# XXI. NEUROLOGY*


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## A. WORK COMPLETED

Brief summaries follow of theses accepted by the departments, and in partial fulfillment of the requirements for the degrees, indicated.

1. Geometrical Transformations of Vectorcardiograms, S. B. Thesis, Department of Biology, M. I. T., June 1964.

Various geometrical transformations have been made on a number of vectorcardiographic data sets for the purpose of EKG diagnosis. The results of these transformations have been compared visually with each other for the purpose of defining useful diagnostic patterns.

C. H. Benet

2. Transient Probability Distributions of Nerve Impulse Intervals, S. B. Thesis, Department of Physics, M. I. T., June 1964.

The time evolution of the distribution of nerve-impulse intervals was examined by measuring histograms at varying times in the stimulus cycle. The distribution width was found to vary inversely as the stimulus strength. There is an indication that the width also depends upon the stimulus rate of change.

The inverse of the average frequency was found to be the most reliable statistic in characterizing the response data. The mean, standard deviation, and most probable interval were examined and found useful when applicable. The standard deviation is found to be a function of the mean.

For the square-wave response, some nonlinearities have been evaluated and the possible existence of harmonics is discussed.

A brief description of electronic pulse-height discrimination has been given. A method for automatic computer analysis is discussed briefly.

W. C. Carithers, Jr.

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*Major support for this research is provided by the U.S. Public Health Service (B-3055-4, B-3090-4, MH-06175-02), the U.S. Navy (Office of Naval Research (Nonr-1841(70)), the U.S. Air Force (AF49(638)-1313), administered by the Electronic Systems Laboratory, M. I. T.

3. Apparatus for Experiments on Respiratory Control in the Cat, S. B. Thesis, Department of Electrical Engineering, M. I. T., May 1964.

The purpose of this thesis is the construction of a servo respirator for a cat designed to convert the dc output of a pulse-rate integrator into a proportional pressure output. The input signal is to come from the rate of neural firings of the phrenic nerve of the cat, and the output pressure is to be fed in the cat's lungs by means of a tracheognomy.

The respirator was designed with two feedback loops, one for pressure feedback, and one for rate feedback to provide stability. Using input frequencies of the order of a cat's breathing rate and artificial reservoirs to simulate a cat's lung, we made an evaluation of the pressure control system. We found that the gross response of the system was satisfactory, but the pressure output function lacked the desired smoothness. Several reasons for this are given in my thesis and solutions are proposed. There is also a brief discussion of the types of experiments to be carried with the aid of this apparatus.

E. W. Dreiss

4. Simulation of a Biological System: Gnats, S. B. Thesis, Department of Electrical Engineering, M. I. T., May 1964.

The simulation of a gnat swarm is the basis for a more complex simulation of fish schooling behavior. Models of the swarm are made by assuming gnats to be dimensionless particles moving under the influence of inter-gnat and external forces. Emphasis is laid not only upon obtaining a model, but also upon finding the best methods of evaluating models of this type.

Several programs testing different models were run. It was found that, within certain restrictions, the motions of the swarm are independent of the type of forces used. Several interesting motions were noted, including orbiting, oscillation, splitting, following, and schooling. A subjective visual examination of the displayed swarm was found to be the best way to judge the models, although a statistical description may be adequate.

C. V. Gaylord

5. Optokinetic Nystagmus in Human Subjects, S. B. Thesis, Department of Biology, M. I. T., May 1964.

Moving, vertical stripes were used to elicit optokinetic nystagmus in normal human subjects under controlled laboratory conditions. The eye movements were photoelectrically measured and recorded.

Interactions between the OKN response and various aspects of the stimulus, between the two phases of OKN, and between the phases and tracking movements were examined, in an effort to determine the functional relationships between the phases and the stimulus.

The results of the experiments suggest that the OKN response has the function of

compensating for the relative field velocity (with respect to the retina), rather than for the absolute velocity. Various empirical relationships between the phases and the stimulus have been established. The two phases were distinguished on functional grounds from the two tracking movements. The fovea was shown not to be necessarily implicated in the response. The OKN response was shown to be identical in each eye. Teleological relationships between unfixated and fixated OKN responses are discussed. Some speculations on the nature of the control system are discussed.

E. G. Merrill

6. MONITOR II – A Monitor System for the GE-225 Computer, S. B. Thesis, Department of Mathematics, M. I. T., May 1964.

The GE-225 computer in use at the Electronic Systems Laboratory, M. I. T., is a general-purpose fixed-word digital computer with an 8K memory. It has provision for I/O via punched cards, magnetic tape, keyboard, and analog devices.

The computer is used extensively for analyzing data from electro-biological experiments, often in real-time. The use of telephone tie lines for data and teletype signals allows remote experiments to be supervised by the computer. In addition to the direct experimental usage, a fair amount of computer time is spent in the system-programming effort which supports the experimental operations.

With the acquisition of magnetic tapes, the need was seen for a monitor system to permit easy and efficient use of this auxiliary memory. As a result, during the fall semester, two monitor systems were developed to fill this need. It was found that these first monitor systems were fairly inflexible and often difficult to use. They were also limited in application. MONITOR II was developed as a second-generation system, utilizing the experience gained through its predecessors. The result is a more powerful monitor that is easier to use, faster in operation, and more sophisticated than the first-generation efforts.

MONITOR II permits complete teletype control of remote or local experiments, calling the required programs from tape files, permitting communication with these programs, and regaining control on program exit. A wide variety of utility programs is available within the MONITOR, to aid both experimenters and programmers.

The present system has been under development for the second term and has just been released for general use.

J. A. Moore, Jr.

7. Computerized Rhythm Diagnosis of an Electrocardiogram, S. B. Thesis, Department of Electrical Engineering, New York, June 1964.

A successful computer system has been developed for the rhythm analysis of clinical electrocardiograms. The first part of this system, the detection of heart beats against

a background of noise, is primarily concerned with the differentiation of an electrocardiogram that has been digitalized and then smoothed. The second part of this system, a comparison of the time between two adjacent beats by a variable average time interval relates to the detection of ventricular premature beats. The rhythm diagnosis is finally given by an interpolation of the irregularity information and the heartrate information.

N. Orloff

8. A Tracking Experiment Using Auditory Input, S. B. Thesis, Department of Electrical Engineering, M. I. T., June 1964.

An experiment has been designed to permit separation of those portions of the response of the human motor coordination system into one component that is due to the eye and one that is due to the arm. In the experiment binaural lateralization in a compensatory tracking task was used to study the ear-arm system for comparison with existing data on the eye-arm system. Although the intended purpose was not fulfilled, the ear-arm system has been characterized as a linear system with saturating and threshold elements.

A. A. Smith

## B. SACCADIC SUPPRESSION ASSOCIATED WITH MICROSACCADES

### 1. Introduction

Microsaccades are the small involuntary eye movements associated with "steady" fixation. Their function is generally thought to be correctional, returning the image of the fixation target to the fovea after the image has drifted off the fovea. The average magnitude of microsaccades has been reported as approximately 5 minutes of arc,[1-3] although other investigators, as well as ourselves have found that figure somewhat small.[4]

Saccadic suppression is the elevation of visual threshold that occurs before and during a saccadic eye movement. This phenomenon has been demonstrated for the fast phase of vestibular nystagmus[5] and for voluntary horizontal saccades, and the time course of the phenomenon for the last type of movement has been well delineated.[6-8]

Ditchburn[9] has reported that subjects are unable to see the displacement of an oscilloscope trace when the displacement occurs simultaneously with the subject's microsaccades. The demonstration of saccadic suppression associated with microsaccades extends the generality of the phenomenon to the smallest involuntary saccadic eye movement. Furthermore, it has important consequences for anyone who has ever determined a visual threshold during steady fixation.

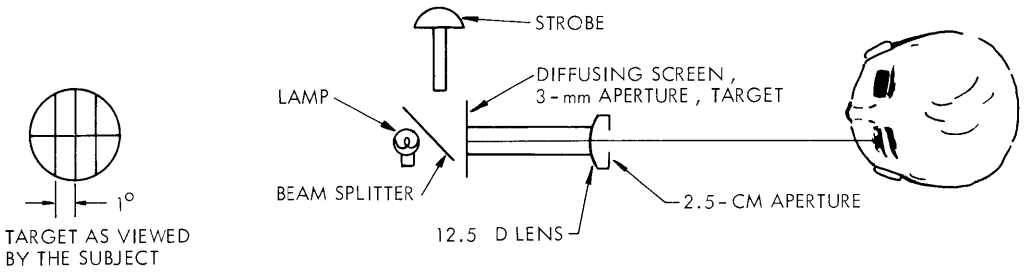



Fig. XXI-1. Diagram of the apparatus and the fixation target.

2. Experimental Methods

(a) Fixation Conditions – A representation of the fixation target is shown in Fig. XXI-1. It consists of three vertical lines and one horizontal line. The angular separation of the vertical lines is 1°. The right and left vertical lines serve as calibration targets, while the intersection of the central vertical line with the horizontal line serves as the fixation target. The lines are made of 0.005-in. diameter wire which, under the viewing conditions, subtends an angle of 5 minutes, of arc. The relative size of this target might account for our having seen larger saccades than noted by previous investigators.

(b) Viewing Conditions – A sketch of the apparatus is shown in Fig. XXI-1. The target is placed at the focal point of a 12.5 D lens and is illuminated from behind by a diffusing screen. The strobe (General Radio, 1531-A) test flash illuminates the entire field (c. 4°) through the beam splitter as shown in Fig. XXI-1. The subject's head is stabilized by use of a bite board and head rest. Viewing is monocular with the left eye, the right eye being occluded with an eye patch.

(c) Recording the Eye Movements – Eye movements are measured by using an apparatus that has been previously described.[10] This system was modified in that the light sensors are the semiconductor light sensors described in previous reports.[8] Such a system has a limit of resolution of approximately 15 seconds of arc.

(d) Synchronization of the Test Flash with the Eye Movement – The signal proportional to eye position was differentiated and amplified and used to trigger a pulse generator (Argonaut, LRG 051). This in turn triggered the strobe. Thus horizontal microsaccades in one direction only caused the presentation of a test flash. In general two conditions were employed: the pulse generator was used with no delay, i.e., the flash was presented at the beginning of the movement, or the trigger pulse was delayed, thereby causing the presentation of the test flash during or after the movement.

3. Results

When the test flash was presented periodically with no synchronization with the eye movement it was clearly visible every time.

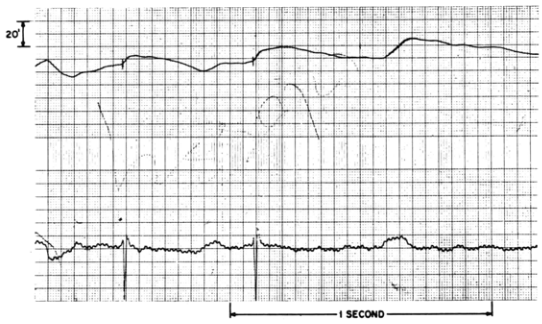



Fig. XXI-2. Records showing test flashes (sharp downward pulse, lower trace) occurring at the beginning of microsaccades. These flashes were undetected by the subject.

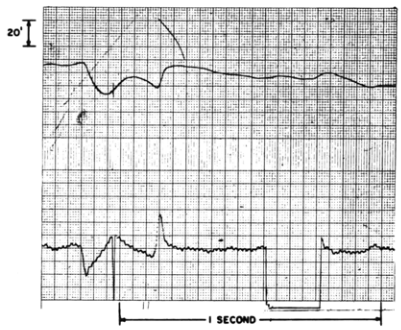



Fig. XXI-3. Flash occurring during a movement of unknown origin. Broad downward pulse is subject's indication of perception.

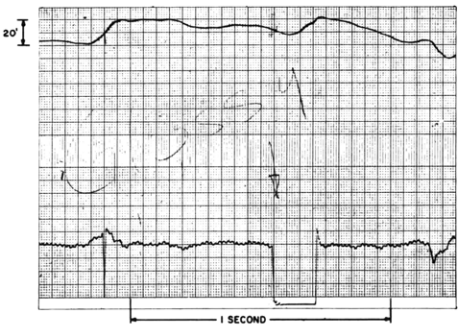



Fig. XXI-4. Detected test flash occurring during drift.

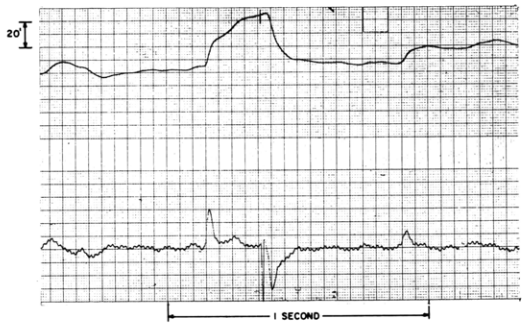



Fig. XXI-5. Test flash triggered by the first saccade and delayed. By chance the flash occurred during the suppression interval surrounding the second saccade, and was, therefore, undetected.

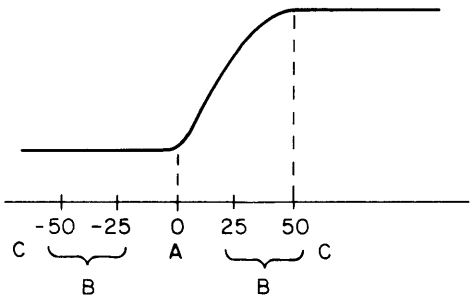
Figures XXI-2-XXI-5 are time functions illustrating results obtained during the various conditions of the experiment. In all cases the upper trace represents eye position as a function of time. The lower trace represents: (a) the derivative of eye position; (b) the trigger pulse to the strobe (sharp downward spike), and (c) the subject's indication of perception (broad downward pulse). Figure XXI-2 shows several test-flash presentations occurring at the beginning of microsaccades. Note that the subject's indication of perception is absent. It sometimes happened that the strobe was triggered by some phenomenon, the nature of which was not entirely clear, perhaps small eyelid movements, rapid drift or rapid drift with a superimposed microsaccade. In such cases the temporal relationship between the test flash and microsaccades was unclear. Such a case is shown in Fig. XXI-3. The subject indicated having seen this flash. Figure XXI-4 shows a test flash occurring during drift. This is seen by the subject. Figure XXI-5 shows two successive, oppositely directed saccades. The first saccade causes the presentation of the test flash but it is delayed by the pulse generator. It happened that the test flash occurred approximately 20 msec before the beginning of the second saccade. It was not seen, since it fell within the period of elevated threshold associated with the second saccade.

The results of the entire experiment are presented in Table XXI-1. Test flash presentations are classified (horizontally) as seen, unseen, total, and per cent seen; and (vertically) as those occurring within ±25 msec of the beginning of a saccade, those occurring within the interval 25-50 msec before or after the beginning of the saccade, and those occurring outside the latter range, i.e., $50 < t < -50$ msec. The results are obvious. A flash is not seen if it occurs as much as 25 msec before or after the beginning of a microsaccade. Flashes occurring more than 50 msec before or after a microsaccade are seen 90 per cent of the time.

A fourth category in Table XXI-1 accounts for stimulus presentations in which the temporal relationship between test flash and microsaccades is questionable. In such

Table XXI-1. Classification of responses to flashes according to time of flash presentation.

| POSITION OF FLASH | SEEN | UNSEEN | TOTAL | % SEEN |
|---|---|---|---|---|
| (A) $-25 < t < 25$ | 0 | 89 | 89 | 0 |
| (B) $25 < t < 50$ <br> $-50 < t < -25$ | 1 | 7 | 8 | 12.5 |
| (C) $50 < t < -50$ | 61 | 7 | 68 | 90 |
| QUESTIONABLE | 8 | 24 | 32 | 25 |




cases the strobe may have been triggered by small eyelid movements, rapid drift or rapid drift with a superimposed microsaccade. The present recordings do not allow us to choose among these possibilities. It is clearly unlikely that these 32 responses could significantly alter the striking results illustrated in the other categories.

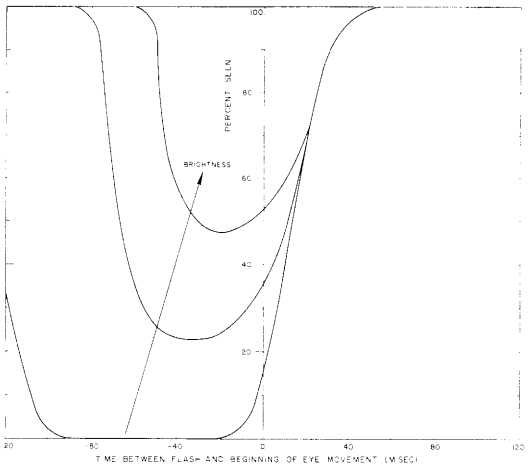



Fig. XXI-6. Schematic representation of the influence of test-flash intensity on the shape of the saccadic suppression curve.

4. Discussion

The saccadic suppression associated with microsaccades might be expected to exhibit a time course similar to that observed with voluntary saccadic eye movements.[6-8] We have also noted that the shape or time course of the saccadic suppression curve for voluntary saccadic eye movements is parametrically determined by the intensity of the test flash. This is shown schematically in Fig. XXI-6. As the intensity of the test flash is decreased, the dip in sensitivity becomes broader and

deeper. A similar effect might be expected in relation to microsaccades.

If the threshold of vision is elevated during the microsaccades that accompany "steady" fixation, threshold cannot be validly determined by presenting flashes to a subject without controlling for the effects of the transient changes in threshold caused by saccadic suppression. Such an uncontrolled determination would correspond to an attempt to perform a static test on a system that is not in the steady state. It should be remembered that we have been able to record only movements that have a detectable horizontal component. If we were able to record all movements, regardless of direction, it would become evident that microsaccades occur more frequently than is indicated by our records. Since the suppression effect of these movements is likely to be independent of the direction of the movement, it is possible that uncontrolled attempts to determine visual threshold are rather significantly affected.

5. Conclusions

It is clear that saccadic suppression, a period of increased visual threshold, is associated with horizontal microsaccadic eye movements; thus the generality of this phenomenon is extended to the smallest involuntary saccadic eye movements.

These results indicate that measurements of visual threshold might be more validly carried out if such determinations were controlled for the transient effects of microsaccadic eye movements or visual sensitivity.

B. L. Zuber, Anne Crider, L. Stark

References

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## C. SUPPRESSION OF THE PUPILLARY REFLEX ASSOCIATED WITH SACCADIC SUPPRESSION

### 1. Introduction

In continuation of the study of visual suppression during eye movement,[1] an attempt was made to determine the degree to which the pupillary reflex is involved in this phenomenon. The exact site of the suppression mechanism is highly speculative, and we hoped that these experiments might elucidate whether or not this mechanism might be attributable to the sensory end of the system. Little research has dealt with concurrent pupillary and visual suppression. Barany[2] indicated that during retinal rivalry there is a decrease in the pupil reactivity to a flash of light presented to the eye that is being suppressed. There have been no reports of pupillary suppression during voluntary eye movements.

### 2. Method

The apparatus that was used was the infrared direct-recording pupillometer. Two fixation points, one on the periphery of the field of vision, and the other in the center were provided. The subject made a horizontal eye movement from the peripheral fixation point to the center, a movement that covered 10° and lasted 100 msec. A suprathreshold flash of light, 20 msec in duration, was presented to the eye at the onset of the eye movement. This flash illuminated the entire field of vision. The lens system of the pupillometer is designed so that the flash of light is focused at the center of the pupil. The background light is minimized to lessen any pupillary response caused by illumination of new retinal areas exposed by the eye movement. Both fixation points are equidistant from the eye to eliminate pupillary changes associated with accomodation. The intensity of the light in the 20-msec flash was bright enough to elicit a pupil response to every flash presented during eye fixation, but dim enough in intensity so that the subject experienced visual suppression during the eye movement, but not during fixation. All pupillary responses for each test were averaged on the GE225 computer.

### 3. Results

Control experiments of the pupil response were conducted (a) when the eye was centrally fixated, (b) when the eye was peripherally fixated, and (c) when the eye moved laterally from the periphery to the center without receiving a flash. It is estimated that 90 per cent of the flash-illuminated retina was common during the movement from peripheral to central fixation. Since the latency of the pupillary reflex is approximately 250 msec, all pupil responses during eye movements were measured when the eye was centrally located.

The results of the fixation controls (Fig. XXI-7) show similar averaged pupillary

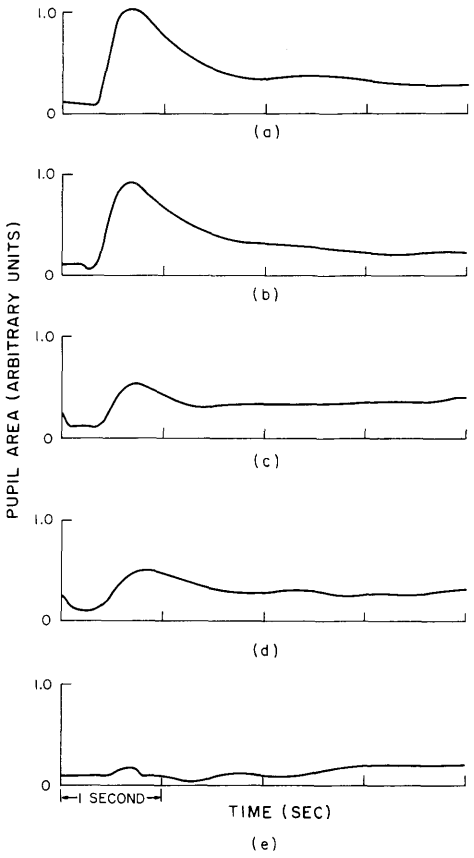


Fig. XXI-7.

(a) Central fixation (12). Peripheral fixation (16). (c) Eye movement with flash (17). (d) Eye movement without flash (16). (e) Pupil response to flash presented during eye movement (curves (c) and (d)). Duration of sampling, 4 sec. (Numbers in parentheses refer to number of responses averaged on the computer.

contraction to a flash of light, regardless of whether the eye was centrally or peripherally fixated. The control test in which the eye movement occurred without a flash (Fig. XXI-7d), and therefore with pupillary changes caused only by accommodation and/or illumination of new retinal areas, shows some pupillary contraction. The averaged results of the pupillary contraction during the identical eye movement with the presentation of the flash (which started ~20 msec after the onset of the eye movement) gave a comparable pupillary contraction (Fig. XXI-7c). To determine the effect of only the flash on the pupil response during an eye movement, the eye-movement control is subtracted from the results obtained with a flash during the movement. The resulting response (Fig. XXI-7e) indicates that the pupil response to a flash of light was indeed suppressed.

These results demonstrate that there is a suppression mechanism affecting the pupillary response to flashes that were visually suppressed during eye movements. Future experiments will involve variation not only of the flash intensity and duration but also of the time of presentation of the flash with respect to the eye movement, to see if the time course of pupillary suppression is identical to that of visual suppression.

M. Lorber, B. L. Zuber, L. Stark

## References

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## D. LIGHT INHIBITORY EFFECTS IN THE CRAYFISH SIXTH GANGLION

While engaged in the study of the nonlinearities that the sixth photosensitive ganglion of the crayfish exhibits as a light intensity to frequency transducer, we found some inhibitory light effects that can be considered important in the analysis of the nonlinearities of the system.

### 1. Methods

Experiments have been performed with in vitro and in vivo preparations of the ventral ganglionic cord.

In the in vivo experiments the sixth ganglion and its roots were left intact, attached to the body of the animal. The fifth and fourth ganglion were isolated by cutting the ganglionic roots and the surrounding connective tissue. The ganglionic chain was cut between the fourth and third ganglion.

The electric signal was picked up by a pair of platinum electrodes, one of which was positioned between the fifth and the fourth ganglion, thus supporting the chain in the air; the second was connected to the animal in the vicinity of the sixth ganglion.

In the in vitro experiments the sixth ganglion was detached, and the whole chain was transferred into a Ringer solution bath.[1] During the recording, only the sixth ganglion was immersed in the Ringer, while the chain was lifted in the air by one of the recording electrodes. The second electrode was immersed in the Ringer bath.

The preparations were maintained in a recording chamber with 100 per cent humidity and constant temperature (around 20°C).

The electric pulses generated in the cord were amplified and passed through an

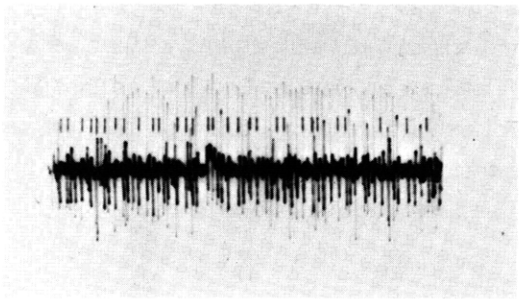

Fig. XXI-8. Oscilloscope display of the nerve impulses from the ventral ganglionic chain of the crayfish. The pulses selected by the electronic window are tagged by means of the Z modulator.

electronic window that selected only the pulses of the two light sensitive fibers.[2] The adjustment of the window so that the desired pulses were picked up was facilitated by tagging the selected pulses with the help of the Z modulator of an oscilloscope (see Fig. XXI-8). The output of the window was fed through an averaging electronic circuit to a Sanborn recorder.

2. Results

In some in vitro preparations that were kept for as long as 24 hours, the delay of the light response increased to several seconds. In such cases an "on-inhibition" of the spontaneous activity was observed a few seconds after the light stimulation (Fig. XXI-9). A similar type of on-inhibition has been observed in crayfish preparations artificially photosensitized with dyes.[3]

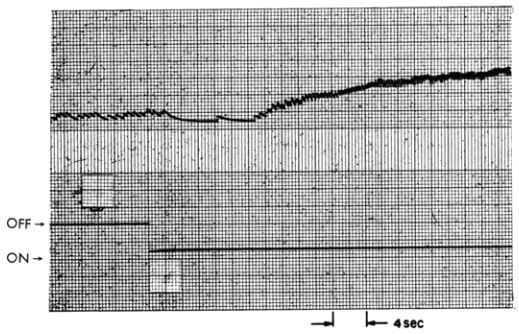


Fig. XXI-9.

On-inhibition. Paper recording of the average response to a step of light. The low activity of the preparation allows the individual pulses to be seen. Notice the inhibition of the spontaneous activity following the onset of the stimulation.

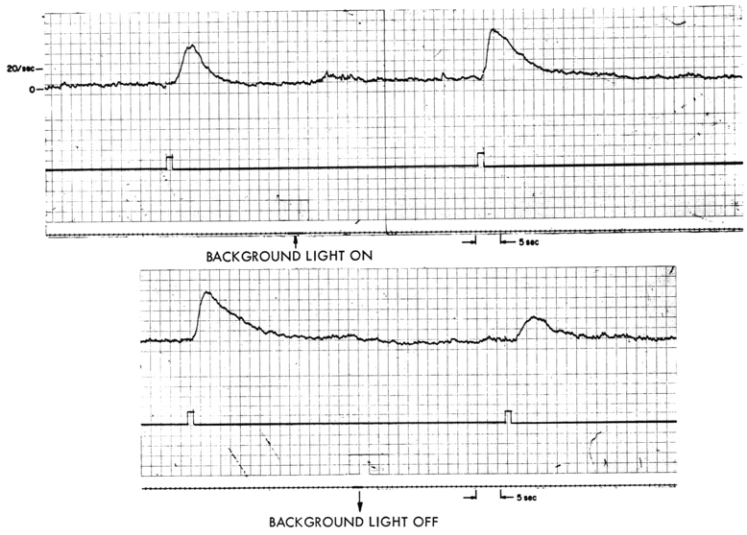


Fig. XXI-10. Off-inhibition. Average response to light pulses under different background illumination. The two fragments of the figure belong to a continuous record, the lower following the upper one. Notice that when the background illumination is removed the response to the light pulse is considerably lower than before or during the background illumination.

Another type of inhibition, "off-inhibition," was caused by the removal of a background light (Fig. XXI-10). Short-pulse stimulation was applied before, during, and after the background illumination. We see in Fig. XXI-10 that the response to the pulses is smallest following the removal of the background light. At higher intensities of the

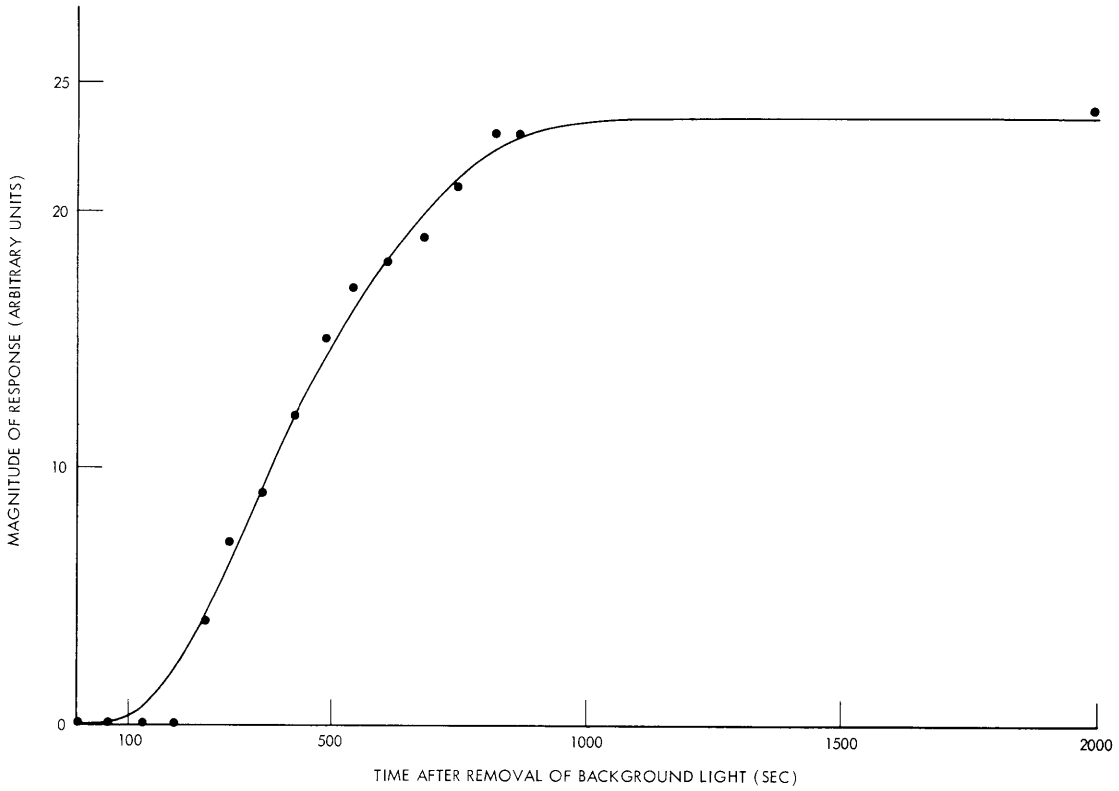


Fig. XXI-11. Time course of the off-inhibitory effect.

background light the response could be eliminated completely. The off-inhibition caused by the removal of the background light recedes slowly over a period of a few minutes (Fig. XXI-11).

From the described experiments, it appears that an inhibitory period follows both the onset and the removal of a light stimulation. The fact that the on-inhibition was seen only in long-lasting preparations could be explained by the effect that the long usage of the preparation has on the timing of competing excitatory and inhibitory mechanisms. The off-inhibition, following the removal of the light, seems to affect the excitability of the system and not the DC response.

J. Negrete, Guillermina N. Yankelevich, G. Theodoridis, L. Stark

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## E. SIGNAL INFORMATION CARRIED BY A TRAIN OF NERVE PULSES

The photosensitive 6$^{th}$ abdominal ganglion of the crayfish has been used before in this laboratory to study the relationship between the light signal and the generated nerve pulses. The mean-pulse frequency was found to be proportional to the logarithm of the light intensity and a transfer function has been established for this system.[1]

The purpose of this research was to find out if, besides the mean-pulse frequency, there are other carriers of signal information in the pattern of the generated nerve pulses. The crayfish sixth ganglion is particularly suitable for this type of study as it contains only two independent photosensitive units[2] that can be compared with respect to the way in which they transmit the common light signal. Separating the two light-sensitive fibers by microdissection and recording their pulse trains simultaneously, we found them to be uncorrelated as far as the detailed pulse pattern is concerned. If the detailed timing of the individual pulses carried useful information, there would be a very large amount of information transmitted through the generated pulse trains. Our results indicate that this is not the case in this system, and that the light-signal information is transmitted through the mean-pulse frequency and possibly through some other parameter as, for example, the variance.

### 1. Methods

The procedure for handling the ganglionic chain and recording the nerve impulses of the photosensitive cells was outlined in Section XXI-D.

In order to be able to compare the simultaneous activity of the two light-sensitive fibers, the ganglionic chain was split longitudinally in two halves through the fourth and the fifth ganglion, reaching almost as far as the sixth ganglion. As soon as the surrounding connective tissue was dissheathed, the chain could be easily separated into two cords, isolated from each other, even through the fifth and the fourth ganglion.

In order to have the fiber activity in a form easily usable by a computer, the output of the electronic window, which selected the desired pulses from the light-sensitive cells, was fed to a flip-flop circuit that produced an on-off type of record as presented in Figs. XXI-13, XXI-14, and XXI-15.

Each change of level in the output of the flip-flop circuit corresponds to a recorded pulse coming from the nerve. The output of the flip-flop was recorded on tape and then played back at one-eighth the original speed in order to be recorded on a paper Sanborn recorder.

### 2. Results

The first step was to establish that there are only two light-sensitive fibers in the nerve cord, as has been indicated by previous work.[2] The pulse trains obtained under

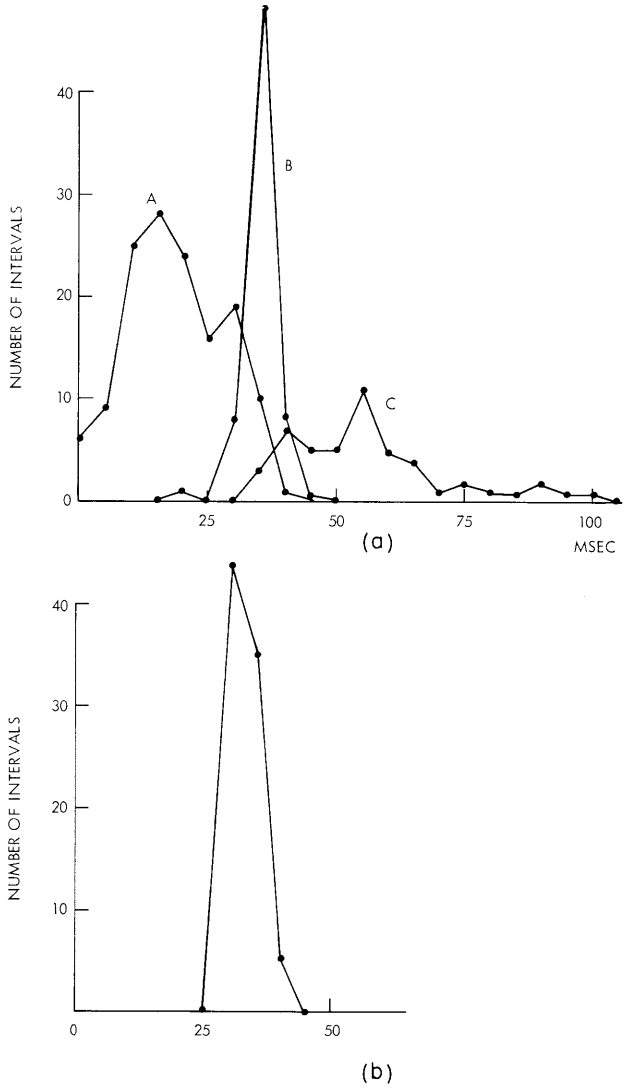


Fig. XXI-12. Interval histograms of the activity under stimulation of the two light-sensitive cells.
(a) The two cells recorded by the same electrode. Histograms are presented for the intervals between successive pulses (curve A), between every second pulse (curve B), and between every third pulse (curve C).
(b) Histogram of the intervals between successive pulses in one of the cells recorded separately.

light stimulation, before splitting the cord, looked like two superimposed periodic pulse sequences. This is made clear by the interval histograms presented in Fig. XXI-12a. This figure contains histograms of intervals between successive pulses (A), between every second pulse (B), and every third pulse (C). One can observe that the distribution becomes very sharp as we go from the single-interval to the double-interval histogram, and widens again when triple intervals are taken. When the cord is dissected, the single-interval histograms of each separated branch show a very sharp distribution similar to a double-interval histogram of the complete cord (Fig. XXI-12b). The apparent randomness of the combined signal is due to the superposition of two fairly periodic signals.[3]

Different types of spontaneous activity were observed in our experiments. A feature that was present in several cases (although not always) was the appearance of coupled pulses (see Fig. XXI-13) with a time separation of 10-40 msec. The distance between the couples can be rather irregular, ranging from approximately 150 msec (Fig. XXI-13a) to ~1 sec (Fig. XXI-13b), or can be quite irregular (Fig. XXI-13c). Usually the in vitro preparations presented higher regularity than the in vivo ones. Often the in vitro preparations, after a few hours, presented practically zero spontaneous activity.

When the activity of the two dissected branches was recorded simultaneously, no correlation between the timing of the pulses of the two fibers was observed (Fig. XXI-14c and d). In Fig. XXI-14e, f, and g several histograms are given of the intervals between a pulse in one fiber and the next pulse in the other fiber. We see that the histograms are approximately linear on a semi-logarithmic scale, as it should be if the pulses of

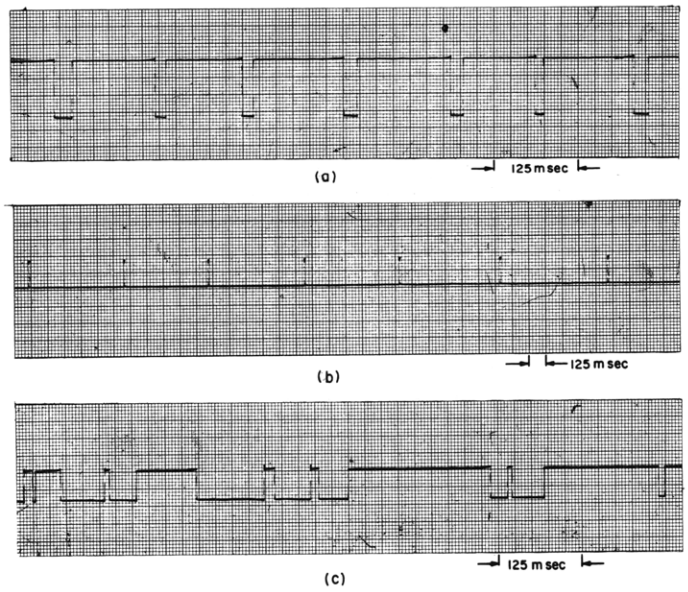


Fig. XXI-13. Pattern of spontaneous activity observed in different isolated fibers. Records (a) and (b) in vitro, (c) in vivo.

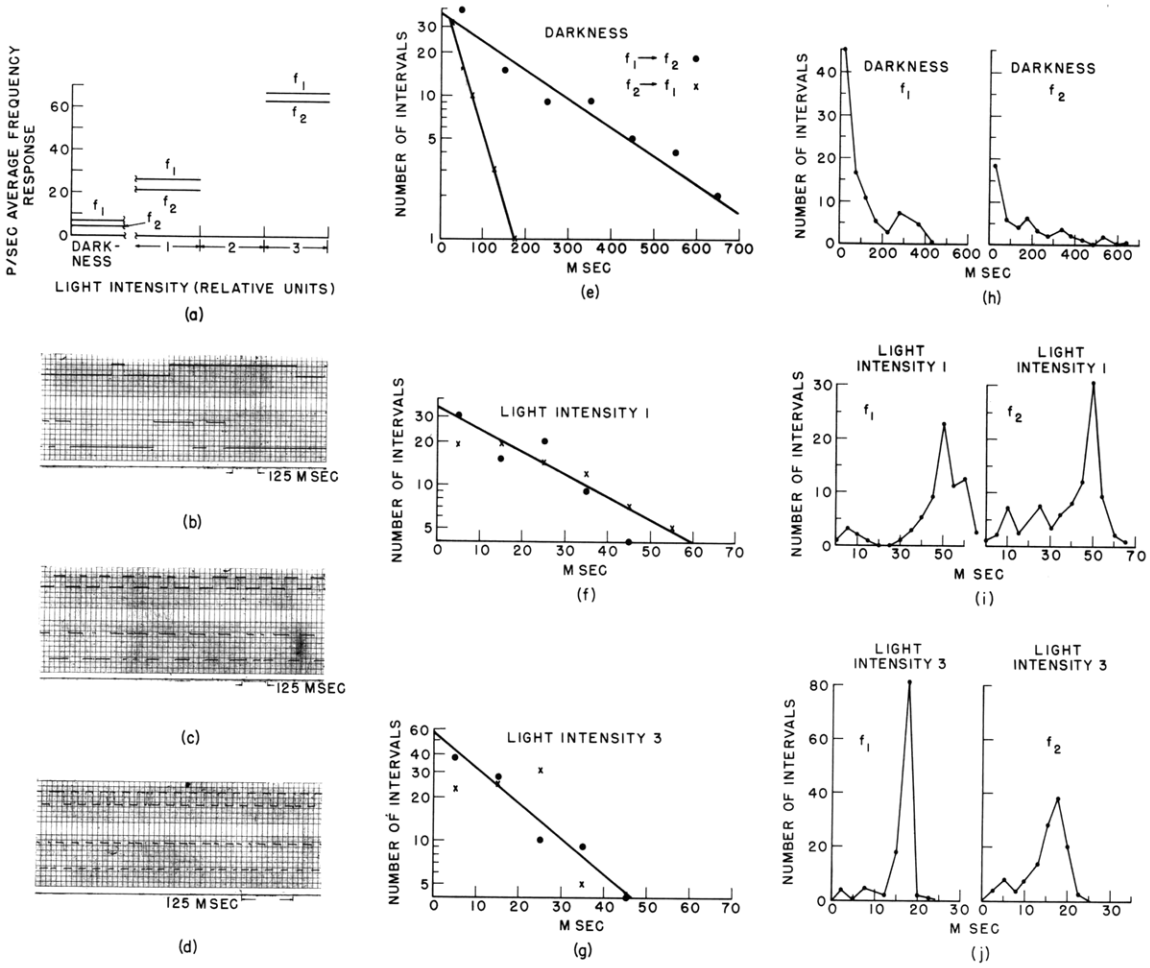


Fig. XXI-14. Comparison of the activity of the two light fibers ($f_1$ and $f_2$) recorded in vivo simultaneously, but separately under various light intensities. (a) Average frequency response of the fibers in darkness and at two different light levels. (b), (c), and (d) Firing pattern of the two cells in darkness (b) and at the lower (c) and higher (d) light levels. (i), (f), and (g) Histogram of intervals from one pulse in one fiber to the next pulse in the other fiber. (h), (i), and (g) Interval histogram for the activity of the two fibers ($f_1$ and $f_2$) in darkness and at two different light levels.

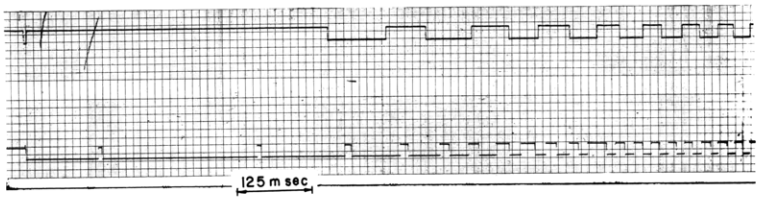


Fig. XXI-15. Pattern of the transient response of the two fibers after the onset of light.

the two fibers were uncorrelated; therefore, the intervals follow a Poisson distribution.

Further evidence of the anatomical independence of the two fibers is the fact that in some cases the average frequency of the spontaneous activity is very different in each of them.

When the light stimulus was applied in the form of a step with a short rise time the two fibers responded with different transients, as can be seen in Fig. XXI-15. This may be taken as evidence regarding lack of redundancy. In this particular experiment the fiber of the lower trace, which showed a sharp increase in frequency, had a lower spontaneous activity. At the steady state both fibers reached approximately the same frequency.

A general feature of the transient responses to a high level of light is that they present a peak in the average frequency approximately 1 sec after the start. The peak frequency is twice as big as the steady-state frequency that follows.

The main feature of the steady-state response to light is the increased regularity in the intervals between pulses in both fibers in contrast with the spontaneous activity that presents a high irregularity (Fig. XXI-14h, i, and j). The light-response regularity is more accentuated in the in vitro preparations, as can be seen by comparing the two histograms given in Fig. XXI-16.

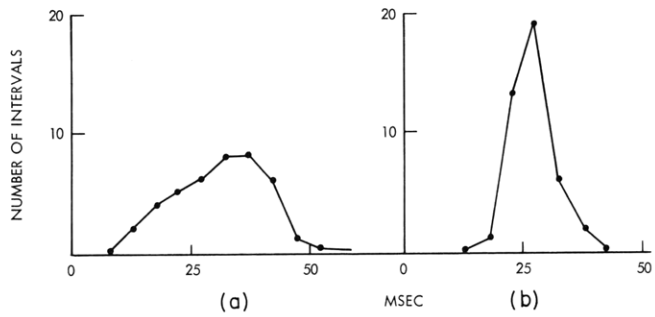


Fig. XXI-16. Interval histograms of the activity under light stimulation of a single fiber in vivo (a), and in vitro (b).

When the level of the stimulating light was very low, we observed a slow increase of the average frequency which, after several seconds, settles to a slightly higher level than the spontaneous activity without a considerable change in the irregularity of the intervals. More experiments in this region of low light levels are now under way.

One can, however, find experiments in which in darkness and at different light intensities, the average frequency differs little between the two fibers (Fig. XXI-14a). Direct inspection of the records shows a completely different pulse pattern of activity between them (Fig. XXI-14b-d). The lack of correlation of the interfiber interval histograms, between a pulse in one fiber and the next pulse in the other, still can be shown (Fig. XXI-14e and f).

The interval histograms of each fiber show, in this same experiment, that the mode interval, the mean interval, and the dispersion of the intervals can be correlated with the light levels (Fig. XXI-14h, i, and j) and thus with each other.

3. Discussion

The main conclusion that can be drawn by observing simultaneously, but separately, the response of the two light fibers is the absence of correlation between the detailed timing of the pulses in the two sequences. This fact indicates that the large amount of information contained in the detailed pulse pattern[4] is not used for physiological purposes. This conclusion is based on the assumptions that both pulse sequences will go through an identical decoding mechanism and that they are carriers of the same signal.

The carrier of the information seems to be the average frequency of the pulse discharge or possibly another parameter of the interval distribution as, for example, the variance. This point will be examined further by exploring the region of low light stimulation where some change in pulse frequency seems to occur without a parallel change in the shape of an interval distribution.

The observed pattern of the pulse trains, particularly during spontaneous activity, may contain some information on the nature of the pulse-generating process. The presence of paired discharges was a characteristic feature in several preparations. The interval between the paired pulses ranged form ~10-40 msec, being rather constant in some cases and fairly varied in others. The intervals between the pairs covered a much wider range (from ~50 msec to more than 1 sec), and were also rather regular or more or less random, in different cases. Some times, when the light stimulus was applied, the pairs started to appear at increasingly smaller intervals until a regular pulse sequence resulted. The interval then was almost equal to the short interval between the paired pulses of the spontaneous activity (Fig. XXI-15, lower trace). This picture seems to indicate that in the generation of the pulses, two processes may be involved in the generation of the pulse pattern:

1. A "fast process" responsible for the short interval between the paired pulses.

The size of the small interval may be determined either by the refractory period of the neuron or by an excitatory oscillation in the dendrites.

2. A "slow process" responsible for the long intervals between the pulse pairs and connected to the light sensitive mechanism. Noise in the light-sensitive mechanism may cause the variations that are sometimes seen in the size of the long interval during spontaneous activity, and so account for the more irregular pulse patterns observed. Under strong light stimulation the cells are firing at a maximum rate that corresponds approximately to the small interval set by the fast process.

J. Negrete, Guillermina N. Yankelevich, G. Theodoridis, L. Stark

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## F. SINUSOIDAL LIGHT STIMULATION OF THE HUMAN PUPIL SYSTEM

In previous work we have described the use of an on-line digital computer in biological experiments.[1] We now present some preliminary results of experiments done with the on-line computer in investigating the detailed behavior of the human pupil system's response to sinusoidally varying light. The computer generated the required stimulus voltage variation, took in the direct analog response, and then printed out the Fourier analysis soon after termination of the experiment.

Figure XXI-17a is a gain vs frequency description of the pupil response to varying light of three different mean-to-peak amplitudes. Note that the gain in all relevant figures is defined as the ratio of the change of transducer voltage representing pupil area and the change of voltage input into the voltage-to-light transducer. This gain may be converted to the more physical gain definition used earlier[2] by multiplying every value of gain by 0.9. Also, in Fig. XXI-17 the average value of pupil area is ~25 $mm^2$, and to find the actual mean-to-peak excursion of pupil area in $mm^2$ multiply the gain by 0.04 and the input amplitude.

In Fig. XXI-17b we see the phase lag of the system as a function of frequency (all three input amplitudes have almost the same phase lag). Figure XXI-17c illustrates the rectifying properties of the system.

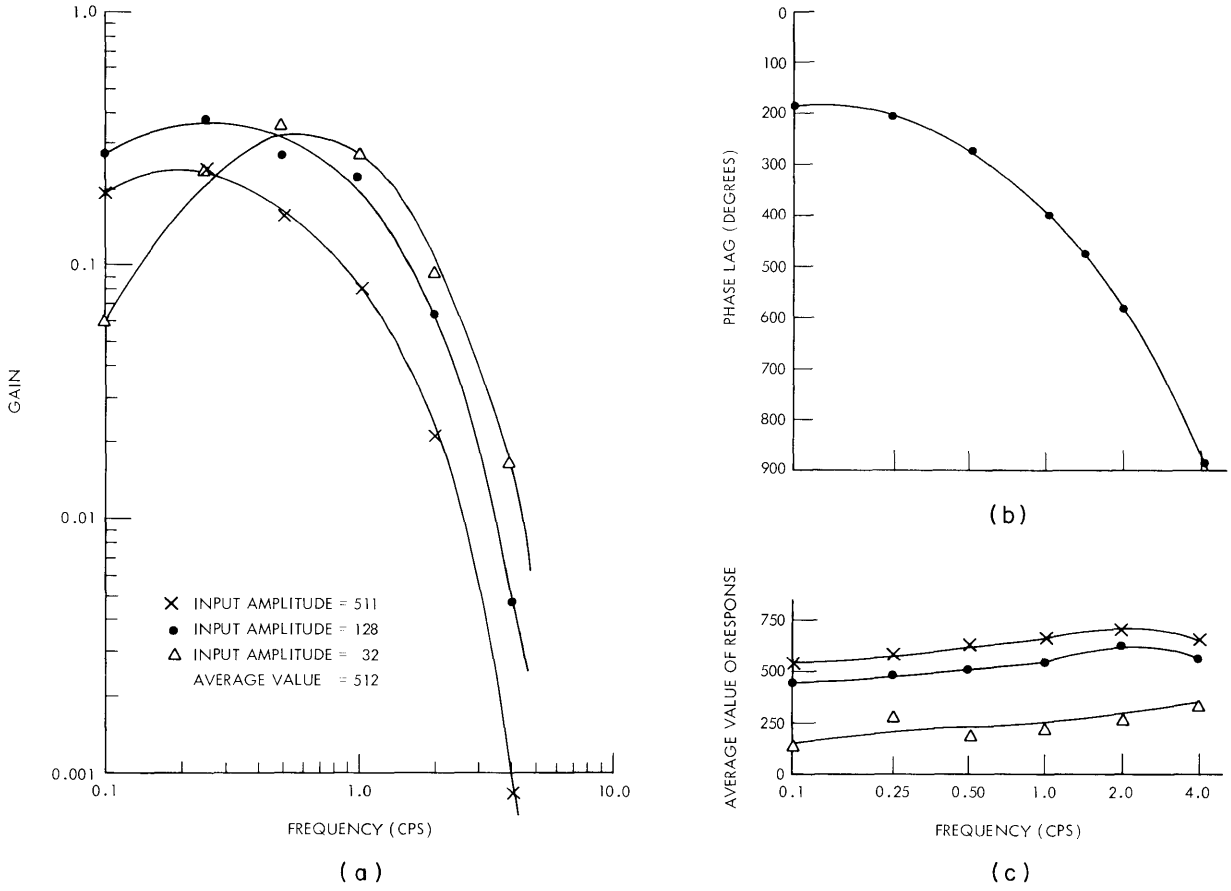


Fig. XXI-17. Gain vs frequency with amplitude of stimulation as parameter.

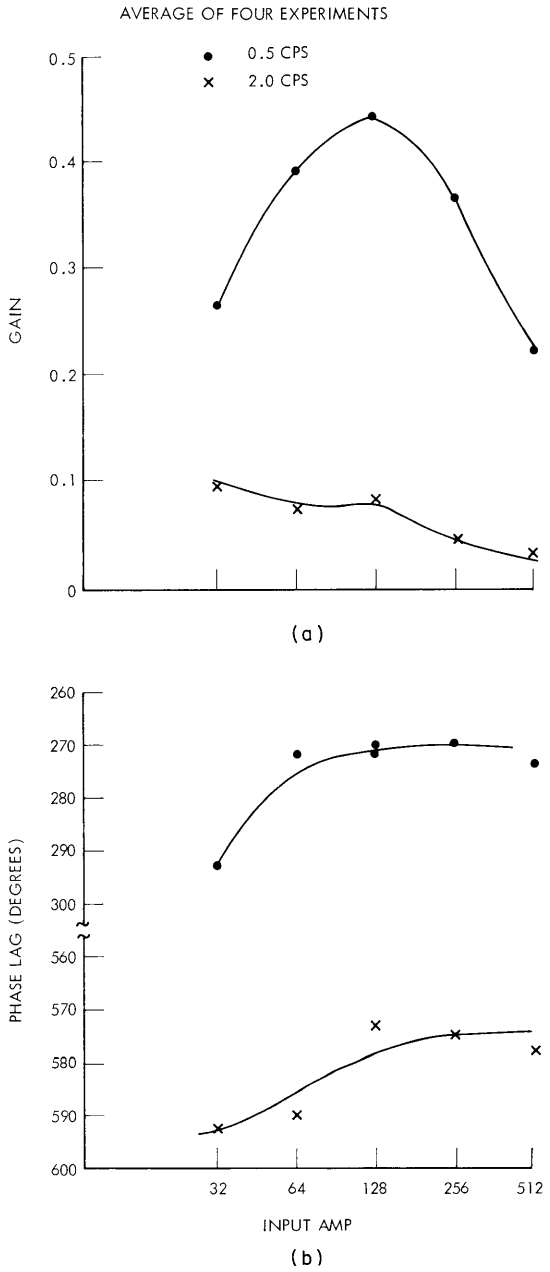


Fig. XXI-18. Gain vs amplitude with frequency as parameter.

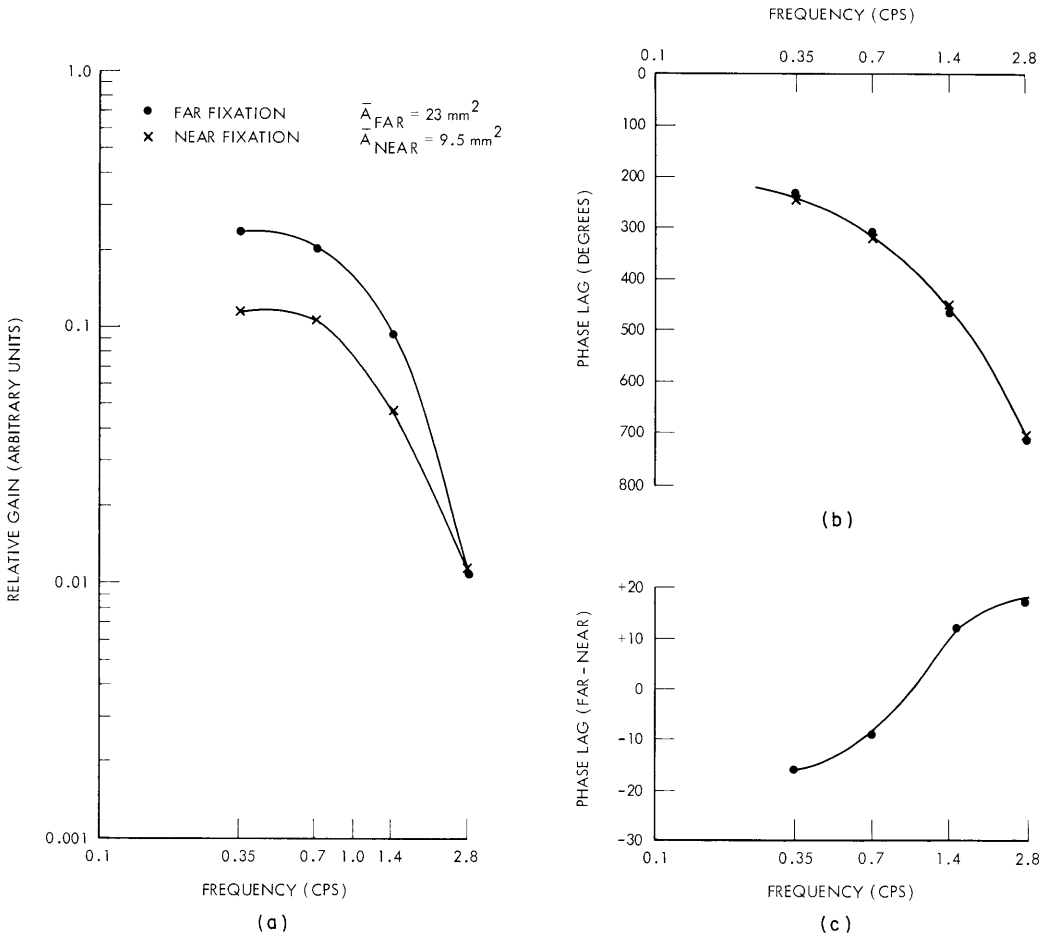


Fig. XXI-19. Gain vs frequency. (Average of seven experiments.)

The pupil response to sinusoidal light variation of different amplitudes has been further investigated to obtain a better understanding of some of the nonlinearities in the system. In Fig. XXI-18 we see the gain and phase of the system plotted as a function of input amplitude for two different frequencies. Note the sharp drop in gain for low-amplitude stimuli on the 0.5-cps curve. We believe that this represents the effect of a visual threshold operator on the pupil response. The reduction in gain with increasing amplitudes of input signal represents the usual scale compression or saturating nonlinearity.

The accommodative pupillary response, the change of the pupil size with fixation distance, is an extremely useful and relatively easy method for observing the effect of the average value of pupil size on the steady-state light reflex of the pupil. Specifically, this well-known accommodative response causes the pupil to constrict as fixation distance is decreased. The average of seven experiments, each one investigating simultaneously gain and phase vs frequency of the light-reflex system at near and far fixations, is seen

in Fig. XXI-19. Careful examination of Fig. XXI-19a reveals an asymptotic slope of -3 for the far-fixation curve, and a slope of approximately -2.5 for the near-fixation curve. This half-order difference of the two states of the system is seen to be consistent with Fig. XXI-19c where the asymptotic phase difference seems to be approaching 45°. Note that the -3 slope for far fixation is identical with that obtained earlier.[2]

A. A. Sandberg, L. Stark

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## G. EFFECT OF MYDRIATIC DRUGS ON PUPILLARY DYNAMICS

This report deals with the effect of seven locally administered pupil-dilating drugs: (a) three of which paralyze the iris sphincter (parasympatholytic action); (b) two of which stimulate the dilator muscle of the iris (sympathomimetric action); (c) two combinations of (a) and (b). The actions are represented in Fig. XXI-20.

One subject, a blue-eyed, white female, 25 years old, with no evidence of eye

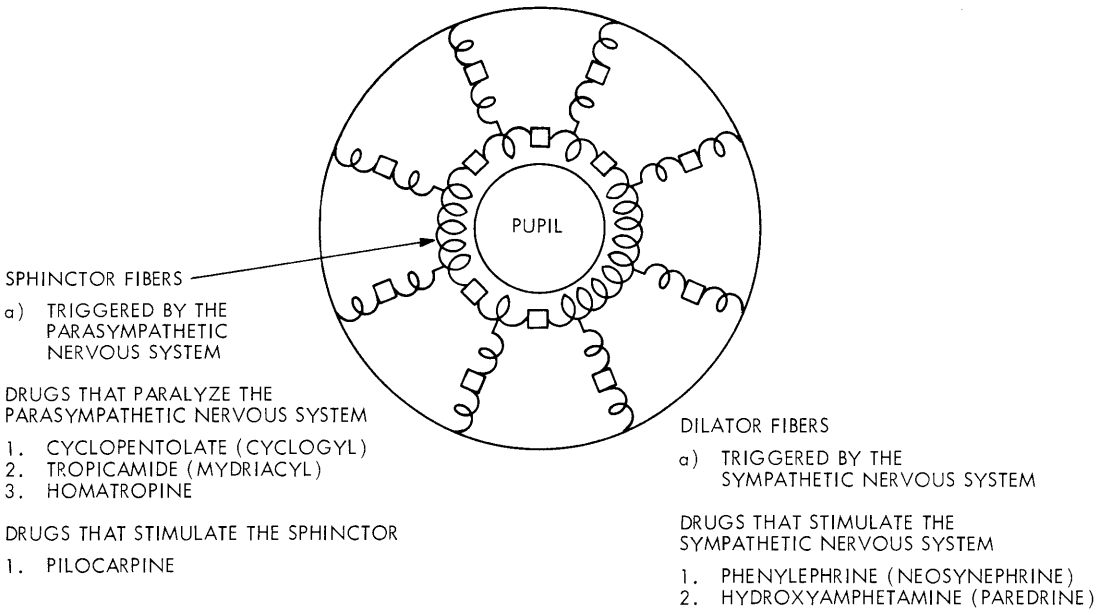


Fig. XXI-20. Pharmacology of various drugs on the pupil.

pathology and a minimal refractive error was used for all the mydriatics tested. The subject was firmly positioned in front of the pupillometer[1] utilizing a bite board and head rest. Alignment was checked by the experimenter by using a combination camera and sighting device. After a constant 10-minute period of dark adaptation, a series of ten 100-msec light impulses, each separated by a time interval long enough to allow the pupil to return to its prestimulus level, was flashed into the subject's eye. One drop of mydriatic was then carefully placed over the surface of the cornea. The subject then returned to the apparatus, and a record of the pupillary size and reaction to light was made on two channels of a Sanborn recorder at 5- or 10-minute intervals until the pupil had reached maximal mydriasis.

The different drug experiments were spaced seven days apart, so that the effects of one pharmacological agent would not influence the next. The following local agents were used: 1% tropicamide (Mydriacyl), 1% hydroxyamphetamine (Paredrine), 1% cyclopentolate hydrochloride (Cyclogyl), 10% phenylephrine hydrochloride, (Neosynephrine), 2% homatropine hydrobromide, combinations of 1% cyclopentolate and 10% phenylephrine, and 2% homatropine and 10% phenylephrine.

Within the range of pupillary diameters from 5.8 mm to 8.3 mm all of the drugs caused the pupil to enlarge while progressively decreasing the pupillary light reaction specifically; the sphincter-paralyzing drugs (tropicamide, cyclopentolate, and homatropine) caused pupillary dilation while progressively decreasing the pupillary light response to zero. The dilator stimulating drugs (neosynephrine and paredrine) increased the pupillary size while limiting the pupillary reaction to a low but measurable level. The combination of the two classes of drugs increased the level of pupillary enlargement above that produced by either component. The dilator stimulating agent did not, however, hasten abolition of pupillary paralysis.

Table XXI-2. Results.

| Agent | Time for pupillary reaction to stabilize | Maximum pupil size |
|---|---|---|
| 1% Cyclopentolate (cyclogyl) | 22 minutes | 7.8 mm |
| 1% Cyclopentolate + 10% Phenylephrine | 22 minutes | 8.3 mm |
| 1% Tropicamide | 22 minutes | 7.4 mm |
| 1% Hydroxymphetamine (pacedrine) | 55 minutes | 7.8 mm |
| 10% Phenylephrine (neosynephrine) | 70 minutes | 8.0 mm |
| 2% Homatropine | 43 minutes | 7.4 mm |
| 2% Homatropine + 10% Phenylephrine | 43 minutes | 8.0 mm |

Table XXI-2 illustrates the time to abolition or stabilization of pupillary response for all seven agents.

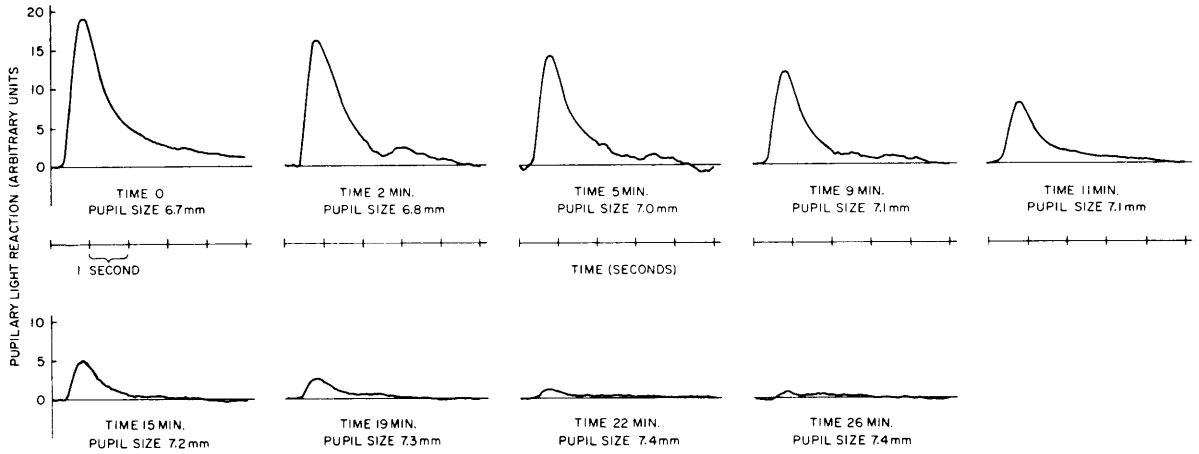


Fig. XXI-21. Computer-derived average pupillary light response representations at various intervals in time after the local administration of one drop of 1% tropicamide.

Figure XXI-21 represents the progressive, symmetrical diminution of the pupillary response to light under the influence of 1% tropicamide. This particular record

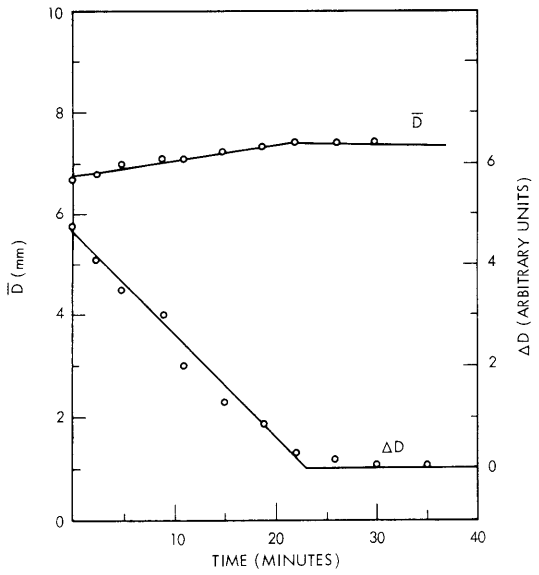


Fig. XXI-22. Time course of 1% tropicamide on pupil size ($\overline{D}$) in millimeters, and amplitude of pupillary light reaction ($\Delta D$) in arbitrary units.

represents an averaging by the G. E. 225 computer of pupillary responses for each of the intervals of measurement. The base line, although changing as the pupillary

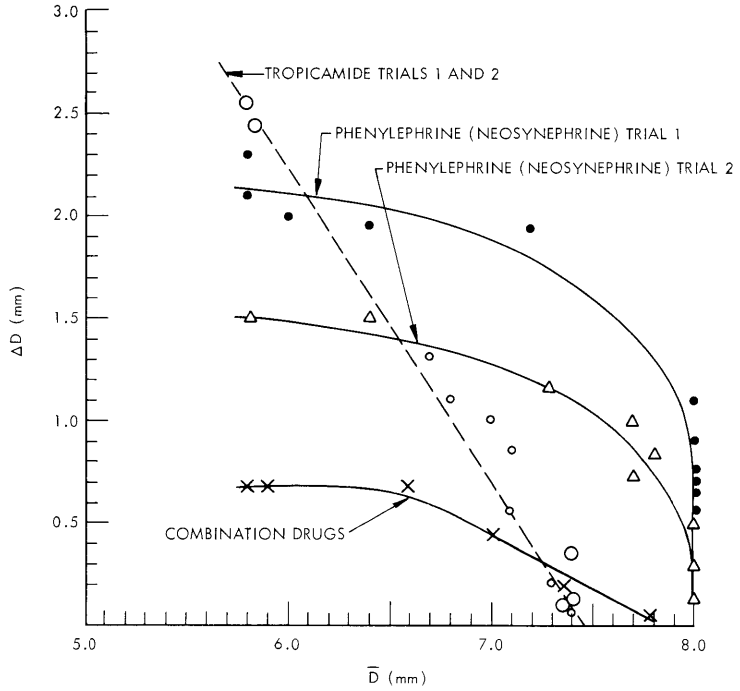


Fig. XXI-23. Relationship of pupillary diameter $\overline{D}$ in mm to amplitude of pupillary contraction $\Delta D$ in mm for trial 1 and trial 2 of the dilator stimulating drug phenylephrine. Trial 1 and trial 2 of the sphincter-paralyzing drug tropicamide, and an average of the experiments in which the combination drugs homatropine and phenylephrine and cyclopentolate and phenylephrine were used.

diameter increases during the experiment, has been adjusted to display more graphically the degradation of the response.

Figure XXI-22 illustrates the time course of 1% tropicamide on pupillary diameter and pupillary reaction.

Concentrations of 4% pilocarpine hydrochloride (a sphincter stimulator) could not alter maximal mydriasis or reactivate a paralyzed pupil during 4 hours of observation following instillation of cyclopentolate (a parasympatholytic agent). One per cent tropicamide was able to reverse 4% pilocarpine miosis and achieve maximal mydriasis in 30 minutes. Four per cent pilocarpine induced significant miosis in a pupil maximally dilated by 10% phenylephrine in 20 minutes.

Figure XXI-23 shows the relationship of pupillary diameter $\overline{D}$ to amplitude of pupillary contraction to light $\Delta D$. In general, as $\overline{D}$ increases, $\Delta D$ decreases; however, the relationship varies for each category of drug. The dilator stimulating drug phenylephrine markedly increased $\overline{D}$ while having a small effect on $\Delta D$. The portion of the curve showing a constant $\overline{D}$ with a diminishing $\Delta D$ suggests a saturation effect on pupillary sizes with a concomitant weakening effect on active sphincter contraction. The

sphincter-paralyzing drugs tend to change $\overline{D}$ and $\Delta D$ in a more dependent fashion. This is consistent with the idea that the parasympathetic sphincter system is more important than the dilator system in pupillary constriction. These experiments further indicate that the effect of different types of drugs on pupillary reaction, $\Delta D$, is not solely through their control of pupillary size.

D. Miller, L. Stark

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## H. TIME COURSE OF ACTION OF SYSTEMIC DRUGS ON THE PUPILLARY RESPONSE

The primary motivation for this experiment was to set up a protocol for future pupil-drug experiments. These experiments will determine the time course of action of drugs on the pupil system, with the Smith-Kline Pupillograph[1] used as a monitor of pupil diameter, and a G.E. 225 computer used on-line to provide both pulse stimuli and a computational facility[2] for averaging the responses and providing immediate graphical representation of these averaged responses.

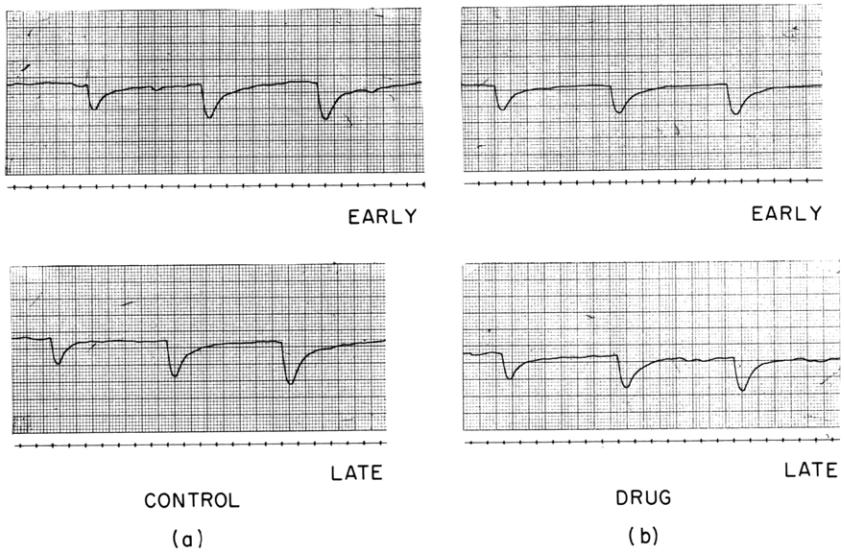


Fig. XXI-24. Monitored pupil responses.

For our initial study 8 mg of cyproheptadine was administered under the supervision of Dr. David Miller, of the Massachusetts Eye and Ear Infirmary. The pharmacology[3] of cyproheptadine (Periactin) makes it appropriate for the study of muscular organs like the iris. Its major properties are (a) antagonizes seritonin induced smooth muscle contraction in dogs, and guinea pigs, (b) antagonizes histamine induced smooth muscle contraction in the same animals, and (c) acts as a central nervous system depressant in monkeys.

The experiment consisted of two sections. A 3-hour drugless control preceded a 3-hour experiment with the drug used. Physically, stimulation was provided uninocularly by a glow-modulator focused on the iris and pulsed automatically by the analog output of the computer. All pulses were superimposed over a background level of illumination that was sufficient to just keep the glow-modulator in the "on" or "ready" position, its lowest level of illumination. Three different pulse heights (all 47.7 msec wide) were used and their responses averaged individually.

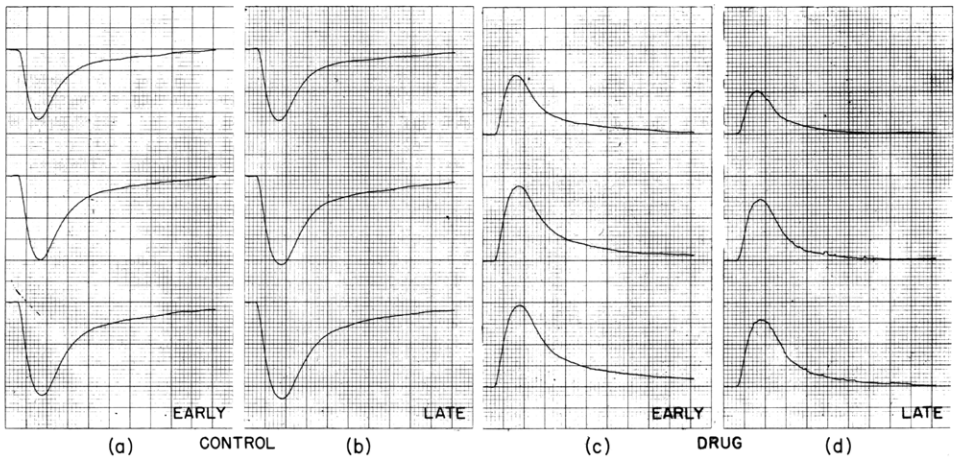


Fig. XXI-25. Average of nine responses for three pulse heights.

Figure XXI-24 shows the individual monitored responses. The averaged responses in Fig. XXI-25 are the result of averaging 9 responses for each of the 3 pulse heights. The final results derived from these data are illustrated in Fig. XXI-26.

The most significant result is shown in Fig. XXI-26b. After 2 hours, there occurred a sizable contraction of the pupil; this lasted for somewhat more than 30 minutes, at which time the pupil returned to its normal size. There was a small change in the response $\Delta D$ during this period, but this is felt to be relatively insignificant, as comparison of Fig. XXI-26c and d shows little difference between the control and the drug experiment. In Figs. XXI-24b and XXI-25b noise can be seen in the monitor responses

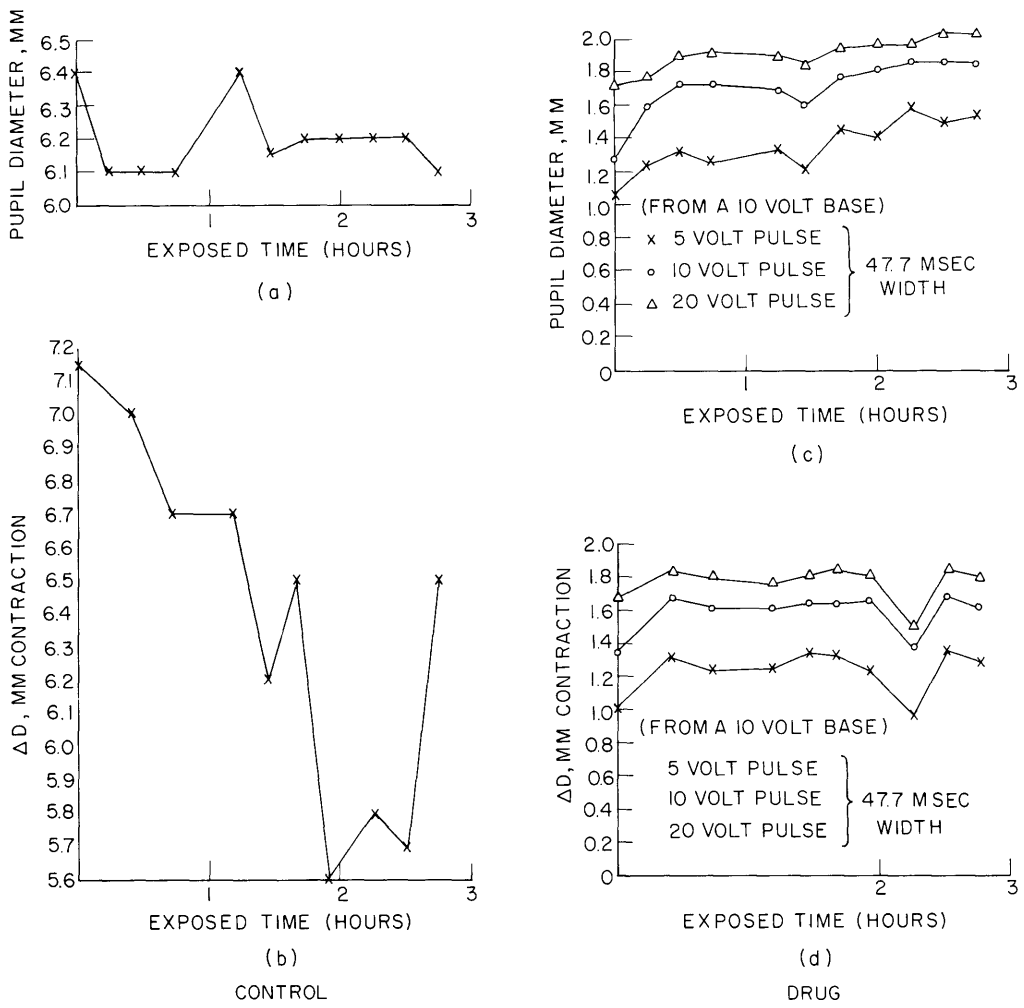


Fig. XXI-26. (a) and (b). Pupil diameter vs time. (c) and (d). Response amplitude vs time. (Three different stimuli.)

and averaged responses. This corresponds in time with both the subject's feeling of drowsiness and with the period of contraction.

D. Miller, R. Reitman, L. Stark

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