

## ACCOMMODATIVE RESPONSE OF THE EYE TO ELECTRICAL STIMULATION OF THE CILIARY GANGLION IN CATS\*

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### INTRODUCTION

The peripheral parasympathetic pathway for the control of accommodation is well known. The preganglionic fibers appear to originate in the Edinger-Westphal nucleus of the IIIrd nerve center. These fibers help form the oculomotor trunk and go to the ciliary ganglion in the orbit. After a cell station, the medullated postganglionic fibers emerge from the ganglion in numerous short ciliary nerves which pierce the sclera in a ring around the optic nerve. Losing their medullary sheath, the fibers course through the sclera to the ciliary plexus, thence to the ciliary muscle.

The smooth ciliary muscle contracts in sphincter-fashion and, through the zonule fibers releases the tension on the capsule of the crystalline lens. In response to the contraction of the capsule, the lens takes on a higher curvature, thus increasing the refractive power of the eye.

Up to the present time studies of the nervous pathways controlling accommodation (reviewed by Morgan<sup>1</sup>) have been concerned not with the mechanism of accommodative gradation but with the pathways for parasympathetic and sympathetic control of accommodation and their relative roles. The results of these studies indicate that in general only the parasympathetic should be considered of practical significance since the sympathetic, through the long ciliary nerves to the eye, controls

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only about 1/10 of the total dioptric range, and this in a negative direction.

The general purpose of this study is to investigate the peripheral parasympathetic mechanism for the graded control of accommodation. Specifically, this paper is concerned with the accommodative response of the cat's eye to electrical stimulation of the ciliary ganglion. This is, perhaps, a first step in the study of the neural mechanism controlling accommodation.

How is accommodation controlled by parasympathetic impulses? It is generally believed that the gradation of maintained motor function depends on two characteristics of nerve propagation: (1) The number (and perhaps distribution) of active fibers in the nerve bundle. (2) The frequency of discharge of these active fibers. These characteristics of motor gradation have been studied in voluntary motor systems<sup>2</sup> and in autonomic effectors<sup>3</sup> such as the sympathetically controlled nictitating membrane of the cat and the parasympathetic (vagus) control of the heart. In so far as we have been able to determine, no one has investigated these control characteristics in the parasympathetic accommodation of the eye.

#### APPARATUS AND PROCEDURE

A Grass Stimulator (Model 3C) provided the electrical stimulus. This oscillator generates monophasic or biphasic wave forms with variable voltage, frequency and pulse duration. The stimulus was applied to the ciliary ganglion by two polyethylene-insulated solid silver wires (No. 24) held together by a larger polyethylene tube. The electrodes were bared at the tip for about two mm. and separated by about one mm. The electrodes were either hooked around the ciliary ganglion or placed astride it. Generally, biphasic pulses\* were used. These were obtained by the differentiation of rectangular waves so that zero potential was reached at the end of each rectangle. The pulse duration of the rectangular waves from which the biphasic pulses were derived was fixed at one msec. Trials with monophasic stimulation (rectangular waves) yielded similar results. Exploratory data with pulse time as a variable indicated that one msec. gave optimum response. Calibration of the stimulator with a cathode-ray oscilloscope against standard laboratory oscillators and the 60 cycle power mains indicated that the stimulator scale readings were 20 per cent high for peak voltage (without a load), 5 per cent high for frequency and 18

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\*Two stimulus pulses, one positive and one negative, were presented in each cycle. These were spaced only one msec. apart and therefore were considered as a single stimulus pulse. The biphasic wave forms were used to minimize polarization.

per cent high for the pulse duration used. These errors are not considered serious and are not corrected in the following data and graphs.

The ciliary ganglion was exposed following the procedure of Shen and Cannon.<sup>4</sup> Nembutal was generally used, but in some instances decerebration provided the anesthesia. A portion of the zygomatic process and orbital wall was cut away and the inferior oblique muscle exposed. The nerve innervating this muscle was followed back to the ciliary ganglion, which was found between the lateral rectus and the optic nerve. After the electrode was fixed on the ganglion, the wound was closed with metal Michel suture clips which also held the electrode in place. In order to avoid eye movements upon stimulation, two or more of the extraocular muscles usually were severed.

Circulation to the eye usually was not seriously disturbed. Only a few of the anterior ciliary arteries and veins which accompany the recti muscles were severed. Generally only two muscles were cut so that even these vessels were not all disrupted. The ciliary body was still served by its usual primary supply, the long posterior ciliary arteries and the venous return through the vortex veins.

A Rodenstock Eye-Refractometer provided an objective measure of the state of refraction of the eye. The spectacle-plane refraction in diopters was read directly from the instrument dial after the target on the fundus was optically focused. A few drops of 1½ % sodium bicarbonate solution were dropped on the cornea after each three measurements. This maintained its good optical quality and prevented it from drying.

Young, fully grown cats were partially iridectomized from several weeks to several months before they were used for measurements. This surgery was necessary since stimulation of the ciliary ganglion would close the normal slit pupil, making optical measurement impossible. It was convenient to have a piece of intact iris which by a slight contraction following stimulation provided a check on adequate placement of the electrode on the ciliary ganglion. There was no need to employ an artificial pupil as would be necessary in a skiascopic determination of the refractive state, since the entrance pupil of the eye-refractometer was smaller than the exit pupil of the eye. Thus no difficulty was experienced because of the increase of optical aberrations arising from the large pupil of the partially iridectomized eye.

The stimulus was applied for about two seconds, just long enough to obtain a measurement of the refraction. This was read and recorded, again taking about two seconds during which time no stimulation was applied to the ciliary ganglion. Each stimulus value was used three times and the corresponding refractions averaged. Stimulus values were applied in ascending order.

## RESULTS

Figure 1 shows the relation between the stimulus electromotive force (E.M.F.) in volts applied to the electrodes at the ciliary ganglion

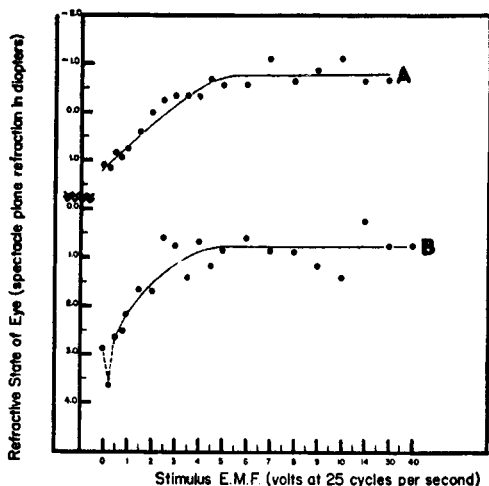


Fig. 1. Stimulus—response curves varying the stimulus E.M.F. A. One eye. B. Contralateral eye of the same cat. Frequently this type of curve plateaus at 3 volts rather than at 5 volts as illustrated.

and the refractive state of the eye as measured at the spectacle plane in diopters. A graded response of accommodation as seen in Figure 1A is produced by varying the voltage of the stimulus. Grading is probably effected by the increasing number of neural elements brought into action by the increasing voltage.\*

Figure 1B shows substantially the same result for another eye. It is worth noting that the accommodative amplitude appears to be about two diopters (D.). One interesting difference in Figure 1B is the apparent initial dip in the curve before the rise. Although the dip in this curve is based on only one point, it may be significant as it occurred frequently in similar curves from a large number of cats. However, it

\*We have no way of determining in this experiment the effect of E.M.F., nor of frequency on the individual structures responding to the stimulus. Such data could be obtained by microelectrode recording techniques and is left for future research. As a first assumption the following two points seem reasonable: (1) The frequency threshold of the individual structures responding to the stimulus is generally of the same order and gradation is effected by the frequency response of the individual effectors *pari passu* with that of the stimulus; (2) The E.M.F. threshold varies over the full range of voltage sensitivity and the number of receptors activated provides gradation. This is necessary to remain within the framework of the all-or-none law. However, no such limitation is required for the frequency mechanism where it is reasonable that the individual structures responding to the stimulus will follow the stimulus pulses up to their maximum response frequency which is certainly not reached in this experiment.

must, for the time being, be considered an artifact since there appears to be no likely explanation in terms of present accepted knowledge of the physiology of the eye.\*\* Not infrequently the gradation portion of the E.M.F.-response curve tended to be linear as seen in Figure 1A, but generally this function was curved.

Figure 2 illustrates the effect on accommodation of varying the frequency of the stimulus to the ciliary ganglion. The open circles

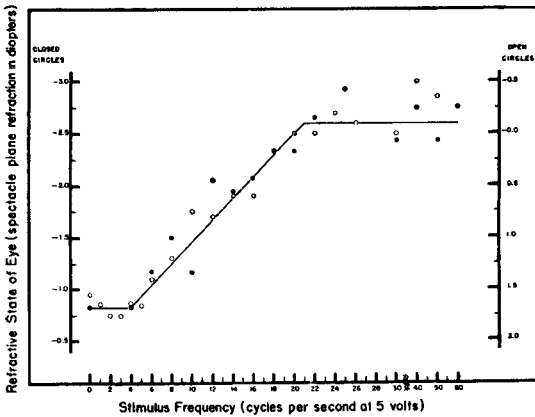


Fig. 2. Stimulus-response curves varying the stimulus frequency. Open circles and scale on the right represent cat under nembuted; closed circles and scale on the left with decerebration.

represent the data from one eye of one cat and the closed circles from one eye of another cat. The ordinates were adjusted to provide superposition of the curves as may be seen from the two scales, one on the left and the other on the right. The stimulus frequency threshold appears to be at about four cycles per second and from other curves not shown here it may vary between two and six cycles. After the threshold, there appears to be a linear relationship between frequency of stimulation and accommodation in diopters. At about 21 cycles, (with a 5 volt stimulus) accommodation appears to reach its maximum and increasing the frequency does not appear to have further effect. The effect of frequency on accommodation can be expressed as the slope of the active linear portion of the curve which, in these instances at 5 volts is 0.10 diopter per cycle. It may be noted that the amplitude of accommodation for both curves in Figure 2 is the same as for both curves in Figure 1, about two diopters. Each of these four curves was obtained from different eyes.

\*\*For example, one could hypothesize that in the cat's ciliary ganglion there are some sympathetic fibers from the third nerve which have a lower electrical threshold than the parasympathetic fibers and are therefore stimulated first. However, this hypothesis would be pure speculation.

In order to determine the importance of the anesthesia used in the present experiment, the curve in Figure 2 corresponding to the ordinate scale on the left (closed circles) was taken after the animal had been decerebrated under ether anesthesia. The other curve (open circles) was taken under nembutal anesthesia. It does not appear that nembutal anesthesia interferes with the experiment and was therefore used generally. The 2.50 D. difference in the ordinates is due to the basic refractive state (ametropia) of these two eyes, not to the anesthesia.

The interrelationship of frequency and E.M.F. on the refractive state of the eye is demonstrated in Figure 3 by a family of frequency

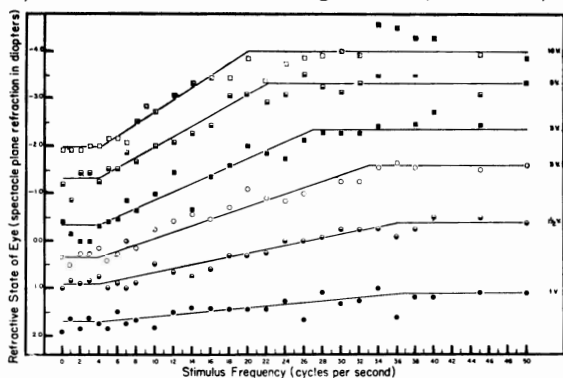


Fig. 3. Family of frequency stimulus-response curves taken at different voltages as noted by numbers at the extreme right. Each curve has been arbitrarily raised 0.50 D. on the ordinate above the curve below it except for the 3 volt curve which has been raised 1.00 D. The shifts were made for clarity of presentation. For fuller explanation, see text.

curves taken at different voltages. The lower three curves (1,  $1\frac{1}{2}$  and 2 volts), represent measurements from one eye and the upper three curves (3, 5 and 10 volts), measurements from the other eye of the same cat. Each curve has been arbitrarily raised 0.50 D. more on the ordinate than the curve directly below it, with the exception of the 3 volt curve where the step is 1.00 D. In other words, the 1 volt curve is as measured; the  $1\frac{1}{2}$  volt curve is shifted 0.50 D. upward on the ordinate; the 2 volt curve, 1.00 D.; the 3 volt curve, 2.00 D.; the 5 volt curve 2.50 D.; and finally the 10 volt curve 3.00 D. This separation was made for clarity of presentation by avoiding interlacing of the distributions.

It seems clear that the frequency threshold, independent of voltage, is four cycles per second. It also appears that the sensitivity of the frequency gradation mechanism increases with increasing voltage. This is seen in the slopes of the linear central portions of the curves. As the E.M.F. increases through 1,  $1\frac{1}{2}$ , 2, 3, 5 and 10 volts, the frequency

sensitivity increases through 0.02, 0.04, 0.06, 0.08, 0.10 and 0.12 diopters per cycle respectively. The maximum accommodative response, regardless of frequency, appears to be two diopters. However, this maximum, as already suggested by Figure 1 is not reached until the E.M.F. is raised to between 3 and 5 volts. Within a certain central range of frequency and voltage, these two parameters may be substituted for each other to provide a given level of accommodative response.

#### DISCUSSION

Bozler,<sup>5</sup> in his classification of muscle, calls smooth muscle "multi-unit" when it is motor nerve controlled and has many units (not syncytial) and hence acts somewhat like skeletal muscle. The nictitating membrane and blood vessel musculature are included in this class. Allen<sup>6</sup> has provided further evidence, based on the latent period of, and temporal summation in the ciliary muscle of an enucleated eye, which puts the ciliary muscle in this group. Further, as Allen points out, the ability to grade accommodation is additional evidence that accommodation is effected by multi-unit smooth muscle. The fine mechanism of accommodative gradation has been quantitatively investigated in the present paper.

The gradation of function of an effector, as already mentioned, is controlled by changing either the number of active units or their frequency of discharge. Lindsley,<sup>2</sup> in an investigation of the electrical activity of human motor units during voluntary contraction, found that changes in both the number and frequency of units operate together throughout the range of contraction intensities. He concluded that change in frequency is probably the more delicate grading mechanism and change in number the more effective. The lowest regular frequency of response that he found in striated muscle was three cycles per second, and the highest 50 cycles per second.

The results illustrated in Figure 3, showing a stimulus frequency gradation sensitivity from four to at least 37 (35 corrected) cycles per second make it appear that smooth ciliary muscle has a frequency innervational pattern similar to that of striated muscle.\* It seems, further that either the number of fibers, or the frequency of discharge can control the state of accommodation anywhere within its full amplitude provided a certain minimum frequency, (about 20 cycles per second) or a certain minimum number of units (corresponding to about 3 volts) is maintained.

Unfortunately, there is no simple way to determine the quantitative

\*It should be noted, however, that striated muscle will respond to frequencies less than four cycles per second although the response may not be tetanic.

relationship between the E.M.F. and the relative number of active fibers in the pathway between the ciliary ganglion and the ciliary muscle. However, it is clear that with a constant E.M.F. (i.e. with a given number of units active), the state of accommodation in diopters is directly proportional to the frequency of stimulation. One might use the term "neurodiopter" to express that unit of neural innervation which changes accommodation one diopter, a term similar to the myod diopter of Flieringa and van der Hoeve.<sup>7</sup> Assuming that the frequency of stimulation may be considered the degree of neural innervation, Figure 3 shows that the neurodiopter is a linear unit when frequency is the gradation mechanism in cycles per second (the reciprocal of the sensitivity) becomes a smaller unit as the E.M.F. (i.e. the number of active fibers) increases and Figure 3 shows a decrease of neurodiopters from 52 cycles to eight cycles. In other words, the sensitivity of the frequency mechanism (the reciprocal of the neurodioptric value) is a function of the stimulus E.M.F. (or the number of active fibers). Contrariwise, it appears that the sensitivity of gradation, regulated by varying the number of active fibers, is a function of the frequency.

Are the frequency and number mechanisms independent of each other? This appears to be true at the low frequency threshold where the value is four cycles regardless of the E.M.F. However, there is a significant deviation from independence at the high frequencies where the maximum frequency which increases the response appears to decrease as the number of fibers increases.

Figure 4 is a redrawing of the curves of Figure 3 with the base line of each curve put at the same level on the ordinate. The solid lines show the actual curves, which at the 3, 5 and 10 volt level appear to be prevented from reaching their full height, i.e., amplitude of accommodation. The broken lines in Figure 4 are obtained by extrapolation based on the distance between the curves and the shift of the inflection point of each curve. They indicate as Hess and others<sup>8</sup> believe, that the neuromuscular phase of accommodation (physiological accommodation) is greater than that limited by the suppleness of the crystalline lens (physical accommodation). In Figure 4, the physical accommodation is two diopters, and the physiological accommodation is presumably about three diopters. This could also be checked by using homatropine as a partial cycloplegic as did Flieringa and van der Hoeve but using the length of the slope as an indication of the full elicitation of the frequency mechanism. In other words, the lower voltage curves appear to show the full function or amplitude of the frequency mechanism. If this full frequency amplitude could be shown with the higher voltages

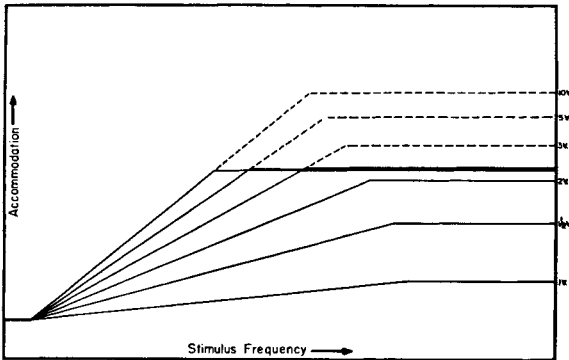


Fig. 4. Solid lines are the curves from the previous figure with all base lines set together on the ordinate. Broken lines are extrapolations. For interpretation, see text.

with homotropinization of the eye further justification would be provided for the extrapolation of the curves in Figure 4.

As mentioned earlier, there has been considerable study of the frequency response of autonomic effectors. A summary of these investigations has been published by Rosenblueth.<sup>3</sup> Generally, autonomic frequency-response curves measured in degrees by the angle of movement of pilomotor action in a cat's tail or the isometric or isotonic contraction of the nictitating membrane of a cat's eye are rectangular hyperbolas. The frequency gradation mechanism of accommodation, however, becomes linear when measured in diopters after being transformed into the sphincter-like action of the ciliary muscle and then into dioptric power by changes in the physical configuration of the crystalline lens.\* This is indeed a wonder. It brings to mind another interesting linearity, the relationship between accommodative-convergence expressed in angular measure such as degrees or centrad and accommodation expressed in diopters.<sup>9</sup> This relationship is abbreviated AC/A. If, as has been demonstrated here, the relationship between the frequency of accommodative stimulus and accommodation is linear, and if the AC/A is linear, then it can be concluded that the relationship between convergence and the frequency of convergence innervation is linear. This could be confirmed directly by a similar experiment stimulating the extraocular muscles.

The fact that the peripheral mechanism of accommodation appears to have a linear gradation system would seem to imply that the whole AC/A neuromuscular innervational chain is composed of linear links. For if one link in an innervational chain is linear and the system as a

\*However this function is hyperbolic when accommodation is measured in linear units, i.e., meters.

whole is linear, then it seems likely that each separate section of the system is also linear.

#### SUMMARY

An investigation was made of the maintained gradation of parasympathetic innervation of accommodation by electrically stimulating the ciliary ganglion in cats. Electrical stimulation was provided by condenser differentiation of the output of a square wave oscillator to provide biphasic waves. The refractive state of the eye which showed the accommodative response was measured from the partially iridectomized cat's eye *in situ* with an eye refractometer. The relationship between stimulus voltage applied to the electrodes at the ciliary ganglion and the refractive state of the eye in diopters was determined. Varying the frequency while maintaining constant voltage yielded a linear relationship. Nembutal anesthesia does not appear to affect the peripheral accommodative mechanism because similar results were obtained with decerebration in place of nembutal.

The lower frequency threshold, independent of voltage, is four cycles per second. The upper frequency threshold is dependent on voltage and was found at least up to 35 cycles per second. The sensitivity of the frequency gradation mechanism increases with increasing voltage from 0.02 diopters per cycle to 0.12 diopters per cycle for the voltages used. The amplitude of accommodation in young cats appears to be about two diopters. Within a certain central range of frequency and voltage, these two parameters may be substituted for each other to provide a given level of accommodative response.

The significance of this data in the classification of the ciliary muscle as multi-unit muscle is discussed.

The term "neurodioptr" is proposed to express that unit of neural innervation which changes accommodation one diopter.

Extrapolation of the data indicates a physiological range of accommodation above the physical range as proposed by Hess.

The linearity of the frequency gradation mechanism of accommodative innervation is discussed in relation to the linearity of the ratio of accommodative convergence to accommodation ( $AC/A$ ).

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