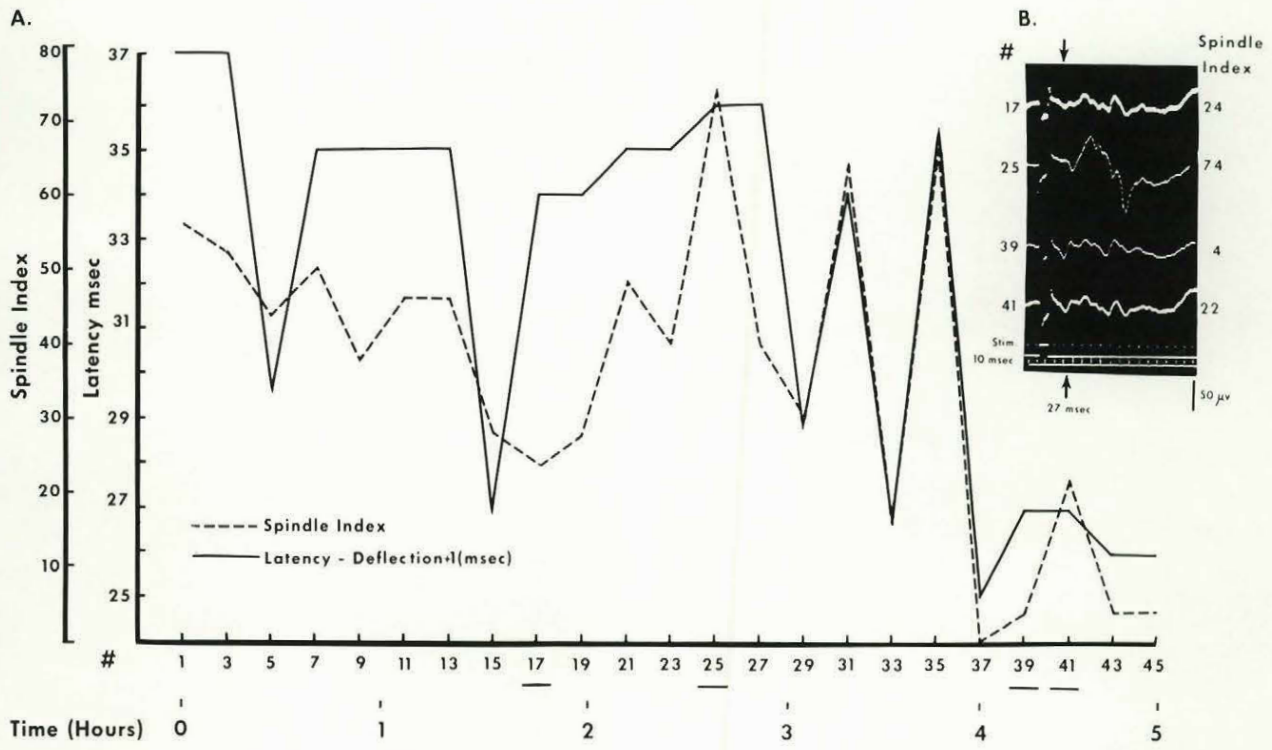


Fig. 42

Spindle index and latency of deflection (1) during 5 h. of repetitive stimulation (A). Latencies were measured from onset of current to peak of deflection. Parameters are the same as in Fig. 40. Sample averages at different SI levels (B). The averages sampled in (B) are indicated by underscored points on abscissa in (A). (In A the underscoring of #17 is an error as it should read #15, similarly in B, top response).

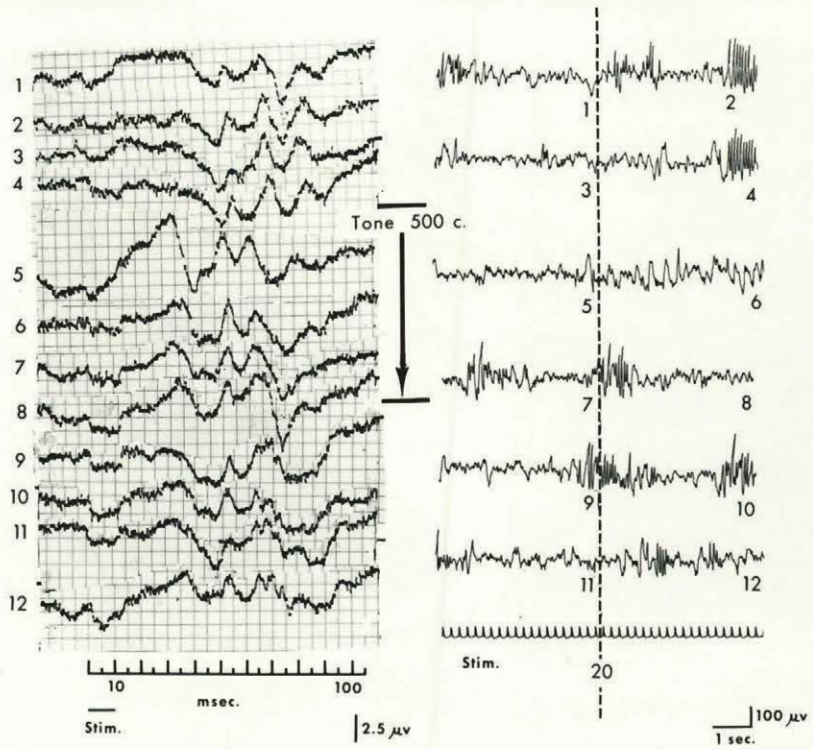


Fig. 43

Averaged evoked responses during sleep and arousal, N-20, analysis time 125 msec. Stimulus rate 5/sec., otherwise parameters as in Fig. 40. The corresponding ECoG records are the complete tracing for each averaging period. 1-4: during sleep. 5-8: aroused by 500 c/sec. tone. 9-12: return to sleep. (In 5 the pronounced shift in baseline at 10-40 msec. was the result of an artifact).

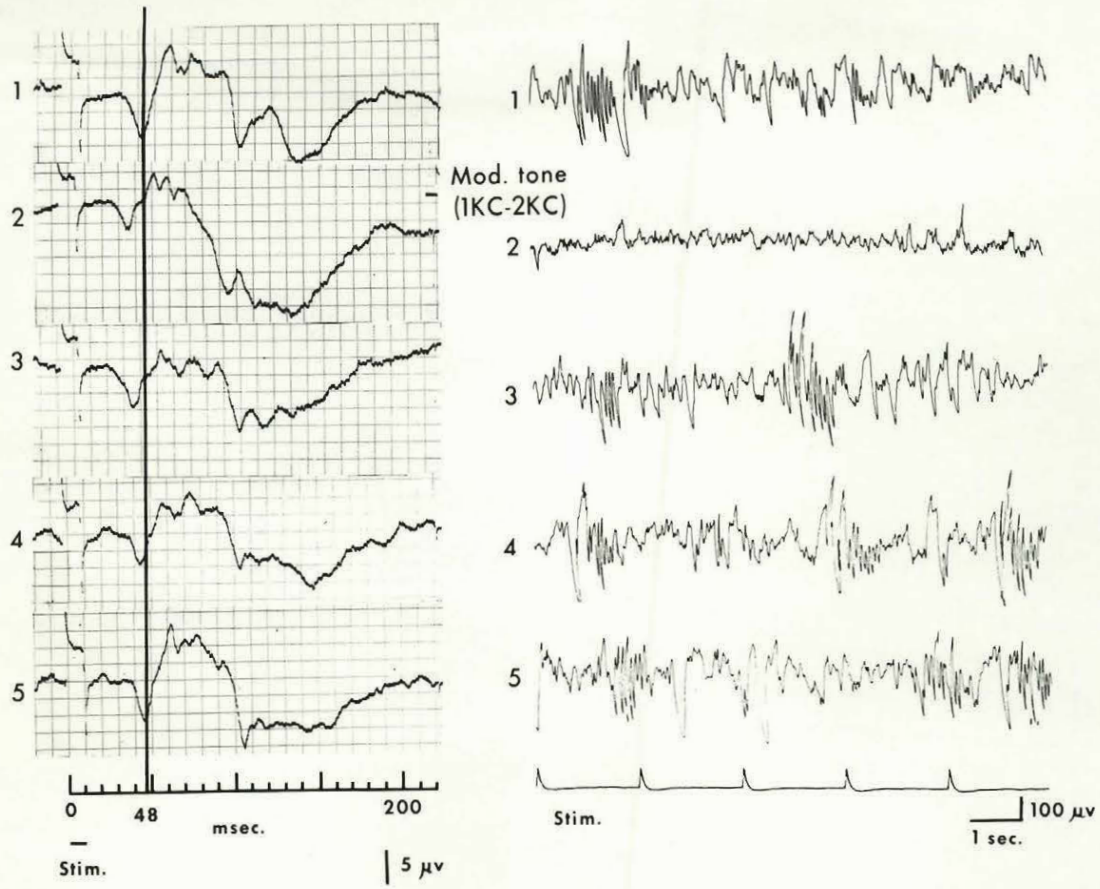


Fig. 44

Averaged evoked responses during sleep and arousal, N-20, analysis time 250 msec. The averages are consecutive. Photic stim.: Contact occluder, 10 msec. flash, 30 mL, right eye, 1/2 sec. Bipolar recording. Corresponding samples of ECoG were recorded from right pericruciate area. 1: during sleep. 2: aroused by modulating tone. 3-5: return to sleep. (In 2, the prominent shift in baseline at 75-150 msec. was the result of an artifact).

III. DISCUSSION

Reticular formation activation

Evoked response alterations were observed at the visual cortex and optic radiation following stimulation of the brain stem reticular formation. In the acute experiments, response analysis excluded the period during RF stim. and therefore only "after-effects" were studied. The alterations described were confined to response enhancement (excluding the decrease in amplitude of the short latency cortical response). Inhibitory effects, if present during the period of RF stim., were missed. However, in the chronic experiments, analysis included the stimulation period and again only facilitation was observed. The after-effect progressed in continuity from these earlier changes.

The response definition provided by averaging was a sensitive tool for assessing response change. Amplitude of the initial response components was only one of several parameters effected by arousal. The analysis was expanded to include: (1) multiple temporally dispersed components which together formed the complete response to light, and (2) measurements of latency and duration. Regardless of the direction of amplitude change of the initial components,

facilitation was expressed as a shortening of latency. The deflections were sharper, i.e., exhibited more rapid rise and fall times, and were shortened in duration. These changes were not limited to particular rates of flash repetition since in the chronic preparations they were observed at rates of 1/2 sec. to 5/sec. However, facilitation was more prominent at the higher rates (2/sec. - 5/sec). Although there may be a physiological factor related to rate, it is important that at higher rates more flash stimuli occur per unit time. Therefore, the sensitivity of the average response analysis as a method for appreciating response change per unit time was increased. That a facilitatory effect may be expressed as a latency change was observed in the early studies of Bremer and Stoupel (1958, 1959) and Dumont and Dell (1958, 1960) for the "electrically" evoked response. Latency changes with flash stimulation were suggested in several reports (Bremer 1961; Akimoto et al 1961; Sokolov 1963) and in man, Ebe and Mikami (1962) noted a prolongation of the latency of the initial positive wave of the photic response during sleep.

Evoked response facilitation was also expressed by an enhancement of the long latency rapid afterdischarge.

The duration of the afterdischarge was lengthened, and individual components were increased in amplitude. In 1950, Bremer and Bonnet observed that the rapid afterdischarge following the primary auditory cortical evoked potential was enhanced in awake (unanesthetized) as opposed to sleeping preparations. A decade later Bremer (1961) briefly noted a similar facilitation of the fast afterdischarge of visual cortex. Similarly, Fuster and Doctor (1962) reported an amplitude increase of a "secondary" cortical response (latency 150-300 msec.) in the implanted rabbit. Analysis of unit responses in chronic cat also provided a related observation. Evarts (1963) reported that the major factor underlying increased unit responsiveness during waking was the enhancement of flash-evoked unit discharge at a long latency (80-100 msec.). The analysis of latency was limited, however, by the high flash rate (5/sec.) to only a 200 msec. period.

Facilitation of sensory evoked activity at the cortex can not be considered without also examining concurrent subcortical events. Observations at the LGN-OR confirm the findings of those investigators who had reported response enhancement (Dumont and Dell,

1958, 1960; Bremer and Stoupel 1958, 1959; Steriade and Demetrescu 1960; Suzuki and Taira 1961; Taira and Okuda 1962; Ogawa 1963; Hotta and Kameda 1964). Observed changes were in the form of increased amplitude of the negative deflection of the primary complex, and augmentation of amplitude and increase in number of the superimposed oscillations. Although this response was not analyzed for pre- and post-synaptic components, the absence of OT changes and the histological control of electrode position suggested that the arousal-related changes concerned components of post-synaptic origin. However, the increased amplitude of the slow negative component is difficult to interpret for a greater augmentation followed the thiopental injection (i.e., amplitude increase is not necessarily equivalent to response facilitation). The increased number of oscillations, i.e., their presence at longer latencies, suggests an overall increase in sensitivity of the responding elements of the geniculate nucleus. It is not necessary to postulate an increase in the number of responding elements and thereby the question of the presence or absence of a geniculate subliminal fringe can be circumvented (Morlock and Marshall 1964). Similarly the latency enhancement

occasionally observed, can be explained as due to an increase in excitability of the responding elements leading to a greater synchrony of discharge.

These data suggested that reticular facilitation could occur separately at visual cortex and lateral geniculate nucleus. This interpretation is limited, however, by the restricted location of recording electrodes, i.e., a response change observed at VC but absent at OR might have been observed if the OR electrode were at a different location. However, a number of investigators have observed a similar duality of effect, suggesting the activity of separate pathways. Two observations of Dumont and Dell (1960) are particularly relevant: (1) The degree and time course of response enhancement differed for deflections 3 and 4 (of cortical origin) as opposed to deflection 1 (of OR origin), in the cortical response to ON shocks. (2) When the geniculate was circumvented by stimulating the optic radiation instead of the optic nerve, facilitation of the cortical response was still present. Narikashvilli (1963) and recently Walsh and Cordeau (1965) also reported similar findings for the "electrically" evoked response and Steriade and Demetrescu (1960) for the response to flash.

In a few experiments shortened cortical latencies were interpreted as resulting from changes primarily located at the LGN. The cortical and geniculate responses evolved in parallel and additional evidence for increased cortical excitability was lacking. More often, however, cortical latency reflected cortical facilitation. This is supported by the observation of cortical facilitation sans geniculate facilitation in the thiopental experiments. The great magnitude of the cortical change demanded in these experiments some indication of geniculate facilitation if the primary change was subcortical.

The exact mechanism responsible for shortening of response latency resides in the physiological fine structure of the cortex. Certainly, reticular input converging on the same neurones which receive optic radiation fibers and acting to lower response threshold could result in sharper peaks and a more rapid evolution of the population response (Jung 1958). However, other mechanisms, e.g., pre-synaptic facilitation or inhibition of inhibitory elements might also provide the basis for facilitation.

Increased excitability of cortical elements could also be responsible for the afterdischarge enhancement.

In the majority of experiments this explanation probably suffices since concomitant subcortical changes at this long latency were not observed. However, regular oscillations were sometimes present at long latencies (depending on flash rate and number of previous flashes) at the LGN-OR, and again electrode localization prevents a more definitive conclusion.

Cortical response facilitation was usually related to the presence of low voltage fast activity in the background record. In fact, the most prominent response facilitations were observed when sleep tracings became abruptly aroused (Dumont and Dell 1960; Bremer 1961; Walsh and Cordeau 1965). Yet, neither the abrupt onset or the low voltage fast pattern itself was a necessary precondition for the occurrence of evoked response facilitation. This dissociation was also noted by both Bremer and Dell (in the discussion of Bremer's paper, Bremer 1961b). However, in the present work, a number of additional comments pertaining to the physiological validity of this observation are required: (1) The method of measurement used to assess arousal level, i.e., visual inspection of the electrocorticogram, is far less sensitive as a method than that employed to

measure evoked potentials, i.e., computer averaging. (2) Every preparation was atropinized to some extent and "pharmacological dissociation" might have occurred (Bradley 1958).

Of these two factors, only the first would seriously decrease the physiological significance of the observed dissociation. Pharmacological dissociation, on the other hand, suggests that the source of the low voltage fast pattern is not identical with the mechanism producing response facilitation. This interpretation is supported by the thiopental experiments. Reticular stimulation, while not altering the background cortical activity, produced dramatic enhancement of the evoked response, again a type of pharmacological dissociation. In addition, under thiopental, the facilitation followed a fluctuating course after RF stim. Similarly, in unanesthetized preparations, evoked response recovery and the return to a resting electrocorticogram pattern did not always occur in parallel. Dumont and Dell (1960) also demonstrated fluctuations in the course of response facilitation which were independent of ECoG patterns.

Ingvar (1958) demonstrated that the increased cortical blood flow observed during arousal was not only

a function of systemic hypertension but was also a by-product of an increase in cortical metabolism. This suggested that the blood flow change is secondary to increased demand. It would still be possible, however, to explain the neural facilitation on the basis of the greater nourishment provided by the circulatory change. In the present work, similar circulatory effects were produced by methods which did not yield reticular activation and response facilitation was not observed. Therefore, by analogy, the response facilitation of arousal did not result from a change in blood flow.

Repetitive stimulation

In both the acute and chronic experiments a progressive diminution or disappearance of the evoked potential was not seen. No clear evidence was found for habituation of the evoked response, thus supporting the findings of Fernández-Guardiola et al (1961) and Gallardo et al (1962). In the course of the experiments, however, changes in the form of the response did occur. Two different factors were identified which together partially explain these response variations. At the cortex and LGN-OR, the alterations related to fluctuations in arousal level were already discussed.

A second factor contributing to the response characteristics was light adaptation. During repetitive stimulation, as light adaptation progressed, oscillatory deflections appeared in optic tract and optic radiation. At the cortex, however, oscillations at the same frequency as those of the subcortical paths were only occasionally observed.[6] Yet, their presence in the cortical input pathway suggests that they must have a significant influence on cortical response change during repetitive stimulation. Similarly, although thiopental generally depresses neural transmission, the loss of the multiple deflections of the cortical response may result, in part, from the striking depression of the oscillatory potentials in the OT response.

The disappearance of the long latency cortical afterdischarge was also related to a concomitant diminution of long latency oscillations in OT and LGN-OR. Certainly the change at the optic tract cannot be described as habituation but was related to the <u>starting</u> of the oscillatory mechanism and its evolution to the Osc-R during repetitive stimulation. Therefore, the loss of

6. Cobb and Morton (1961) described them in the occipital response of man at a frequency of 100/sec. They have also been observed in the primate (Doty and Kimura 1963; Hughes 1964), but have always been difficult to record in cat (Doty and Kimura 1963).

the cortical afterdischarge cannot simply result from cortical habituation or cortical refractoriness during high frequency flash repetition. However, a cortical excitability change may also contribute to the diminution of the cortical afterdischarge, since in some experiments tract and radiation oscillations were not accompanied by fast cortical afterdischarges.

CHAPTER V

SUMMARY AND CONCLUSIONS

Summary

1. The population response recorded in the optic tract of cat to a 10 microsec. flash was of two principle forms--simple or non-oscillatory and complex or oscillatory. The frequency of the oscillation was 100/sec. (80-110) and was unchanged by alterations of flash intensity or rate. The oscillatory response of the dark adapted retina was enhanced by repetitive flash stimulation. Evolution from the non-oscillatory to the oscillatory form was more rapid at high flash rates (2/sec., 5/sec.). The rapid development of oscillations at the higher rates paralleled suppression of the b wave of the electroretinogram.

2. The oscillatory response was also enhanced following light adaptation. In addition, when the retina was dark adapting (following light adaptation), alterations of the OT responses paralleled the stages of b wave recovery. Enhancement of the oscillations occurred during the initial, rapid phase of b wave recovery, while depression accompanied the second, slower phase of recovery. Finally, at the

completion of dark adaptation (no further change in b wave amplitude), stabilization of the optic tract response occurred.

3. Oscillations were also observed which were not a part of the immediate response to flash. These occurred: (a) "spontaneously," after exposure to an adapting light, (b) at long latencies, following the initial flashes of a repetitive series, prior to the appearance of the oscillations of the evoked response complex (Osc-R), or (c) at long latencies after exposure to many flashes of a repetitive series. The oscillations which were present at long latencies to individual flashes (c), were usually at one-half the frequency of the Osc-R.

4. The optic tract population responses recorded in the rod-dominant retina of the albino rat did not exhibit 100/sec. oscillations. Alterations of response form, related either to flash repetition or light adaptation, were not observed.

5. Unit responses to 10 microsec. flashes were recorded from individual optic tract axons. The oscillations of the population response were represented at the unit level

by grouped discharges of single fibers at an intergroup period identical to the period of the oscillations (for any one preparation). Therefore, unit grouping was also enhanced by repetitive stimulation and light adaptation and, in fact, the changes at this level closely paralleled the alterations of the oscillatory response.

6. The short periods of inhibition and facilitation of unit discharge (grouping) were superimposed on longer periods of fluctuating excitability associated with the on-off response. Under photopic conditions all units exhibited grouping, regardless of their on-off classification, and it was observed during both the primary and secondary phases of excitability.

7. Apart from the oscillatory response alterations, no other changes were observed at the optic tract during repetitive stimulation. In addition, the response did not alter with reticular activation when the pupillary diameter was fixed in relation to the light source.

8. Population response recordings from the lateral geniculate nucleus-optic radiation also exhibited 100/sec. oscillations which evolved in parallel with the optic

tract response. Similarly, no additional changes occurred during repetitive stimulation. However, reticular activation produced response alterations that were interpreted as facilitatory. The amplitude of the long duration slow negative deflection increased, and oscillatory components increased in number and amplitude. Rarely, a shift to a shorter latency was observed.

9. The major components of the visual cortical response did not disappear, and were not markedly diminished during repetitive stimulation in both acute and chronic preparations. Long latency oscillations of OT and LGN-OR, which followed the initial flashes of a repetitive series, were often associated with high frequency cortical afterdischarges. In addition, disappearance of the cortical afterdischarge paralleled the disappearance of the subcortical oscillations. Reticular activation also produced cortical response facilitation. The response decreased in latency and the initial deflections were more sharply peaked and of shorter duration. These changes were observed at all flash rates but were more prominent at higher rates (2/sec., 5/sec.). The late cortical discharge (125-250 msec.) was also enhanced by reticular activation.

10. Evidence was presented that response enhancement occurred independently at LGN-OR and VC, although related facilitatory effects at these two levels were occasionally observed.

11. Cortical response facilitation was most readily observed when the ECoG was converted from spindling and high amplitude slow activity to a low voltage fast pattern. However, response enhancement was also present when ECoG signs of cortical arousal were not observed (e.g., following thiopental).

12. Elevation of the systolic pressure (femoral artery) and local cortical temperature with intravenous adrenaline or hypercapnia did not produce the response facilitation observed with reticular activation.

13. Intravenous thiopental depressed responses at all levels of the primary visual pathway. Retinal effects were marked, including the disappearance of the oscillatory response.

14. Recording of the cortical response in chronic preparations corroborated the finding of response enhancement (changes in latency and duration of initial deflections) during

distinct periods of induced arousal. In addition, the following relations to spontaneous changes in level of arousal (as judged by the ECoG) were observed: (a) The mean amplitude of all deflections, exclusive of the initial short latency response increased during sleep and decreased during arousal. (b) The mean latency of the initial deflection was decreased during arousal.

Conclusions

Two factors influenced response form during repetitive flash stimulation: light adaptation and state of arousal. The former altered the discharge pattern of retinal ganglion cells, the change being transmitted to the geniculate relay and visual cortex, while the latter effected transmission at both the lateral geniculate nucleus and visual cortex.

Light adaptation produced grouping of ganglion cell discharges, and oscillations in the population response, at a frequency of 100/sec. (frequency of oscillation or intergroup frequency). This was interpreted as resulting from the activation of a neural retinal mechanism, cyclically inhibiting and facilitating ganglion cell excitability, a mechanism distinct from that producing long duration excitability changes related to the receptive

field organization. It was further suggested that this rapid oscillatory mechanism is restricted to the cone system. The course of the oscillatory response (a) while the retina was dark adapting, and (b) during the initial flashes of a high frequency repetitive series (e.g., 5/sec.), indicated a competitive interaction between the neural processes of light and dark adaptation.

Reticular activation facilitated photic evoked responses of the visual cortex and lateral geniculate nucleus. At the visual cortex alterations in latency, duration of deflection and afterdischarge indicated enhancement of excitability based upon the convergent effect of a "non-specific" input. Response facilitation at the lateral geniculate nucleus was similarly understood, however, separate "non-specific" pathways to geniculate and to cortex were postulated. The occasional observation of evoked response facilitation unrelated to electrocortical arousal suggested that separate mechanisms might underlie these two frequently related events. Evidence was also presented supporting a neural, as opposed to a circulatory, basis for response enhancement.

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