Recent Developments in Vision Research (1966)

Pages
236

Size
6 x 9

ISBN
0309299993

Whitcomb, Milton A., Editor; Armed Forces; Committee on Vision; National Research Council

The activities of the Armed Forces—National Research Council Committee on Vision are supported by the U.S. Army, Navy, Air Force, Federal Aviation Agency and National Aeronautics and Space Administration through a contract between the Office of Naval Research and the National Academy of Sciences. The Secretariat of the Committee is located at the National Academy of Sciences—National Research Council
2101 Constitution Avenue, N.W.
Washington, D. C. 20418

Copies of this report (NAS-NRC Publication No. 1272) may be obtained for $4.00 each from the Publications Office
National Academy of Sciences—National Research Council
2101 Constitution Avenue, N.W.
Washington, D. C. 20418

RECENT DEVELOPMENTS IN VISION RESEARCH

Edited by MILTON A. WHITCOMB

ARMED FORCES - NRC COMMITTEE ON VISION

Publication 1272
NATIONAL ACADEMY OF SCIENCES - NATIONAL RESEARCH COUNCIL
Washington, D. C. 1966

CONTENTS

SOME RECENT ADVANCES IN THE STUDY OF PHYSIOLOGICAL REFLEX MECHANISMS IN VISION

SOME RECENT ADVANCES IN INSTRUMENTATION AND PROCEDURES IN VISION RESEARCH

THE EFFECTS OF DRUGS ON VISION

SOME RECENT ADVANCES IN THE STUDY OF PHYSIOLOGICAL REFLEX MECHANISMS IN VISION

Glenn Fry, Chairman

INTRODUCTORY REMARKS BY THE CHAIRMAN

Glenn A. Fry
School of Optometry
The Ohio State University

Vision is a complex process which involves active manipulation of the eyes as well as the passive transfer of information through the pupils onto the retina and along the optic nerve. By contraction of the ciliary muscle each eye can be focused for various distances, and the pupil, which is the aperture stop of the eye, can be regulated in size by the dilator and sphincter muscle fibers of the iris. The most remarkable thing about vision, however, is that two eyes are simultaneously involved and, in spite of the fact that two optical images are formed on two separate retinas, the impressions transmitted to the brain can be integrated into a single image. The simplest way to visualize this integration is to suppose that there are two layers on the surface of the cortex representing the two eyes on which the retinal impressions are arrayed. The two layers must interact with each other in such a way that the rivalry and fusion of the impressions of the two eyes can bring about a single image. This interaction must also generate the activity which forms the basis for stereoscopic perception, and it must also generate the fusional movements of the eyes which keep the impressions properly registered on the two cortical surfaces.

The first requirement for binocular vision, therefore, is to have the primary lines of sight of the two eyes converge at some given point. The second requirement is to rotate the eyeballs around their lines of sight in opposite directions until the two optical images are properly oriented on the two retinas. These adjustments in convergence and cyclorotation are accomplished through reflex fusional movements. The failure of fusional movements to produce perfect congruence between the two impressions is called fixational disparity.

The fusional movements of the eye are imposed upon a background of reflex activities associated with the labyrinth and neck muscles which produce cyclorotations and divergences of primary lines of sight, all of which have to be compensated to obtain proper registration.

By voluntarily switching his attention from an object at one distance to an object perceived to be at another distance the observer can change the degree of convergence and accommodation. The size of the pupil also

changes along with this change in accommodation and convergence. This combination of three responses in one is called the triad response. In this response, accommodation and convergence are associated in a fixed relation which may be such that when the eyes are focused for one distance the two primary lines of sight may be converged for another, and the slack between the two functions has to be taken up by the reflex movements of the eyes. The constriction of the pupil associated with accommodation and convergence serves a very useful purpose in near vision. The depth of focus is increased.

The pupils respond not only to the concentration of attention on objects near at hand, but also to the amount of light falling on the retina. This is known as the light reflex and represents an automatic stopping down of the eyes when the amount of light falling on the retinas becomes excessive.

FOCUSING RESPONSES OF THE HUMAN EYE

Gerald Westheimer
School of Optometry
University of California

The function of the human eyeball is to form an image of the outside world on the retina. First-order theory of optics states that there is only one object plane for each image plane, a conclusion which holds for any level of sophistication of physical and geometrical optics.

Man would not be getting the most out of his eyeballs if he did not have an adjustment to take care of differences in object distance. Fortunately, nature has provided the young of the human species with a good mechanism to adjust the focus of their eyes. This physical and physiological mechanism is, however, by no means the only possible one. Other species have other mechanisms, notably the cat, which seems to move its lens back and forth instead of changing the curvature, as does man.

The notorious and universal failure of man's accommodative system about two-thirds through his present life span is clearly a minor error of nature, but one for which evolution cannot be blamed, since individuals have usually played their roles within its framework before presbyopia begins to take its toll. In fact, not being able to change the focus of one's eyes is such a widespread handicap that the appropriate prosthesis—spectacle lenses, particularly bifocals and trifocals—is one of the most ubiquitous and successful contributions of the physical sciences to the health professions.

Now that the subject under discussion has been placed in its proper perspective as a dead-end or lame-duck field, perhaps it does, after all, hold something of interest.

A schema useful in clarifying the operation of the focusing responses of the eye is shown in Fig. 1.

A situation in which a target is sharply in focus on the retina is one in which the target-focus requirement is accurately matched by the accommodation response, and there is no focusing error. If there is a focusing error, it will be recognized by the sensory system of the eye and reported to the central nervous system. Here this information and all the other influences that may also operate on the accommodation

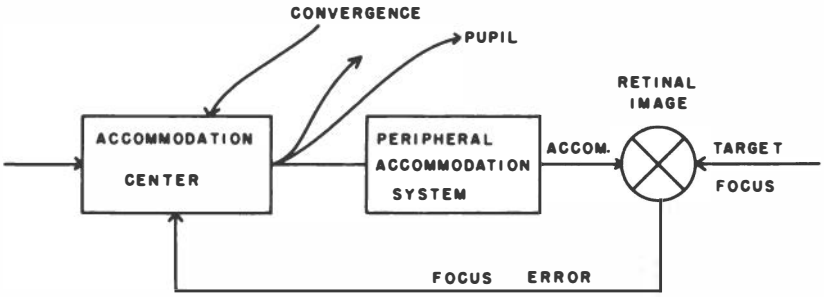

Fig. 1. Schema of operation of accommodation system.

system are collated, and instructions are sent to the peripheral accommodative mechanism which, if all goes well, will result in a new accommodative response which, in turn, may be compared with the current need. The whole process has all the essential characteristics of a servomechanism.

The nomenclature must be correct. An eye with relaxed accommodation whose retina is conjugate to infinity is called emmetropic, i.e., has no refractive error, and it may be assumed in the following that the eyes being considered are either naturally emmetropic, or have been so rendered by spectacle or contact lenses. The total refracting power of the eye is very high, about 60 diopters, or enough to take rays from infinity and image them on the retina. When a response supervenes to take care of a close-up target, the result is an increase in refracting power of the eye; this is what is called accommodation. It is the output of what in Fig. 1 is designated the peripheral accommodative system. It is measured in diopters. The target focus may also be measured in diopters, which is a unit of reciprocals of distance in meters.

The schema of Fig. 1 shows the processes involved in the focusing responses of the eye grouped under three headings:

1. the effector mechanism, located mainly in the periphery;

2. the sensory components, funneled through the retinal image, which permit the comparison between the effector output (accommodation) and environmental demand (target focus) and, as will be seen later, detect other aspects of the visual environment;

3. the central processor, receiving information from the retina and elsewhere, and issuing instructions which constitute the input to the effector mechanism.

There are a few cross-connections which should be noted in view of the fact that this paper is to be followed by one on the pupil and one on fusion. Eye-vergence is known to be influenced by accommodation, and so is the pupil. Conversely, eye-vergence changes may be shown

to bring about slight changes in accommodation when the other inputs to accommodation are eliminated or minimized.

The part of the accommodation loop about which most is known is the operation of the effector mechanism, the chain of events brought about when that portion of the III nerve nucleus subserving accommodation sends impulses to the ciliary ganglion. As a result, the ciliary muscle contracts, setting into effect a number of mechanical and optical changes that were studied in their day by Thomas Young and by Helmholtz, and are now fairly well understood since Fincham's work. There are gaps in knowledge about the effector mechanism—the full details of the innervation of the ciliary muscle, its pharmacology and its myo-neural junctions are some examples. However, on a first superficial description the box labelled "peripheral accommodation system" may be regarded as having sufficiently unique and unitary properties to permit its insertion as such into the feedback loop.

The study of the detailed physiology of the effector mechanism in isolation virtually has to be confined to other species. The results of such studies, while of genuine interest in themselves, cannot, however, be applied to the human accommodative mechanism without assurance that the latter works in approximately the same way as that of the species studied. Reference has already been made to species differences in the mechanical operation of the structures of the eyeball, and probably the same may be said in connection with the innervation, pharmacology, and mechanics of the ciliary muscle.

The sensory components, on the other hand, can be studied in the intact human by several procedures. One can, for example, paralyze the accommodation of the eye, thus keeping at least one input to the sensor constant, and manipulate the environmental variables, such as the target distance. For a response, some other output might be used, such as a verbal one, or hand-tracking, or the accommodation of the other unstimulated and non-paralyzed eye. The latter, an excellent procedure, is predicated on the almost perfect correlation between the accommodative responses of the two eyes in normal subjects.

The target focus demand and the accommodative posture combine in their influence on the retinal image. While it is true that here one is faced with the huge problem of the image formation by the optical system of the eye and the capacity of the visual system to detect, abstract, and transmit the relevant information, your attention is directed to the accommodation-inducing aspects of retinal stimuli and stimulus-changes. Of primary, but by no means exclusive, importance in this connection is the effect of defocusing on the retinal image. Defocus may be in two directions: there may be too much accommodation for the target distance, or too little. Of the several ways in which the eye's imagery may be depicted, the contrast-transfer function is the most promising. Figure 2 shows a recent estimate of the contrast-transfer function of the intact

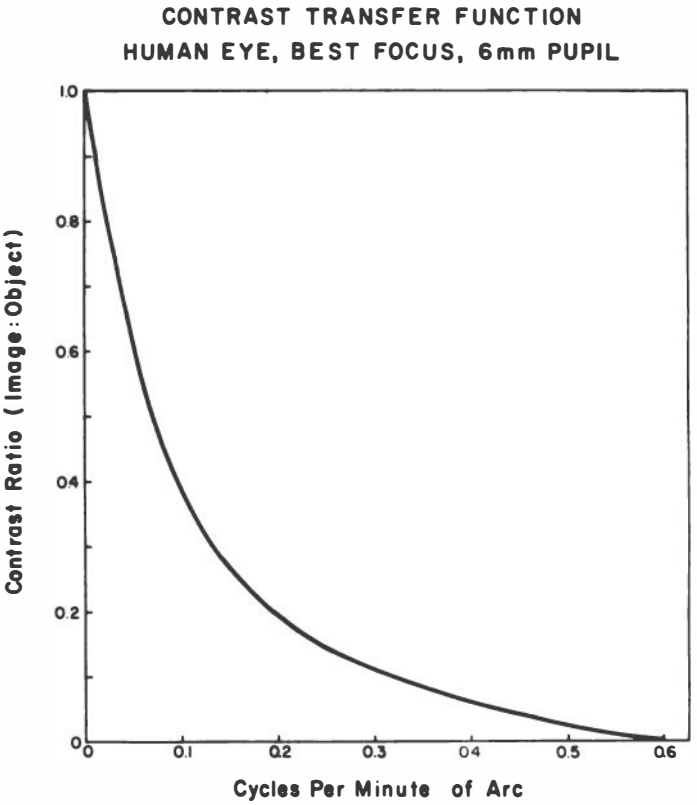

Fig. 2. Estimate of contrast-transfer function for human eye with 6-mm pupil. (G. Westheimer, J. opt. Soc. Amer., in press)

human eye, with cycles per minute of arc as the unit of the abscissa. Figure 3 shows the theoretical contrast-transfer function for a perfect, i.e., only diffraction-limited, optical system like that of the human eye with a 3-millimeter (mm) pupil for various degrees of defocusing. Comparison of the two figures reveals several interesting things. First of all, the actual imaging characteristics of the eye match fairly well those of a perfect eye with a 3-mm pupil when it is 1/3 of a diopter out of focus. This statement becomes even stronger when it is realized that those spatial frequencies in which there is a difference between the two are too high to be accepted by the retina and the visual pathway. While it is true that in the real eye there are additional factors, such as aberrations and inhomogeneities of the lens, one is led immediately to expect a dead zone, i.e., a region of object distances over which retinal images are indistinguishable. This has been known for a long time under the name of "depth of focus"; its extent is inversely related to the pupil size.

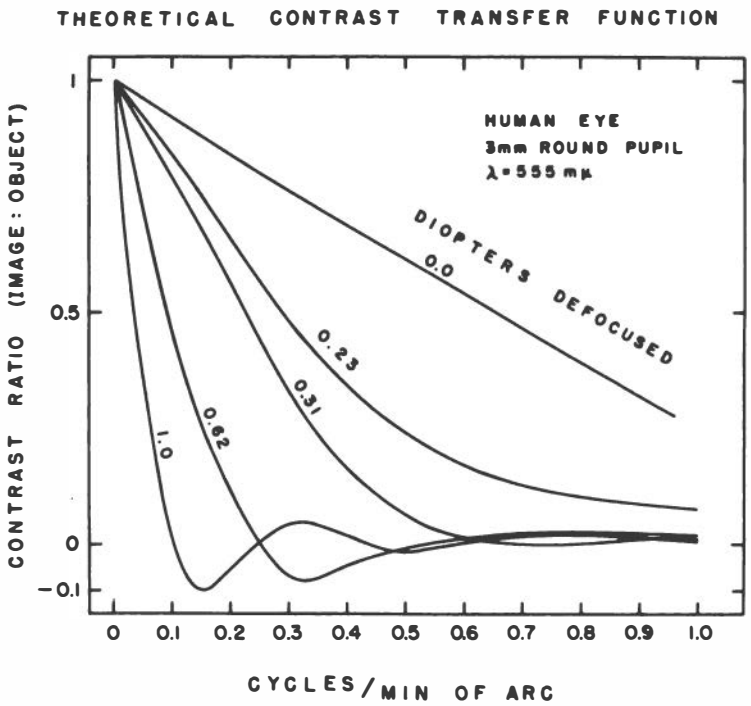

Fig. 3. Contrast-transfer functions of ideal optical system like that of human eye with 3-mm pupil with various focus errors.

The contrast-transfer functions for eyes that are out of focus have spatial frequencies in which there is negative contrast, i.e., there is resolution with inversion of contrast. This should be kept in mind by those who would construct automatic focusing devices by testing for maximum response at some relatively high spatial frequency.

An interesting aspect of the dead zone is that the region of insensitivity to focus changes is not constant but varies with the degree to which the image is out of focus. In Fig. 4 are shown the results of an experiment in which ΔF, the just noticeable difference of focus settings in an homatropinized eye with an artificial pupil, was measured as a function of focus setting. This has a minimum of about 0.2 diopters about 1 diopter away from the middle of the focusing dead zone.

Another feature of out-of-focus imagery is that in a perfect optical system the spatial frequency characteristics are the same on both sides of good focus, and, thus, blur due to over-accommodation could not be distinguished from that due to under-accommodation. When one sets out to prove this experimentally, one runs into difficulties because the eye is not a perfect optical system. Minute asymmetries, such as those

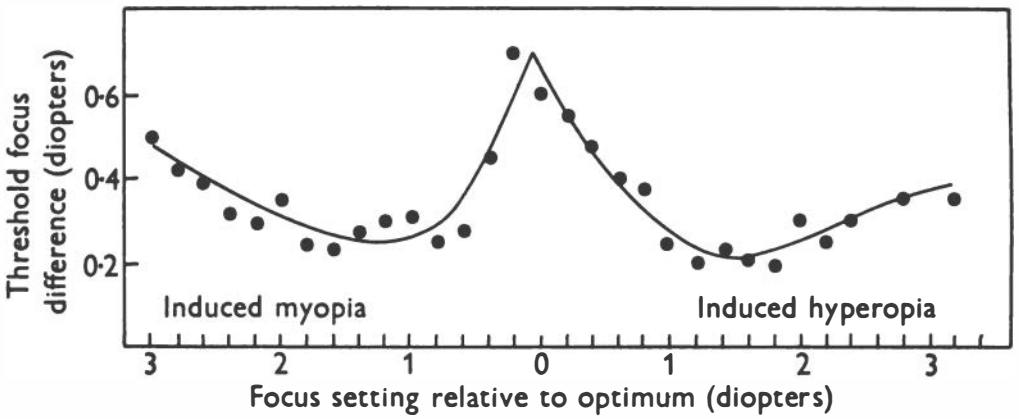

Fig. 4. Experimental determination of just noticeable differences in focus setting for homatropinized human eye with 3-mm artificial pupil. (F. W. Campbell & G. Westheimer, J. Physiol., 1958, 143, 18P)

caused by chromatic aberration, can be detected and made use of by a good subject in the decision of whether to accommodate or to relax accommodation. However, when abstract stimulus conditions are chosen with sufficient care, the direction of focus error cannot be told even by a good observer.

The important word in the above sentence is "abstract." The long history of interest in accommodation among experimental psychologists from Wundt to Wallach testifies to the fact that perception, learning, memory, and many of the other concepts of psychology have a place in defining and specifying accommodative stimuli. What has to be abstracted from the stimuli to make error direction undetectable constitutes a major factor in the determination of the accommodative state under normal observation conditions. The evidence is absolutely convincing that accommodation is not a simple reflex in the way the knee-jerk or even the pupil is. One starts changing one's accommodation when some perceptual clue suggests that a target has come closer, even though its focus position demands that accommodation remain unchanged. Conflicting stimulus conditions may even make accommodation go in the wrong direction. If one wishes a subject's accommodation to hold at a certain level, or move it in a desired direction, one should introduce a maximum of perceptual clues to this end. This is something that many clinical optometrists are aware of, as attested to by the design of their examination and orthoptic procedures. A corollary, the floating of accommodation in empty visual fields, is too well known to need more than passing reference here.

The statement is sometimes made that accommodation may aid in such perceptual tasks as the judgment of apparent distance. Before one can go far along the road suggested by this view, one must examine the

question of whether there is any "proprioception" for accommodation. While there is no existing anatomical evidence to support this, there may be a monitoring system receiving information not of the actual state of contraction of the ciliary muscle, but of the innervation sent to it. This is a concept with which eye movement workers are familiar.

Even if all were known about the effector and sensor elements of the feedback loop subserving accommodation, one would still be unable to define, describe, and predict the operation of the entire loop, since there is present in it yet another component. The only way to analyze it is to study the function of the whole arc, for example, by changing an input and measuring the resultant changes in response. At this point, a few words are necessary about measuring accommodation. The standard optometric tests, such as retinoscopy, or special tests, such as stigmatoscopy or alignment optometry, have for a long time yielded usable discrete data points concerning accommodative responses. Early attempts to secure continuous objective records from the third Purkinje image have been followed by Campbell's high-speed, high-resolution, infrared optometer, which permits continuous recording in the intact human eye. The instrument is not easy to assemble or to operate and has some limitations, but it has been of invaluable help in the analysis of the accommodation loop.

Here are some of the fundamental questions that may be asked concerning accommodation responses and their answers as seen on optometer records.

Question 1. When a change in accommodation requirement is introduced, as by the sudden presentation of a near target, what does the response look like?

Figure 5 answers this. There is a reaction time of the order of 0.3 seconds (sec), and the time taken to complete the response is at least 1 sec, and sometimes even more. The shape of the responses varies, but clearly they are highly damped.

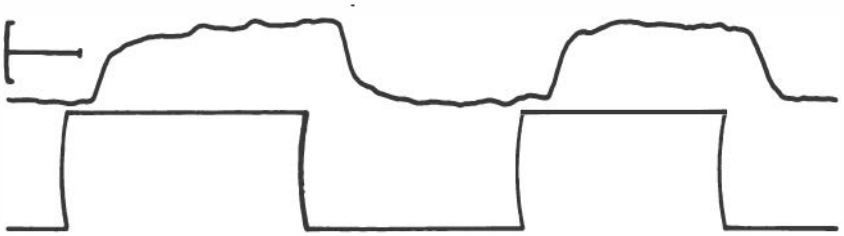

Fig. 5. Accommodation responses to step focus changes in normal human eye. Top line, accommodation (length of horizontal line, 1 sec; height of arc, 1 diopter): upward movement represents far-to-near accommodation. Bottom line, stimulus signal, same scale. Allowance should be made for arc of pen. (F.W. Campbell & G. Westheimer, J. Physiol, 1960, 151, 285)

Question 2. Are these responses of the nature of saccadic eye movements, which follow a predetermined course that cannot be altered once the movement has been initiated, or can they be modified during their course?

Figure 6 answers this. Brief pulses of accommodative stimuli are each followed by a response, but information is taken up during the latent period and during the movement itself, and the movement modified, in this case reversed, as a result of this information.

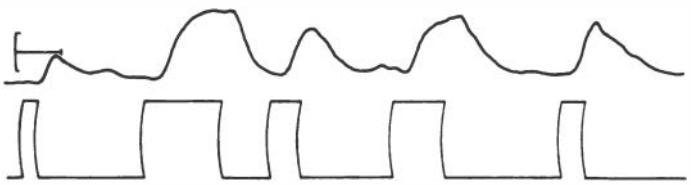

Fig. 6. Accommodation responses to pulse stimuli. (See legend of Fig. 5 for detailed explanation.) (F.W. Campbell & G. Westheimer, J. Physiol., 1960, 151, 285)

Question 3. Is there a steady-state error?

Figure 7 answers this. It illustrates the clinically well-known lag of accommodation. This is a function of the detail in the stimulus

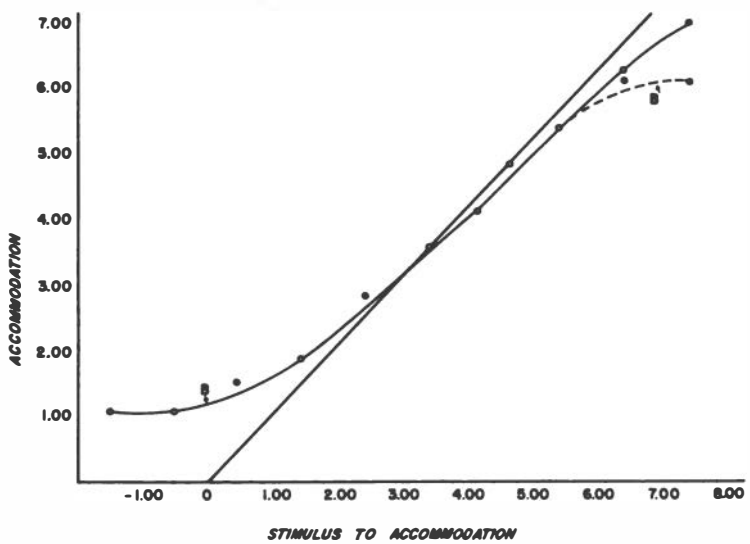

Fig. 7. Relation between accommodation requirement and response, illustrating steady-state error. (M.W. Morgan, Amer. J. Optom., 1944, 21, 183)

configuration, being larger for coarse targets, and of the luminance level, being larger for low luminance levels. The distinction between the measured steady-state difference between stimulus and response shown here, and the dead zone discussed earlier, i.e., the region over which the sensory system cannot appreciate errors, should be clearly understood. The latter is a characteristic of the sensory component of the loop, while what is shown here is a property of the whole loop.

Question 4. How steady is the steady state?

Figure 8 answers this. Fluctuations of accommodation become evident while the ciliary muscle is active. The immediate suggestion

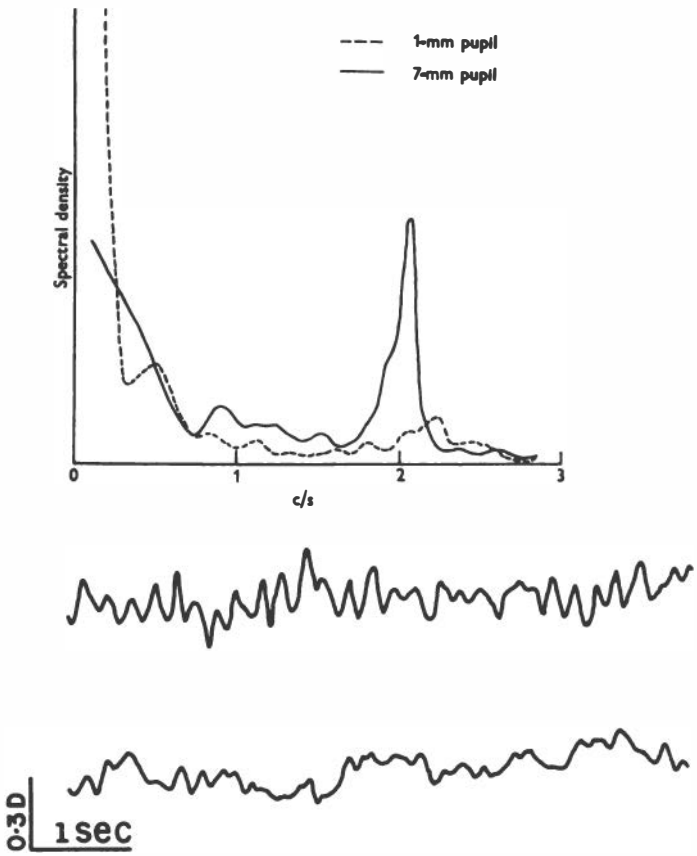

Fig. 8. Accommodation fluctuations under steady viewing conditions. Upper: frequency spectra of two records. Middle: record of accommodation during steady viewing of stationary object at optical distance of 1 meter with 7-mm pupil. Lower: the same, but with 1-mm effective entrance pupil. (F.W. Campbell, J. G. Robson, & G. Westheimer, J. Physiol., 1959, 145, 579)

of a hunting servo oscillating through or at the edge of a dead zone is not borne out by further analysis. The oscillations do not increase in magnitude when the dead zone is widened, and the known time and sensitivity characteristics are not in good accord with the supposition.

Question 5. What is the response of the accommodation system to sinusoidal variations in target focus at various frequencies?

Figure 9 answers this. The closed-loop frequency response starts to fall off at about 0.5 cycles per second (cps) and the maximum frequency of stimulus oscillations at which a concomitant response can be identified clearly is about 4 cps. The phase lag should contain the fixed reaction time plus a frequency-dependent delay, but it has not been fully established what this is, or whether there is any evidence for the phase advance that has been found in eye-vergence.

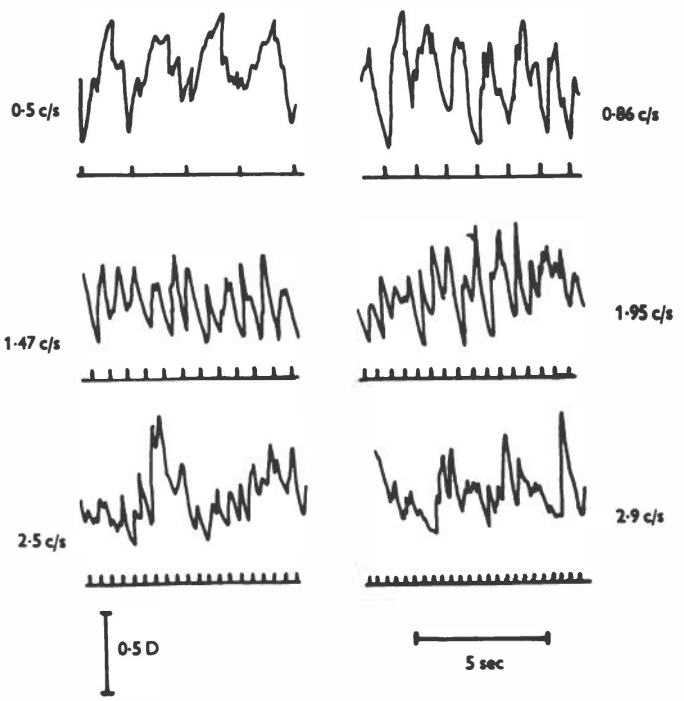

Fig. 9. Accommodation responses to sinusoidal focus changes at various frequencies. (F. W. Campbell, J. G. Robson, & G. Westheimer, J. Physiol., 1959, 145, 579)

Question 6. What is the open-loop response?

Results promised by the several laboratories actively pursuing studies in accommodation are eagerly awaited. One can guess that the peripheral accommodation mechanism probably has the characteristics of a damped second-order system, but further hypotheses, such as the presence of an integrating or a sampling element, remain, for the moment, speculations.

If it seems that there has been a hopeful yet cautious attitude to the approach to the focusing response via servotheory, this is the precise intention of the author. There is no question but that modern servo-analysis already has had and will have a continuously increasing influence on theory-making and on experimental techniques in physiology, particularly neuro-muscular-sensory physiology. There is nothing magical about servotheory. It employs mostly mathematical devices well known for decades if not centuries, and has invented precious few of its own. However, it has developed a way of conceptualizing that is without doubt helpful in approaching physiological problems. But it must be emphasized that when servoanalysis is brought to bear on biological questions it should not be done by a routine and unimaginative application of engineering equations.

When one works with them, it becomes clear rather quickly that biological servos have their own very special difficulties and fascinations, none more so than the focusing responses of the eye. Some of the other ocular responses, particularly the pupillary and vestibular, have simpler neural connections that may make them more amenable to servoanalysis in the present state of the art. When dealing with accommodation, there are several things to combat. One of them is the effector system, which seems more than usually "noisy." The other is the error signal, which is more than usually diffuse. Just compare the exquisite sensory system available to the eye-vergence servo, where one can sense differences in parallax of seconds of arc to the appreciation of blur, which, as has been seen, cannot even be defined except with the aid of an array of parameters. And, finally, there is the fact that the accommodation responses show many signs of utilizing the widest resources of the cerebral cortex—extremely quick learning, good memory, and all that goes along with the concept of perception. The challenge here is to the servotheorist and experimentalist alike. It is necessary to know how to handle systems with nonlinear elements, with statistically varying parameters, with dead zones, with "dither," and with rectified error signals. But, more than anything, good experimental data are needed. Fortunately, several workers in this country have followed Campbell's lead and constructed their version of the infrared recording optometer: Allen and Carter at Indiana University's Division of Optometry; Warshawsky at Northwestern University; Roth, originally at Berkeley and now at U.C.L.A.; and the group in the Department of Ophthalmology of N.Y.U., to mention only those known to the author. The availability of these instruments will

undoubtedly pave the way to a richer understanding of the focusing responses of the eye.

References[1]

Alpern, M. Accommodation. In H. Davson, (Ed.), The eye. New York: Academic Press, 1962, Vol. 3.

Westheimer, G. Optical and motor factors in the formation of the retinal image. (Paper read at 1962 Symposium on Physiological Optics, sponsored jointly by Armed Forces—NRC Committee on Vision and the Optical Society of America.) J. opt. Soc. Amer., 1963, 53, 86-93.

[1] These reviews provide detailed references to the literature.

PUPILLARY MOVEMENTS ASSOCIATED WITH LIGHT AND NEAR VISION[1]

An Experimental Review of the Literature

Irene E. Loewenfeld
Department of Opthhalmology, Columbia University
College of Physicians and Surgeons
and
Presbyterian Hospital, New York \

TABLE OF CONTENTS

---

1 This work was supported by the Harriman Fund and by grants from the U.S. Public Health Service (NB 00253 and 5-K3-NB-16,542-01).

As in all chapters of the literature on the pupil, there have been controversies concerning the role of the pupil in connection with both (1) the perception of light and (2) near vision. The chief questions raised about the first subject relate to the identity of the receptors for the light reflex: even today some authors hold that the rods play no pupillomotor role, while at the same time, the pupillary spectral sensitivity has been reported to show a scotopic curve even under photopic conditions (Bouma, 1962). As to near vision, the relations between accomodation, convergence, and the pupil have been discussed at length. It is the purpose of the present paper to give a reasonably concise experimental review of this literature, and to see what general conclusions can be drawn from it at this time.

Criteria for Selection of Papers

In all surveys of the literature, reviewers are faced with two main difficulties: they have to decide where to draw the limits that will outline the subject at hand most effectively, and they have to bear the nagging awareness that their material may be not at all complete. Were there more time to search for additional material, a large group of papers of most direct interest might be discovered around the next corner... In the present case, then, the publications presented are the ones available to the author at this time, which have as their chief subject either pupillary movements related to the retinal receptor mechanism, or pupillary movements related to near vision. It should

be stressed especially that exclusion or inclusion of a particular paper in this review should not be interpreted as implying an evaluation of its importance. Papers not represented were either missed or they were excluded because they appeared to fall outside the intentionally narrow limits imposed (Table 1).

TABLE 1

Criteria for Selection of Papers

I. Included:	(1) Methods of stimulation by light or near vision; (2) pupillary movements, as related to (a) different parameters of light stimulus, or (b) various factors of near vision reaction.
II. Excluded:	(1) Methods for measuring pupillary size or movements; (2) experiments with chief emphasis on anatomy or physiology of afferent or efferent nerve paths, nervous centers, or effector muscles; (3) experiments with chief emphasis on physiological mechanisms involving the pupil, such as effects of drugs, altitude, gravity, rotation, changes in physiological state (respiration, heart rate, etc.), aging, fatigue;* (4) experiments in which the pupil is considered only in its role as part of an optical system; (5) psychological work concerned with conditioning, discomfort, etc.; (6) statements in general texts, without special experimental work of the author.

*Because fatigue and emotional excitement are all-pervading mechanisms which cannot be avoided in experiments on conscious human beings or animals, their modifying effect on pupillary reflexes is noted; work primarily concerned with other aspects of fatigue has been excluded.

It had been attempted, at first, to limit the review to those papers which contained more elaborate experimental material still applicable today, excluding works of chiefly clinical emphasis, especially when only simple instruments were used, and when they appeared outdated. It was, however, too difficult to draw the line between the mainly experimental and the mainly clinical, and the experiment classed as "simple" today may have been revolutionary and most important historically. In addition, the titles of some publications imply more elaborate physiological work than is actually contained in them, and it was felt that it might be useful to find such papers listed among the simpler experiments of a particular group.

Pupillary Reactions to Light

The kind and approximate number of publications dealing with the different parameters of light stimuli are shown in Tables 2-8. An extensive, thoughtful review of some of this literature has been given by Schweitzer (1955, 1956). The work can be divided roughly into experiments on the pupillary effects of

(1) the intensity of the stimuli,
(2) the time-characteristics of the stimuli (duration, wave form, frequency),
(3) the area of the stimuli (spatial summation),
(4) the retinal location of the stimuli (fovea, parafovea, or periphery), and
(5) the color of the stimuli.

Stimulus Intensity

1. The literature

By far the largest group of publications contains data on stimulus intensity (Table 2, A-C). The early authors used daylight, or various flames (candle, gas, petroleum, amyl acetate or alcohol), as light sources. After about 1900, electric lamps became generally available, and, more recently, electronic flash sources. Infrared, ultraviolet, and even X-ray and radium sources were used occasionally.

Light intensity was varied by means of different apertures or iris diaphragms, by adjusting the distance between the source and an aperture, by rheostats (for electric lamps), by filters (paper, parchment, opal glass, milkglass or frosted glass, and later neutral gray gelatine filters or neutral gray glass filters or wedges), by rotating Nichol prisms or by rotating crossed polaroid filters. The light was measured by recording the current across the lamp and/or the color temperature of the lamp, by photo-electric devices, by thermopile galvanometers, comparison photometers, or spectrophotometers.

In the clinical work contained in Table 2A, light intensity usually was varied by relatively simple means, such as apertures, filters, or different settings of a rheostat, without particular control of area, retinal location, or color. In a few papers included in this group, the authors had merely used an instrument previously developed by someone else, without adding original contributions (Silberkuhl, 1896; Tange, 1901; Groethuysen, 1921; Engelking, 1922; Mehrtens & Barkan, 1923; Gifford & Mayer, 1931; Bömer, 1933; Gasteiger, 1934; Lodato, 1934) or having made only minor modifications (Sander, 1929; Mazzuchoni, 1925; Borsotti, 1939; Loewenfeld, 1956).

TABLE 2

Stimulus Intensity

A. Methods with Clinical Emphasis in Which Intensity Was Varied by Simple Means

Year	Author	Year	Author	Year	Author
1882	Schadow	1920	Landolt	1933	Bömer
1894	Schirmer	1921	Groethuysen	1933	Feldman
1896	Silberkuhl	1921	Kleefeld	1934	Bujadoux & Kofman
1899	Schäfer	1922	Barkan	1934	Gasteiger
1899	Sommer	1922	Engelking	1934	Lodato
1901	Tange	1922-59	Lowenstein	1937	Bujadoux & Gourevitch
1902	Schirmer	1922	Kofman & Bujadoux		
1903	Fuchs	1923	Mehrtens & Barkan	1937	Nayrac & Franchomme
1904	Bumke	1925	Mazzucconi	1939	Borsotti
1904	Piltz	1928	Lehrfeld	1940	Frydrychovicz & Harms
1905, 06	Weiler	1929	Barbieri		
1907	Hübner	1929	Modonesi	1949-54	Harms
1907, 08	Krusius	1929	Nicolai	1956	Loewenfeld
1910	Sachs	1929	Sander	1957-61	Shakhnovitch
1910	Weiler	1930	Engel	1959-61	Samojloff, Sokolova, & Shakhnovitch
1911	Hembold	1931	Gifford & Mayer		

B. Experimental Work in Which Stimulus Intensity Was Varied in Connection with Other Problems

Year	Author	Chief problem	Year	Author	Chief problem
1892-93	Bordier	visual acuity	1939-40	Hecht & Pirenne	color (owl)
1892, 93	Sachs	color	1942	Bartley	frequency, ocular discomfort
1900	Abelsdorff	color			
1903	Friberger	speed	1942	Wagman & Gulberg	color
1903	Schäfer	color	1948	Bárány & Halldén	retinal rivalry
1904	Abelsdorff & Feilchenfeld	color	1948	Morone	dazzling, fatigue
			1952	Wirth	retinal rivalry
1905	Basler	color	1956, 59	Van der Tweel	various
1907	Hess	retinal position	1957	Bleichert	servo-analysis
1907	Polimanti	color	1957	Bleichert & Wagner	servo-analysis (frequency)
1908a	Hess	color (animals)			
1909	Hesse	retinal position	1959	Shakhnovitch	color (cat)
1910	Hess	color (animals)	1959-63	Stark et al	servo-analysis
1923	Laurens	color	1960, 61	Clynes	servo-analysis
1931	Zeldenrust	chronaxia	1962	Alpert & Campbell	color
1933	Machemer	speed	1962	Bouma	color
1933	Stiles & Crawford	directional sensitivity	1963	Feinberg & Podolack	latent period

Note: a in Year column refers to order in References.

TABLE 2 (cont'd)

C. Experimental Work Especially Concerned with Effects of Stimulus Intensity

Year	Author	Static	Flash	Threshold	Difference Threshold	Darkness
1760	Lambert	*				
1881,82	v. Vintschgau		⊓			*
1884	Gorham	*				
1888	Chaveau		↱			*
1888	Cohn	*				
1893	Du Bois-Reymond & Greeff	*				
1897	Garten					*
1898,1905	Ovio	*				
1899,1900	Lans	*				
1900	Vervoort	*				
1907,13,14	Schlesinger		⊓	*	*	
1908	Hess		↱	*		
1914,15,16	Hess				*	
1918	Blanchard	*				
1918	Reeves		↱			*
1919	Engelking		⊓			
1920	Reeves	*	↱			*
1926	Holladay	*				
1927,32	Ferree & Rand	*				
1929,30	Stiles	*				
1932	Gradle & Ackerman					*
1933	Ferree, Rand, & Harris	*				
1934	Biffis		↱	*	*	
1934b	Luckiesch & Moss	*			*	
1936-37	Crawford	*				*
1937	Hartinger	*				
1938	Elsberg & Spotnitz	*				
1938,43	Kappauf	*				
1938	Talbot		↱	*		
1939	Brown & Page					*
1942	Wagman & Nathanson	*				
1943	Bartley	*				
1944	Moon & Spencer	*				
1947	Corrado	*				
1947	Venco & Marucci		⊓			
1948	Flamant					*
1948	Spring & Stiles	*		*		
1949	DeLaunay	*				
1952	De Groot & Gebhard	*				
1953	Alpern & Benson	*				
1953	Fry & Allen		⊓	*	*	*
1954	Fugate		⊓	*		
1955,56	Schweitzer		⊓	*		
1956	Fugate & Fry	*	⊓	*	*	
1956	Hopkinson	*				
1956	Schweitzer & Bouman		⊓	*		
1957	Kadlecová & Peleška	*				
1959	Alpern, Kitai, & Isaacson		⊓	*		*
1959-60	Kawabata		⊓	*		
1959,61	Lowenstein & Loewenfeld		⊓	*		*
1960-63	Hakerem		⊓	*		
1961	Kadlecová			*		*
1962a	Alpern & Campbell					*
1963	Burke		⊓	*		
1963	Lowenstein, Kawabata, & Loewenfeld		⊓	*		

Note: Symbols: static = eye adapted to light stimuli; flash ⊓ = light pulse; flash ↱ = sudden increment; threshold = threshold reactions of dark-adapted eye; difference threshold = increment or decrement of previously steady illumination; darkness = sudden or gradual withdrawal of light.

a,b in Year column refers to order in References.

In Table 2B, a number of experiments are listed in which light intensity was considered secondarily, the chief subject of the investigation being concerned with other problems.

Table 2C summarizes experimental work in which stimulus luminance was of major interest. In these investigations, different kinds of light stimuli were used:

(1) the subject's eye was successively adapted to different levels of brightness of the source, and the pupillary diameter was noted for each intensity step ("static" in Table 2C);

(2) the pupillary reaction to a sudden light-flash was studied. In some cases, this flash was transient, of definite and controlled duration (symbol ⌐¬ in Table 2C); in others the light was left on, and pupillary behavior after the light stimulus was not considered (symbol ⌐→ in Table 2C). In most of these studies the subject's eye was said to be dark-adapted, but it is clear that the intended "darkness" was true darkness only when infrared-sensitive recording or viewing devices were available. Whenever visible light was used for observation, this form of stimulation actually represented a sudden increment of light above the adapted state;

(3) some investigators tried to establish the minimal light increase needed to obtain a just-discernible response ("threshold" in Table 2C). The reservation concerning the quality of "darkness" holds for this kind of experiments also, and, in tests done under observation with visible light, it was actually the incremental threshold that was determined;

(4) in the experiments marked "difference threshold" the authors intentionally looked for the smallest increment or decrement of light that would provoke a just-discernible reaction;

(5) a final group of authors studied the time course of the pupillary dilation that occurs when light to which the eye has been adapted is suddenly turned off. In the case of Flamant (1948), the withdrawal of light was gradual, since she took intermittent measurements while the eyes were exposed to the darkening sky at dusk; these measurements were, then, actually taken during gradually shifting, slow adaptation to darkness, and they could therefore be included with equal justification among the "static" group. Fry & Allen (1953) studied the recovery time of the pupil after exposures to light shorter than needed to adapt the eye.

Because of these different methods of stimulation, a variety of results were found, some of them contradictory. A detailed consideration of these divergencies would lead to endless discussions. In the present paper, therefore, a brief description will be given of the general features of pupillary responses, recorded under various controlled conditions; and the discrepancies in the literature will be discussed in connection with the pupillary phenomena which they concern. Since the differences between the light stimuli listed in Table 2C under "static," "flash," and "darkness" are essentially differences in timing, they are considered in the section devoted to that subject. The descriptions in this section are limited to reactions elicited by 1-second (sec) light flashes of different intensities.

2. Features of the reactions to light of different intensities

When the dark-adapted eye is exposed to light flashes of 1 sec duration, the pupillary threshold is found to be very low. Using appropriate recording techniques (Lowenstein & Loewenfeld, 1958), small but distinct pupillary reactions usually can be obtained well within the first log unit of stimulus luminance above the subject's scotopic visual threshold. As the intensity of the light is increased over a range of approximately 3 log units, the pupillary contractions become more constant and extensive. Throughout this low-intensity range of luminance the responses are, however, typically shallow: the contraction is preceded by a long latent period, and it is slow, inextensive, and of short duration (See Figs. 1, 2, 9, 10A, 11). When the light intensity is further increased the reflexes begin to grow markedly in amplitude, speed and duration, and, depending on the autonomic nervous balance of the subject (cf. below), maximal values are reached about 7-9 log units above the scotopic visual threshold: the reactions outlast the 1-sec light flashes (approximate duration = 1.5-1.8 sec); the latent period has decreased to a minimum (about 0.2-0.3 sec), while extent and peak speed of contraction have reached maximal values (about 4 millimeters (mm) and 7-10 mm/sec, respectively). It will be noted that the increments in pupillary reactivity for equal increments in stimulus luminance become greatly enhanced immediately above the low-intensity range. This sudden increase in effectiveness of the light flashes is due to the fact that the cone-threshold has been exceeded (See Figs. 18, 19). This scotopic-photopic break is typical for the pupillary increment curve when white light is used (See also Flamant, 1948; Kadlecová, 1960; Lowenstein & Loewenfeld, 1959a); it is absent when red light is used, because the pupillary threshold rises above the photopic visual threshold, and the lower part of the increment curve is missing (Fig. 2A, line of squares). It is also absent when white light is used in the pigeon's eye, with a predominantly cone-retina (Fig. 2, lines of triangles).

Very powerful light flashes fail to add further to the amplitude and speed, or to reduce the latent period of the reactions, but they cause marked prolongation of the contraction: after such stimuli, the pupil may remain in spastic miosis for several seconds, and the following redilation is slow. (See section on "Time Characteristics of the Stimuli; Very strong light.")

3. Modifying effects of fatigue and emotional excitement

Fatigue and emotional excitement are so much a part of everyday life, and their modifying influence upon pupillary diameter and reactions so profound, that their effects must be well understood and constantly borne in mind in experiments that, typically, last considerable time.

The light reflex, in spite of its autonomic nature, does not take place independently of the subject's level of consciousness. While the

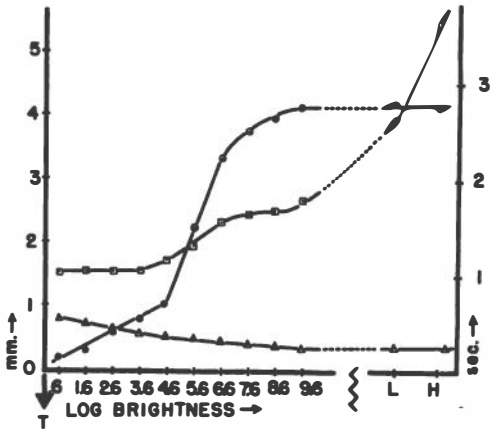

Fig. 1. Extent, duration and latent periods of pupillary reactions to one-second light flashes. Symbols represent average values of 30 individual reactions per intensity step. Subject's eyes dark-adapted. Extent of pupillary contractions (in mm, left-hand scale) and of durations of latent period and of total contraction time (in sec, right-hand scale) plotted against stimulus luminance, with arrow T marking subject's scotopic visual threshold. Log luminance = .6 - 9.6 above visual threshold for 1-sec light flashes emitted by Sylvania glow modulator tube (with 31 mm condensing lens = slightly divergent beam measuring approximately 20 mm at subject's left cornea). L = lowest and H = highest intensity of Grass photic stimulator, seen by both eyes, approximately 9 inches distant.

Circles: Note the characteristic scotopic-photopic break in the rising curve of extensiveness of pupillary contractions (see also Fig. 2, 18, 19). Maximal reflex amplitude was reached at 8-9 log units above visual threshold.

Squares: Duration of the pupillary reflexes remained short in the low-intensity range (see also Figs. 10, 11); at 3-4 log units above visual threshold, duration increased to a new plateau (about 1.6-1.8 sec). In response to very bright light, the contractions were much prolonged, because the pupillary redilation became slow and delayed.

Triangles: Latent period for contraction was inversely related to stimulus luminance, falling from a maximum of more than 500 milliseconds (ms) near threshold to a minimum of about 240 ms at 8-9 log units above threshold. (Absolute time values here indicated are probably somewhat longer than true latent periods. For explanation, see section in text concerning latent period on p. 48).

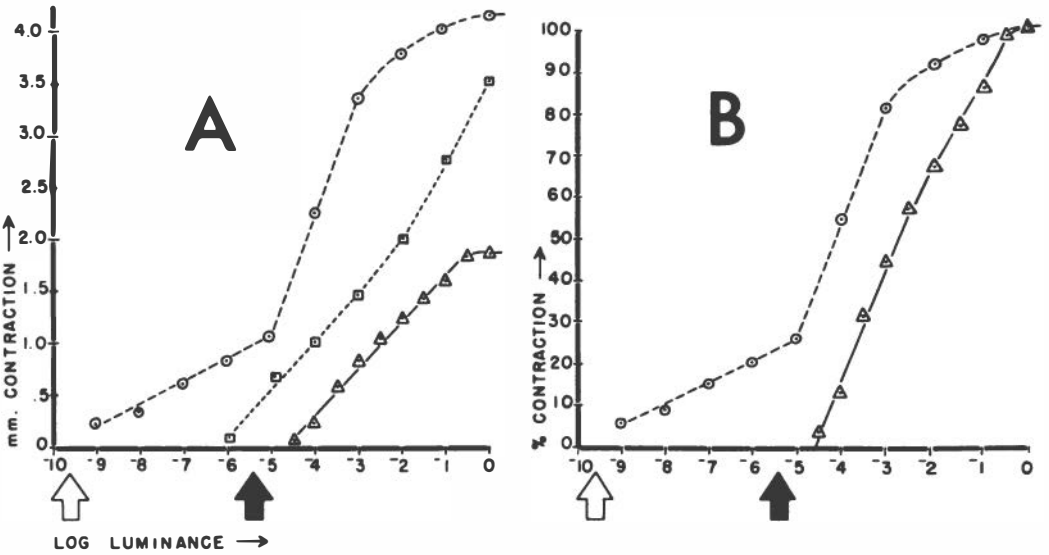

Fig. 2. Extensiveness of pupillary contractions to light in normal human subject and in pigeon (Fig. 20, Lowenstein et al., Amer. J. Ophthal. 57:569-596(1964). In A, actual extent of pupillary contractions plotted as ordinate (in mm); in B, data re-plotted as percentage contraction, taking maximal contractions for human subject and for pigeon as 100 per cent, to correct for smaller size of pigeon's iris; each symbol represents average of at least 20 individual reflexes. Abscissa shows intensity of stimuli in terms of neutral grey filter transmittance, with 0 the maximal output of Sylvania glow modulator tube, used as in Fig. 1. Stimulus duration = 1 sec; stimulus color = white (circles, triangles), or with Wratten #29 red filter (squares). Human scotopic visual threshold marked by white arrows; human visual threshold when using red filter marked by black arrows.

Note the low threshold and distinct double slope of the human pupillary increment curve for white light (circles), the high threshold and single increment curve for the human reactions to red light (squares), and in the pigeon for white light (triangles).

subject is alert, the central synapse of the pupillomotor reflex arc in the Westphal-Edinger nucleus is subject to supra-nuclear inhibitory influences. Simultaneously, hypothalamic discharges, brought into play by sensory or emotional stimuli provided by the environment, or, in man at least, by spontaneous thoughts or emotions, travel via the lower brain stem, cervical cord, and peripheral sympathetic chain to the dilator muscle of the iris (Figs. 3, 4). Under the influence of these mechanisms the pupil in healthy, alert subjects is relatively large and quiet in darkness (7-9 mm, Fig. 5, line B1; cf. also Lowenstein, Feinberg, & Loewenfeld, 1963). In healthy, well-rested subjects this condition may be maintained for long periods of time. But when the subject becomes tired, the pupils

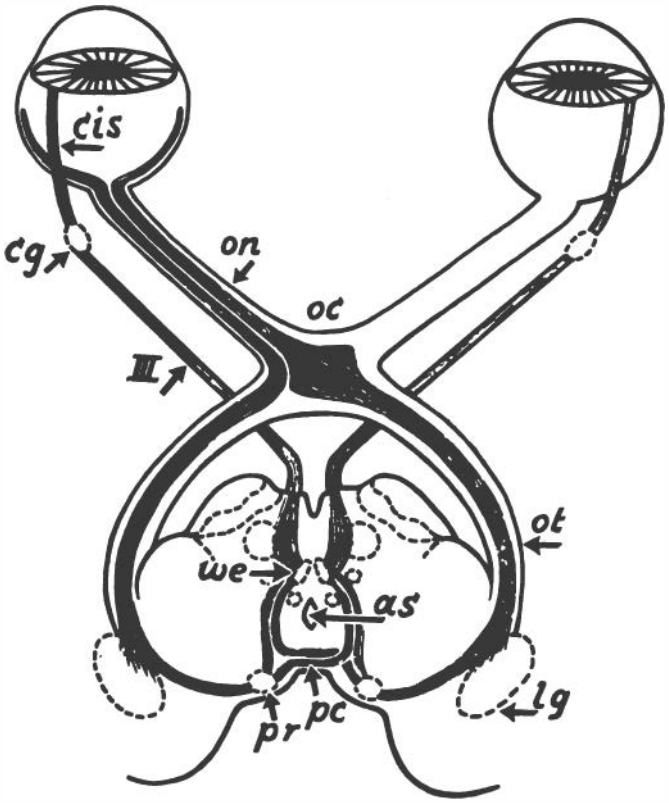

Fig. 3. Schematic representation of pupillary light reflex pathway (Fig. 1, Lowenstein, 1959)

Note: as = aqueduct of Sylvius; cg = ciliary ganglion; cis = short ciliary nerves; lg = lateral geniculate body; oc = optic chiasm; on = optic nerve; ot = optic tract; pc = posterior commissure; pr = pretectal area; we = (Westphal-Edinger) oculomotor nucleus; III = third nerve.

gradually become smaller and begin to oscillate. In ever deepening waves of sudden, spontaneous arousal and gradual slipping into a doze, the pupils dilate rapidly, then re-contract gradually in an unsteady, wavering decline. The more the subject is tired, and the less he tries to suppress his sleepiness, the shorter the time of initial mydriasis, and the deeper and more frequent the following pupillary oscillations. Eventually, the spontaneous intervals of re-awakening cease altogether, and the subject actually falls asleep. At the moment immediately preceding sleep, the pupils are quite small (Fig. 5, lines B2-B3). At this time a psycho-sensory stimulus such as a sudden sound, conversation, etc., restores the waking condition and, depending on the type and intensity of the stimulus, may maintain it for some time. It has been shown that the pupillary oscillations that appear in the tired subject originate in the central nervous system. As the subject drifts toward

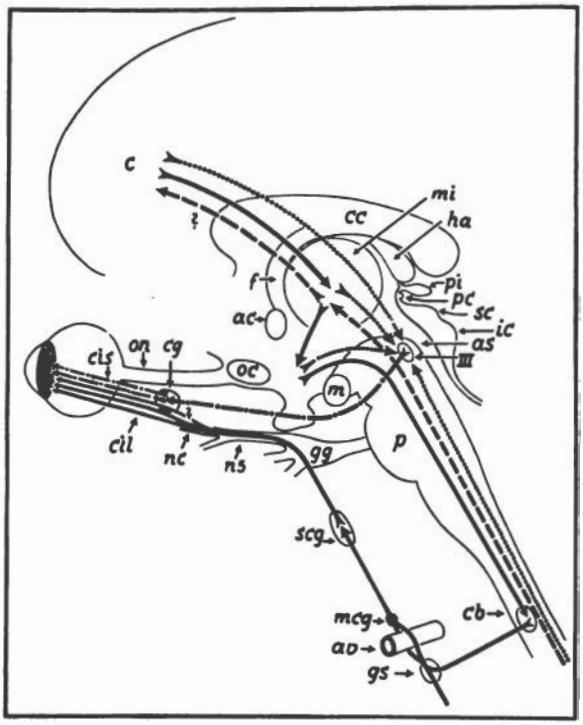

Fig. 4. Schematic representation of pupillary pathways in sagittal view of brain (Fig. 2, Lowenstein, 1959).

Solid lines: Efferent sympathetic path from hypothalamus via cervical cord and peripheral sympathetic chain to eye. This efferent system is under control of cortico-thalamic-hypothalamic mechanisms.

Dash-dot line: Efferent parasympathetic path from Westphal-Edinger nucleus via third nerve and ciliary ganglion to the iris sphincter.

Dotted lines: Inhibitory paths to the Westphal-Edinger nucleus: (1) direct afferent connections in brain stem reticular formation, and (2) descending connections from cortex, thalamus and hypothalamus.

Note: ac = anterior commissure; as = aqueduct of Sylvius; av = subclavian ansa of Vieussens; c = cortex; cb = cliliospinal center of Budge; cc = corpus callosum; cg = ciliary ganglion; cis = short ciliary nerves; cil = long ciliary nerves; f = fornix; gg = Gasserian ganglion; gs = ganglion stellatum; ha = habenular nucleus; m = mammillary body; mcg = middle cervical ganglion; mi = massa intermedia; nc = naso-ciliary branch of the ophthalmic 5th nerve; oc = optic chiasm; on = optic nerve; p = pons; pc = posterior commissure; pi = pineal body; scg = superior cervical ganglion; III = (Westphal-Edinger) oculomotor nucleus.

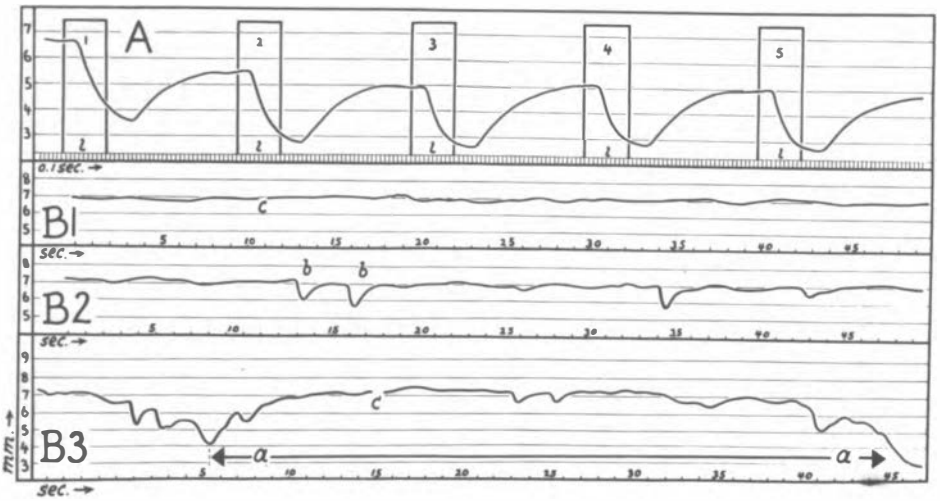

Fig. 5. Spontaneous pupillary movements in tired subject (Fig. 7, Lowenstein et al., 1963). Diameter of right pupil recorded as ordinate (in mm) against time as abscissa (in 0.1 sec units in A, and in seconds in B). In lines B, ordinates reduced approximately to 1/2 size shown in A. In line A, 1-sec light flashes were presented at times framed (intensity 8-9 log units above scotopic visual threshold). Lines B were recorded while the subject sat in complete darkness, fixating on a small, red light spot at about 6-foot (ft) distance.

Line A: At beginning of the test the pupil showed normal diameter, and light flashes elicited normal reflexes.

Line B: The pupil was large and remained relatively quiet during the first minute in darkness (B1). Irregularities appeared soon, with small, fast oscillations prominent (b, b in line B2, showing pupillary movements during the 8th minute in darkness); these sudden, small contractions and redilations, resembling miniature light reflexes, probably are associated with imperfect fixation of the tired subject (cf. Lowenstein et al., 1963, p. 142). Irregular, extensive waves of pupillary dilation and contraction appeared shortly thereafter (a⟷a in line B3, recorded during 16th minute of observation); they accompanied waves of drowsiness and spontaneous arousal of the subject, and became more and more frequent and extensive until the subject finally fell asleep. Spontaneous lid closures, which did not affect the pupil in darkness, marked by c.

sleep, supranuclear inhibition of the Westphal-Edinger nucleus decreases, and sympathetic activity is gradually lost. The consequent relative preponderance of the parasympathetic outflow is revealed by the smallness of the pupil at the time immediately preceding sleep. At the moments of

spontaneous or reactive awakening, sympathetic activity and supranuclear inhibition of the third nerve nucleus cooperate in dilating the pupil.

Chronically increased fatigue is not an uncommon finding, and, unless recognized, will cause difficulties in experiments in which the pupil is used as an indicator. Many persons habitually fail to sleep sufficiently, and the after-effects of various illnesses may be far more long-lasting than is recognized. Many subjects, though neurologically in good condition, will thus be found to be more subject to fatigue than is usual for persons in their age group, or is explained by energy spent during an experiment. When sitting quietly in darkness and not occupied by some activity, it is difficult for such subjects to stay awake. After a brief period of wakefulness with large, steady pupils, the oscillations described above will appear in an exaggerated manner: the pupils will fluctuate wildly over a large range as the subject fights an increasingly overwhelming sleepiness.

Pupillary reflexes are superimposed upon this constantly shifting equilibrium of autonomic innervation of the iris, which is further modified by humoral adrenergic mechanisms (Loewenfeld 1958, pp. 327-344) and by the mechanical limitations of the iris muscles (Fig. 6). A light stimulus of a given intensity and duration will therefore not necessarily elicit a pupillary reflex of predictable speed and amplitude. As the subject or the experimental animal becomes sleepy, the pupil becomes smaller and the reactions less and less extensive; immediately preceding sleep, the miotic pupil hardly reacts to light (Fig. 7, e, f, g). Sensory or emotional stimulation have an opposite effect upon the pupillary diameter: with increasing excitement the pupil becomes larger and larger. The light reflex, however, does not benefit by the large pupillary diameter in darkness; it is supressed when the degree of supranuclear inhibition and sympathetic excitation exceeds an optimal level (Fig. 7, b, c, d).

Figure 7 shows clearly that these changes in the pupillary reflexes are not merely a matter of amplitude. The shape of the reflexes varies with the degree of excitement or drowsiness. The characteristic square, w-shaped, v-shaped, and flattened, inextensive reflexes can be seen. The very same reaction patterns are observed in patients with lesions or irritation at various locations within the nervous network of pupillary control (compare the reactions shown in Fig. 7 with Fig. 8A, D1-D3, F, G1, and G2), and they can be produced at will in experimental animals by electrical stimulation or surgical destruction at the same sites. The only difference between the effects of physiological fatigue and excitement and those of pathological conditions is that physiological reflex changes are transitory and are changed to the normal pattern as soon as the subject or animal calms down, or awakens, as the case may be; in contrast, the pathological reaction shapes are permanent; they can deteriorate further but they cannot be restored to normal form.

The striking similarity between the reflex forms of fatigue and excitement on the one hand, and those of pathological conditions on the other, shows that the effects of emotional and sensory stimulation as well as those of fatigue are not diffuse and disorganized. While the subject gradually falls asleep, specific nervous centers cease to function in orderly sequence, and they are called back into action by increasing psychosensory stimulation.

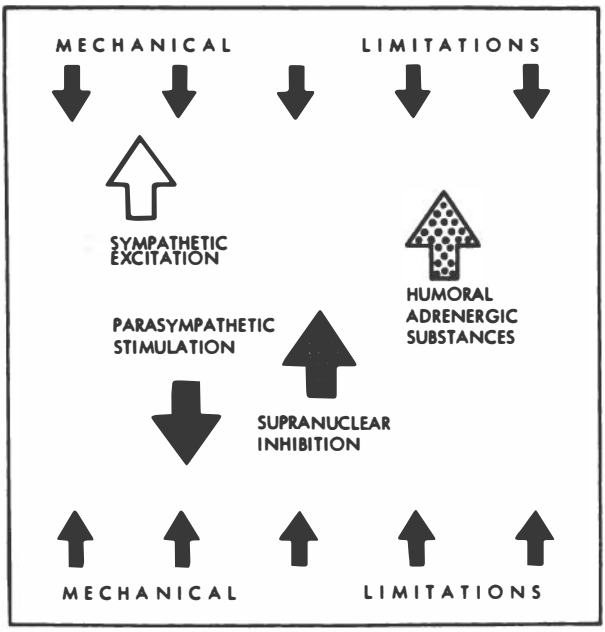

Fig. 6. Mechanisms affecting pupillary size and reactions (Fig. 5 of Lowenstein & Loewenfeld, 1964b).

Parasympathetic innervation causes active pupillary constriction (black arrow), its central nervous inhibition incomplete, passive dilation of the pupil (cross-hatched arrow). Sympathetic excitation dilates the pupil rapidly and completely (white arrow). Adrenergic substances, entering the blood under the influence of central nervous mechanisms elicited by strong sensory or emotional stimulation, may reinforce and prolong pupillary dilation (dotted arrow). Finally, the limits of mechanical capacity of the iris muscles may modify the movements when extremes of mydriasis or of miosis are approached (small black arrows).

These mechanisms are active to a remarkably similar degree in all mammals, and pupillary reactions elicited under similar experimental conditions show relatively minor variations among species (see Figures 7, 8); in birds, with striated pupillary sphincter, the reactions are a great deal faster and show different time-amplitude patterns (see Figure 13).

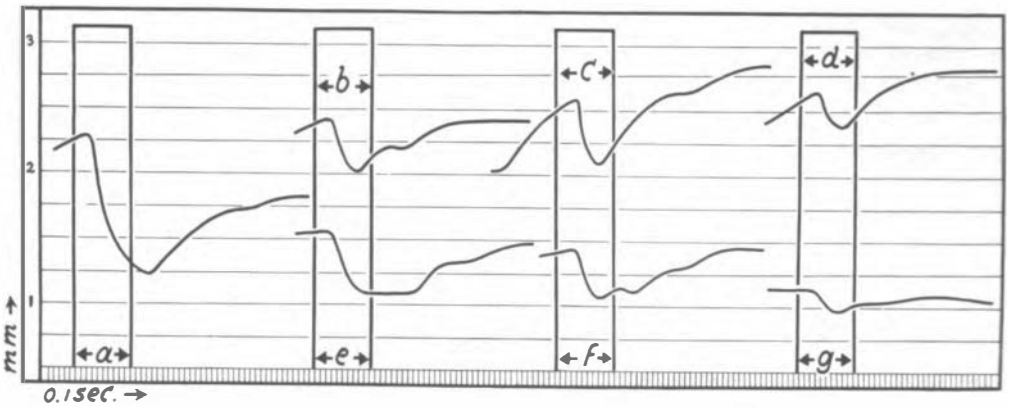

Fig. 7. Effects of emotional excitement and of sleepiness upon pupillary light reflex in normal rats (Fig. 1, Lowenstein et al., 1963). Pupillary diameter recorded (in mm) against time (in 0.1 sec units). Because of smallness of rat's eye, ordinate enlarged by factor of 4, as compared to human pupillograms. Reactions of left eye shown. Animals in darkness except for 1-sec periods framed at a - g when light flashes were presented.

a = Normal light reflex in alert but not excited rat; b-d = inhibited reactions, elicited after sensory stimulation; with increasing emotional excitement, the pupil enlarged and the light reflexes became less and less extensive, showing characteristic w-and v-shapes found in all mammals under similar conditions; e-f-g = light reflexes elicited while the animal was sleepy. Note the square, w-and flattened v-shapes of the responses.

In any experiment concerning the pupillomotor effectiveness of a given kind of light stimulus, or light adaptation, these mechanisms may alter the reactions. Variations due to momentary changes in the physiological state of the subject are especially marked near the pupillary threshold, because the small pupillary reflexes elicited by weak light are easily suppressed by antagonistic influences (Fig. 9). Moreover, in a number of normal subjects the degree of tiredness or of emotional tenseness may vary considerably, and the same experimental situation may elicit different results (see also Section below, "Other Features of Pupillary Reactions to Light," and Fig. 25). It is thus necessary to be aware of such possible alterations in every experiment, and to safeguard the accuracy of the results by using a sufficiently large number of subjects, and by repeating the reactions a sufficient number of times.

TABLE 3

Pathology of the light reflex

		Condition	Pupillary manifestations
MYDRIASIS	D3	Maximal central (diencephalic) irritation	Very large pupils and absence of light reflex, or sluggish, intensive reflex of short duration; bilateral
	D2 D1	Submaximal central (diencephalic) irritation	W- or V- shaped light reflex; pupils larger than normal; bilateral
	C	Parasympathetic (non-irritative) nuclear or post-nuclear lesion of the third nerve	Prolonged latent period; pupils slightly larger than normal; sluggish, inextensive light reflex; unilateral or bilateral
	B	Lesion in the afferent pathways of the light reflex	Prolonged latent period; slower than normal, W- or V- shaped light reflex; pupils remain equal, even in unilateral lesions
	A	normal	optimal reactions to light
MIOSIS	E	Peripheral sympathetic lesion	Pupil smaller than normal; contraction speed slightly increased; second redilation phase absent; usually unilateral
	F	Central (diencephalic) condition	Shortened latent period; pupils smaller than normal; fast, abrupt, though less than normally extensive light reflexes; bilateral
	G1 G2	Central (diencephalic and mesencephalic) condition	Pupils small; W- or V-shaped light reflex; bilateral
	H	Parasympathetic (mesencephalic) irritative condition	Prolonged latent period; inextensive, sluggish light reflexes; unilateral or bilateral

Note: Cf. Fig. 8.

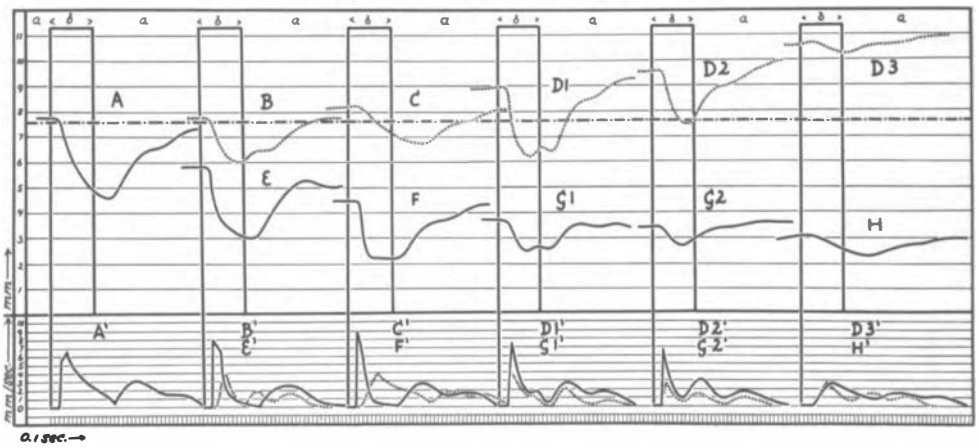

Fig. 8. Dynamic structure of normal and pathological light reflexes (Fig. 4, Lowenstein, 1959).

Eyes in darkness = a; during 1-sec intervals b, exposed to light stimuli about 8-9 log units above scotopic visual threshold. Heavy horizontal dash-dot line indicates diameter of normal pupil in darkness.

In curves A-H, pupillary diameter recorded as ordinate (in mm) against time as abscissa (in 0.1 sec units). Curves A′ - H′ show speed of pupillary contraction and dilation occurring within each reflex. Curves obtained by plotting against time (in 0.1 sec units, abscissa), extent of contraction or of redilation occurring within each successive 1/10 sec (expressed in mm/sec, ordinate).

Normal pupillary light reflex under experimental conditions described = A and A′; dotted lines B, C, D1, D2, and D3 (and corresponding speed curves B′ - D3′) = abnormal reflexes in conditions causing larger than normal pupils; solid lines E, F, G1, G2, and H (and corresponding speed curves E′ - H′) = abnormal reflexes in conditions causing smaller than normal pupils. A summary of pupillary reactions shown in this graph, and of causitive conditions, are contained in Table 3.

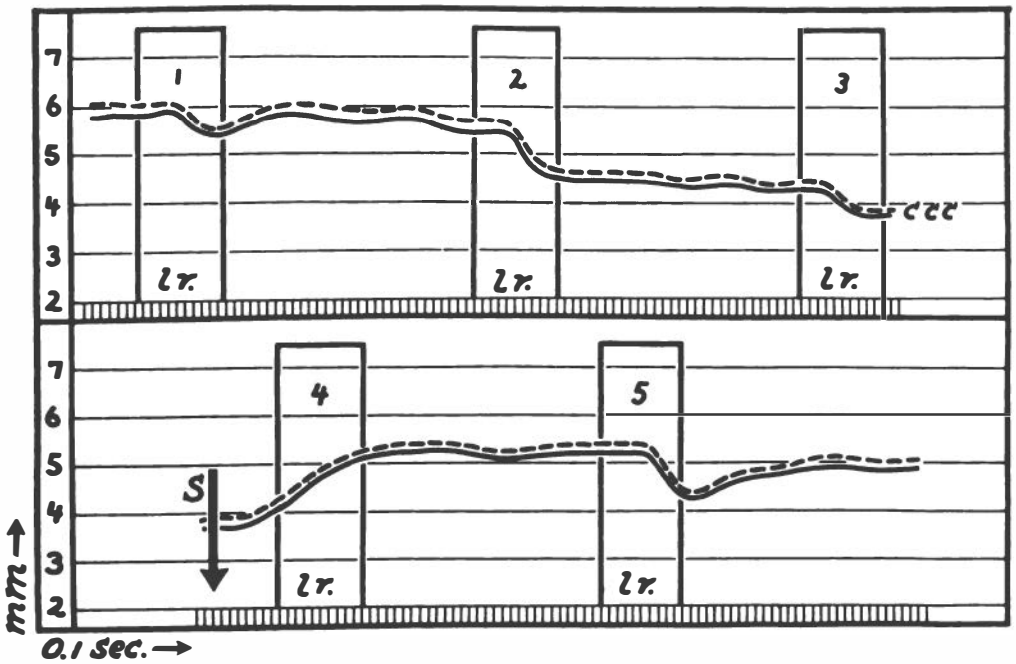

Fig. 9. Enhancement and suppression of low intensity light reflexes by central nervous inhibitory mechanisms (Fig. 3, Lowenstein & Loewenfeld, 1959).

Normal subject (36-year-old man), tired on day of examination; eyes dark-adapted.

Pupillary diameter recorded as ordinate (in mm) against time as abscissa (in 0.1 sec units), with solid line representing direct reflexes of right pupil, the broken line consensual reactions of left pupil. One-second white light stimuli, approximately 2 log units above subject's scotopic visual threshold, were presented at times framed at L.r..

First line: Reactions elicited while the subject gradually fell asleep showed enhanced contractions with no redilation in darkness; at c c c the subject closed his eyes.

Second line: Shortly before 4th light reflex, the subject was awakened by a verbal stimulus ("wake up!"). During awakening, the pupil dilated and the 4th light reflex was suppressed. The 5th light flash elicited a normal threshold reaction.

TABLE 4

TIME CHARACTERISTICS OF STIMULI

A. Simple control of duration by means of mechanical shutters, electric contacts, and electronic flash

Year	Author	Means	R	Year	Author	Means	R
1869	von Arlt	lever, tuning fork	*	1947	Thomson	photo-flash	
1881	v. Vintschgau	lever	*	1947	Thschirren	photo-shutter	*
1882	v. Vintschgau	electric spark		1947	Venco & Marucci	photo-shutter	*
1903	Fuchs	telegraph key	*	1948	Bárány & Halldén	shutter	
1904	Bumke	shutter		1949-54	Harms	photo-shutter	
1904	Piltz	air shutter	*	1949-63	Lowenstein	rotary disk shutter	*
1905	Weiler	lever-shutter	*	1950-54	Cüppers	shutter	*
1907	Schlesinger	falling shutter		1952	Wirth	photo-shutter	
1910	Weiler	lever-shutter	*	1954	Fugate	shutter	*
1913	Schlesinger	shutter		1956	Fugate & Fry	shutter	*
1919	Engelking	metronome	*	1956-63	Loewenfeld	electric flash tube	*
1921, 39	Kleefeld	photo-shutter		1956	Schweitzer & Bouman	rotating disk shutter	
1922-57	Lowenstein	photo-shutter	*				
1923	Gradle & Eisendraht	metronome	*	1956	Petersen	electronic flash	*
				1957	Drischel	photo-shutter	*
1929	Barbieri	electric contact		1957-63	Lowenstein	electronic tube	*
1932	Poursines	falling cam shutter		1957-63	Shakhnovitch	mechanical shutter	*
1933	Walter	falling cam shutter		1959	Alpern, Kitai, & Isaacson	falling shutter	*
1939	Borsotti	photo-shutter	*				
1940	Frydrychovitz & Harms	photo-shutter		1959	Samojloff	mechanical shutter	*
				1963	Burke	electronic tube	*
1943-63	Morone et al	photo-shutter	*	1959-63	Hakerem	electronic tube	*
1947-63	Lowenstein	electric magnetic shutter	*				

R = duration of stimulus was registered

B. Study of effects of duration, wave form, or frequency of stimuli

Year	Author	D	R	S	O	Year	Author	D	R	S	O
1760	Lambert				*	1955, 56	Schweitzer	*			
1801	Himly				*	1956	Fugate & Fry	*	*		
1845	Listing				*	1956	Hopkinson				*
1868	Hensen & Völckers				*	1956, 59	Van der Tweel			*	*
1882	Schadow				*	1957	Becker			*	
1888	Chaveau				*	1957	Bleichert			*	
1903	Friberger				*	1957	Bleichert & Wagner			*	
1904	Piltz				*	1957	Stark & Sherman			*	
1913, 14	Schlesinger		*			1957	Stegemann			*	
1918, 20	Reeves	*				1957	Drischel		*		
1922-65	Lowenstein	*	*		*	1958	Stark & Campbell				*
1923	Laurens				*	1958	Stark & Cornsweet				*
1926	Santamaria				*	1959	Kawabata	*	*		
1929	Nicolai				*	1959a, b	Lowenstein & Loewenfeld	*	*		*
1932	Lythgoe				*	1959	Samojloff	*			
1935	Machemer	*			*	1959	Stark				*
1938	Talbot	*				1959	Stark & Baker				*
1939	Borsotti	*	*			1960, 61	Clynes		*	*	*d
1942	Bartley		*			1961	Stark, Redhead, & Payne				*d
1942	Wagman & Gulberg	*				1962b	Alpern & Campbell			*	
1944	Stern				*	1962	Hakerem	*	*		
1947	Venco & Marucci		*		*d	1962a	Stark	*	*	*	*d
1948	Morone		*			1962b	Stark			*	
1950	Campbell & Whiteside				*	1963	Feinberg & Podolak	*	*		
1950-54	Cüppers	*	*			1963	Lowenstein, Kawabata, & Loewenfeld	*			*
1952	Wybar				*						
1953	Fry & Allen	*	*		*	1963	Loewenfeld		*		
1954	Young & Biersdorf		*			1963	Lowenstein & Loewenfeld				*
1954-55	Du Bois-Poulsen & Loisillier		*			1963a, b	Stark			*	
						1963	Troelstra			*	

Note: Symbols: D = stimulus duration (temporal summation); R = repeated stimuli (trains of intermittent flashes); S = sinusoidal stimulation; O = other time characteristics; d = darkness reflex (cf. text).
a & b in Year column refer to order in References.

Time Characteristics of the Stimuli

1. The literature

Only relatively few authors have done special experiments on the influence of duration, wave form, or frequency of the light stimuli upon pupillary reflexes. In earlier experiments, and in most clinical work in which stimulus duration and frequency were considered at all, they were controlled by simple devices (photographic shutters, or shutters that used a swinging pendulum, swinging cam, rotating disk, or other mechanical device). More recently, electronic flash tubes allow more variable and more accurate control of stimulus duration and frequency (Table 4A).

Experiments specifically concerned with the time characteristics of light stimuli are summarized in Table 4B. They were designed to study the effects of

(1) stimulus duration (temporal summation),
(2) stimulus frequency (intermittent light flashes),
(3) stimulus wave-form (sinusoidal stimulation), and
(4) other time characteristics of pupillary reactions related to light. Under this heading are grouped experiments on
(a) pupillary movements during steady illumination, and
(b) pupillary reactions elicited by short interruptions of steady light ("darkness reflex").

2. Influence of stimulus duration

(a) Moderate intensity range: It has been mentioned above that the duration of a pupillary contraction to a timed light flash depends on the intensity of the stimulus. The effect of changes in stimulus duration, likewise, is different for dim and for bright light. In the low-intensity range, the short-lasting pupillary contraction usually is followed by redilation at about the same time when either short or longer stimuli are used (Fig. 10A), and even when the light is left on continuously (Fig. 11). With brighter light, the contraction movement is sustained by continued stimulation, so that the reaction to a long, bright stimulus is much more extensive than the one elicited by a short, bright stimulus (Fig. 10B). The general statement frequently seen in the literature (usually quoted after Reeves) that "the pupil reaches full contraction after 5 seconds" is thus incorrect, and a measurement of the pupil 5 sec or more after the onset of stimulation will not necessarily reveal the effectiveness of the stimulus. If the light is weak, the transient contraction will have disappeared long before. For this reason, authors who investigated the effectiveness of light by the "static" method generally tended to report much higher thresholds for the pupillary reflex than those who recorded the dynamic responses to shorter light flashes.

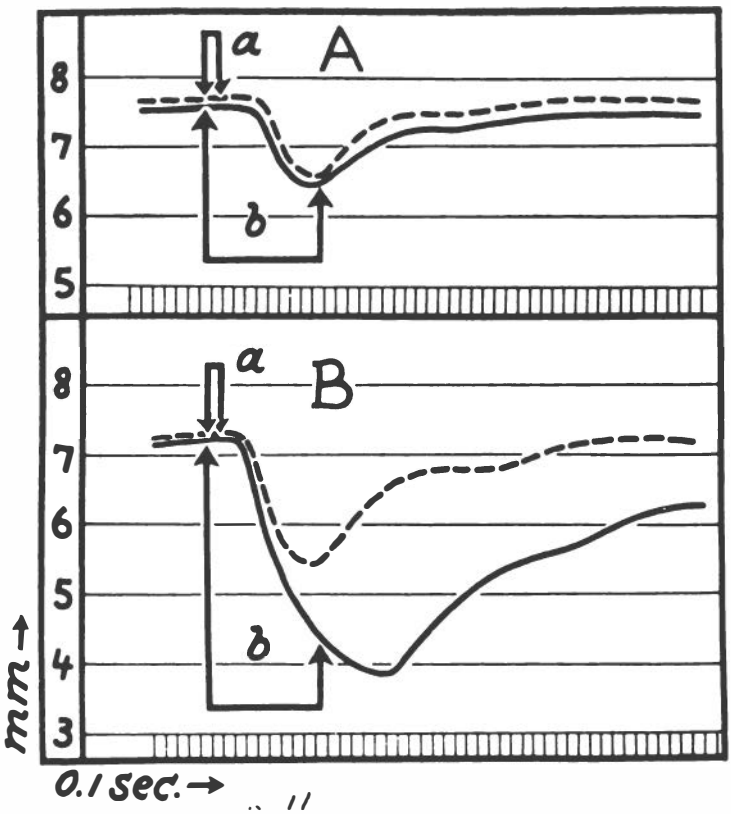

Fig. 10. Reflexes to short and to longer light stimuli at low and at high levels of stimulus intensity (Fig. 4, Lowenstein & Loewenfeld, 1959).

Pupillary diameter recorded as ordinate (in mm) against time as abscissa (in 0.1 sec units). Broken lines show the pupillary responses to 0.1-sec light flashes (double-arrows a); solid lines show reactions to 1.0-sec stimuli (double-arrows b).

A (first line): Dim light was used, about 3 log units above subject's scotopic visual threshold. Reactions to short (a) and to long (b) light flashes were alike; both showed long latent period, low peak speed, small extent, and short duration typical for low-intensity reactions.

B (second line): Light intensity was increased to about 9 log units above visual threshold of the subject. The long, bright light stimulus (b) caused the pupillary contraction to continue for a longer time, and thus to become more extensive than the reflex elicited by the short, bright light flash (a), even though latent period and peak speed of the two reactions were alike: compared to the low-intensity reflexes of line A, the latent period was shortened, and the contraction speed increased.

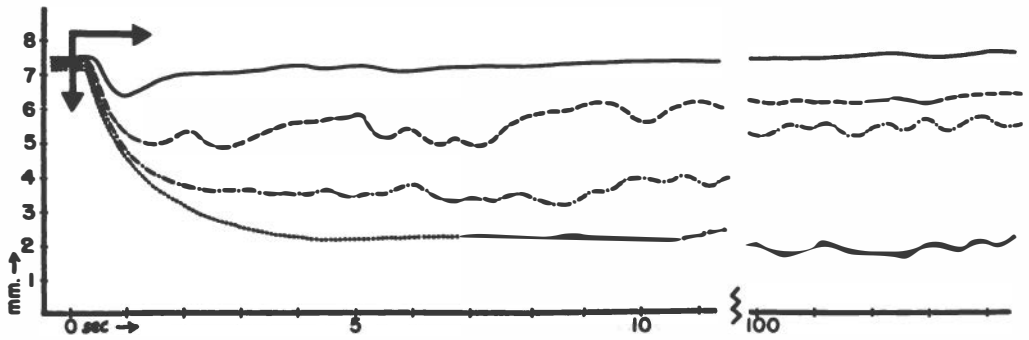

Fig. 11. Pupillary reactions to continuous light stimulation.

Pupillary diameter recorded as ordinate (in mm) against time as abscissa (in seconds). Beginning of continuous light stimulation of subject's left eye (left pupil dilated by cyclogyl) marked by double arrow. Stimulus intensities: 2.6 log units above scotopic visual threshold for solid line, 4.6 log units for broken line, 6.6 log units for dash-dot line, and 8.6 log units for dotted line.

Note the inconstancy of the pupillary contraction to dim light, and development of pupillary oscillations under influence of steady illumination. These oscillations were large, irregular, and inconstant when light of medium intensity was used; they became faster, less extensive, more uniform, and sustained with increasing stimulus luminance.

(b) Threshold reactions: Among the experiments listed in Table 4B, only the ones by Fry & Allen (1953), Fugate & Fry (1956), Schweitzer (1955, 1956), Kawabata,[2] and Hakerem[3] can be said to have considered the question of temporal summation systematically. As a general result, it appears that close to the pupillary threshold the duration of the light flash becomes important: for durations up to approximately 1 sec, the pupil responds to the total energy of the flash, so that intensity and duration are interchangeable in this near-threshold brightness range.

(c) Very strong light: It has been shown in Fig. 1 that the pupillary contractions to intense light stimuli are prolonged. Even a very short, exceedingly bright flash of light will cause the pupil to constrict maximally, and to remain in spastic contraction for a number of seconds. The most probable explanation of this behavior is the assumption that the after-image elicited by such powerful light flashes is sufficiently intense

[2] Personal communications, (H. Kawabata) 1959-1961.
[3] Personal communications, (G. Hakerem) 1959-1963.

to cause a continued pupillary response. There can be no doubt that after-images are capable of affecting the pupil, as shown by an experiment by Alpern & Campbell (1962a). When the eye has been adapted to very bright light, and this light is suddenly turned off, the pupil, after a short delay, begins to enlarge; soon thereafter, however, the dilation is interrupted by a new contraction which may last many seconds before giving way to resumed dilation as the dark-adaptation process continues. In a similar experiment done in the Lowenstein Laboratory of Pupillography (Columbia University), it seemed as though the contraction period coincided with the appearance of a strong positive after-image*. The chapter of possibly related pupillary and after-image phenomena is an interesting one, and should be worked out under better conditions of control than those used by Alpern & Campbell and by the author and colleagues (control of stimulus area and color, simultaneous recording of pupillary movements and of the subject's statements).

(d) Stimulus duration in clinical examinations of the pupil: Numerous authors have realized the importance of standardizing the stimulus duration in clinical examinations of the pupil, and have used various timing devices to control it (Table 4A). Among the investigators who recorded the pupillary reflexes, the question of the most suitable stimulus duration has been discussed (Cüppers, 1954; Drischel, 1957a; 1957b; 1957c; Petersen, 1956). Lowenstein, during the years 1922 to the present, has experimented extensively on the effects of different stimulus durations in clinical pupillographic examinations, and has chosen 1-sec light flashes as the kind of stimuli most likely to allow a clear-cut distinction to be made between the normal and different pathological reflex patterns. Reactions to shorter light flashes show these distinctive features to a lesser degree. In the intensity range usually employed for such tests, they result in a single, short contraction which is followed immediately by redilation. One-second light flashes, on the other hand, cause a continuation of the contraction; and it is during these

* It should be stressed that such a dip in the pupillary redilation curve upon withdrawal of light is never found in alert subjects after adaptation to moderate stimulus luminances. When the eye has been adapted to light up to about 8 log units above the visual threshold, and this light is suddenly turned off, the pupil re-dilates quickly and in a smooth curve, reaching nearly full dilation within less than one minute. Crawford (1936-37) has reported a dip in pupillary size some 5 minutes after the beginning of dark adaptation, and has assumed a shifting from cone to rod function as a possible cause. It is, however, quite certain that, under the experimental conditions described by Crawford, there can be no retinal discharge powerful enough to affect the pupil at so late a time in the dark adaptation process. As has been described above, many subjects become quite drowsy after sitting quietly in darkness for a few minutes, and the pupillary contraction which accompanies fatigue is marked (cf. above, Chapter BI, 3).

later periods of the reaction that the characteristic features of escape from stimulation (W- and V-form), or the flat, square reaction shape (holding action) are prominently displayed (Figs. 7, 8).

It has been objected that prolongation of the stimulus beyond the latent period of pupillary contraction causes the light entering the eye to become progressively reduced, thus setting up a complex situation which was held responsible for the reflex changes described by Lowenstein. It should be realized, however, that in the intensity range used by Lowenstein for such examinations (8-9 log units above scotopic visual threshold) such a reduction is insignificant, because the stimulus luminance may be decreased by a factor of 100-1000 without significant changes in the reflex shape. In any event, these reflex shapes were found unaltered when the patient's stimulated eye was atropinized (with the consensual pupillary reaction recorded), and when the light intensity was thus held constant throughout the 1-sec stimulation period.

Some rather queer notions are sometimes encountered in the discussions about the best possible stimulus duration. Thus, Talbot (1938a) was of the opinion that only the light step, that is, the change to a higher level of brightness acts as stimulus, while continued contraction due to continued illumination constitutes an adapted state during which no energy is expended, while Drischel (1957a, 1957b, & 1957c) is of the opinion that only short light stimuli elicit the "natural" features of the reflex, which would prompt one to conclude that the only "natural" illumination is provided by lightning at midnight. It is the author's opinion that in clinical examinations of the pupil standardization of stimulus duration, and accurate recording of the reflexes, are of greater importance than the particular duration used.

3. Influence of stimulus frequency

The majority of investigations in which repeated light flashes were presented at a fairly slow rate were concerned with alterations of the reflex form and amplitude which develop under the influence of trains of stimuli. These changes are primarily dependent on central nervous reflex mechanisms and are, therefore, omitted from this review.

To the author's knowledge, Bartley (1943) was first to record pupillary oscillations to short, repeated light flashes presented in rapid succession. With the more recent availability of electronic flash sources and of convenient methods for continuous recording of pupillary movements, such studies have become more numerous (Du Bois-Poulsen & Loisillier, 1954-1955; Bleichert & Wagner, 1957; Stark & co-workers, 1957-1963; Kawabata,[4] Lowenstein & Loewenfeld, 1957 to present; Clynes, 1960-61; Feinberg & Podolak[5]).

[4] Personal communications, 1959-1961.
[5] Personal communication, (R. Feinberg & G. Podolak) 1963.

When one or both eyes are exposed to short light flashes in rapid succession, the individual contractions elicited by individual stimuli summate. With increasing stimulus frequency, the summation becomes more pronounced: the mean pupillary diameter decreases, and the individual pupillary oscillations become smaller (Fig. 12). In mammals, the oscillations become very small at the relatively low frequency of 3/sec. Different peak frequencies have been reported by different authors (3-9/sec), and since the fast oscillations are exceedingly small, the top frequency will depend to some extent on the sensitivity of the recording instrument. The author and co-workers did not observe oscillations much above 4/sec. Hakerem[6], using an averaging computer, found slightly faster activity (5-6/sec). The conditions of experiments in which even higher rates were found were, in the author's opinion, not sufficiently controlled to rule out artefacts.

The limiting factor for the fastest rate at which the pupil is able to follow such short light flashes is clearly imposed by the slowness of the smooth muscle effector. In birds, which have a striated pupillary sphincter, much higher frequencies can be recorded. In the experiment on a pigeon shown in Fig. 13, for example, 10 cycles per sec were followed easily, and with greater amplification higher frequencies undoubtedly could be recorded. Stark and his co-workers have found similar high oscillation rates in the owl.

As a clinical tool, the high-frequency reactions have been found by Lowenstein to be most useful. In cases with spastic miosis, just as in normal subjects after conjunctival instillation of physostigmine (Loewenfeld, 1963), the pupil is unable to oscillate normally, and the iris is driven into a tetanic contraction at lower than normal stimulation rates. In contrast, miosis due to sympathetic lesions or to decreased supranuclear inhibition (see p. 24) does not interfere markedly with the fast pupillary oscillations.

4. Sinusoidal stimuli

Some authors used, instead of intermittent light flashes, sinusoidal alternations of brighter and dimmer light, or of light of two colors. Such stimulus wave-forms were produced by changing the current to the lamp, or by inserting a rotating Nichol prism, rotating disk shutter, or rotating crossed polaroid filters into the light path. The majority of these studies were chiefly concerned with problems of servo-analysis that fall outside the scope of this review. Findings of peak speed of the responses agree fairly well with those obtained by intermittent light flashes.

5. Other time characteristics of pupillary reactions to light

(a) Pupillary movements which occur during steady illumination: When one or both eyes are exposed to a constant light stimulus, the pupils

[6]Personal communication, 1959-1963.

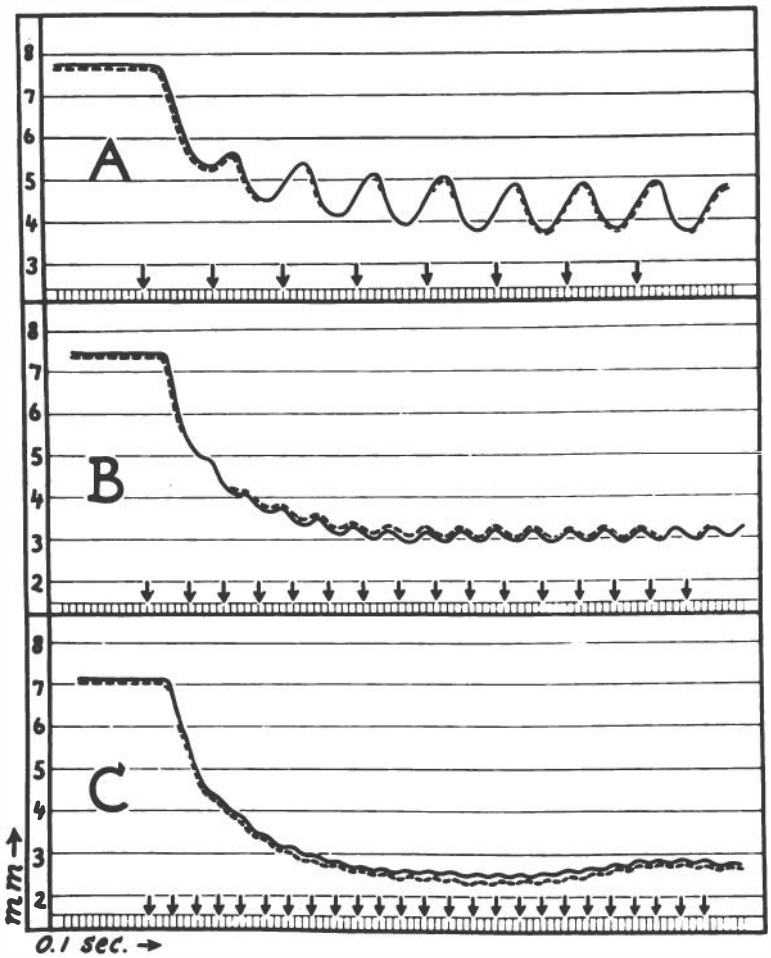

Fig. 12. Pupillary oscillations elicited by repeated short light flashes in man (Fig. 6, Loewenfeld, 1963).

Pupillary diameter recorded (in mm) against time as abscissa (in 0.1 sec units), with solid line representing right pupil, broken line, left pupil. Moments of presentation of 5 ms white light flashes at rate of 1 per sec (A), 2 per sec (B), and 3 per sec (C) marked by small arrows. Light source, Sylvania glow modulator tube; light intensity = about 9 log units above scotopic visual threshold; area = about 5°, centrally fixated, with rest of retina illuminated by intraocular stray light.

In mammals, the slow smooth-muscle pupillary sphincter is driven into tetanic contraction at low stimulus frequencies. Mean pupillary diameter becomes smaller with increasing flash rates, and individual pupillary oscillations less and less extensive.

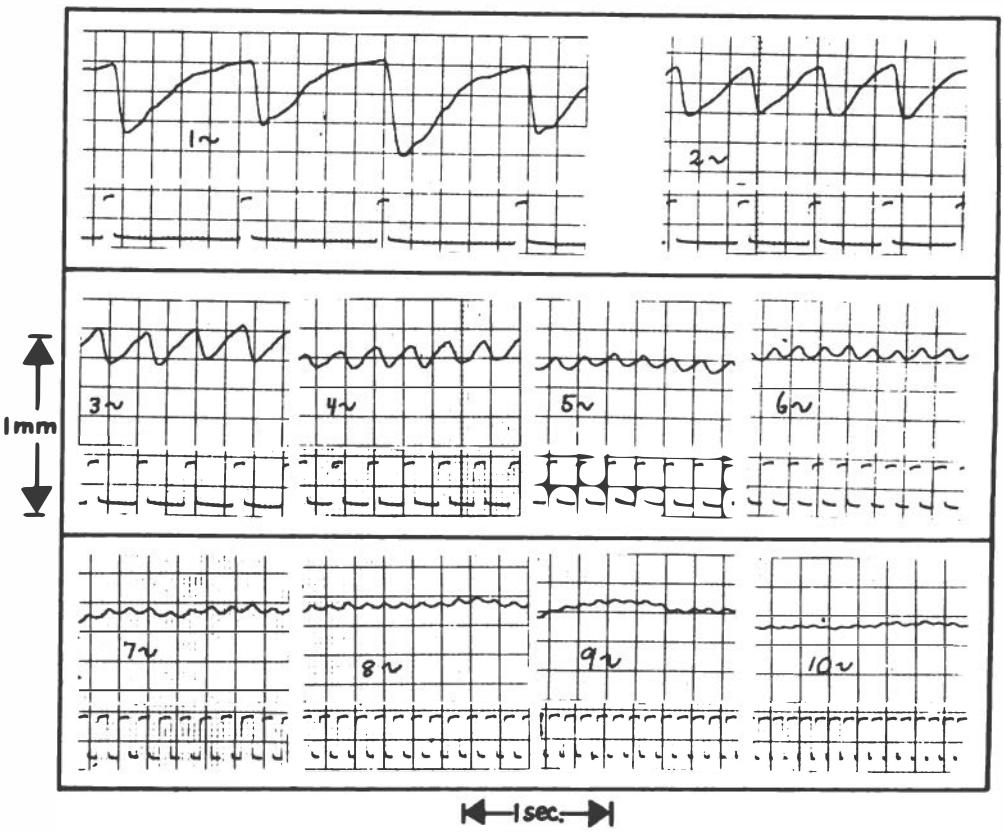

Fig. 13. Pupillary oscillations in pigeon elicited by repeated short light flashes
Moments of presentation of 5 ms white light flashes (same as in Fig. 12) marked by up-strokes of event marker pen; the event marker was run via an electronic relay, actuated by the current to the Sylvania glow modulator tube. The relay circuit had a uniform holding action, independent of the duration of the pulse to the Sylvania tube, i.e., the light flashes were shorter than indicated by the event marker.
Because of the striated iris sphincter, the pigeon's pupil moves much faster than that of mammals, with stimulation rates of 10 per sec followed easily by discrete oscillations.

contract, then redilate partially and begin to oscillate. These movements were observed by many of the early authors, and various interesting attempts were made to measure their rate and amplitude (Table 4B). At a later time, these oscillators played a considerable role in the clinical literature under the names of "pupillary unrest" or, if more marked, "hippus." Their presence or absence was supposed to indicate various pathological conditions.

Several theories were proposed to explain the mechanism of these movements. Most frequently they were thought to accompany the pulse and/or the respiratory cycle, or to be elicited by accommodation, or by psychological influences.

Simultaneous recording of pulse, respiration, and pupillary movements failed, however, to show any phase-coincidence among these functions and the pupillary oscillations. Accommodation can be ruled out by adequate fixation upon a far target, and psychological influences, just as pulse and respiration, should operate in darkness as well as in light, while the pupil, in the absence of tiredness, is large and almost immobile in darkness.

A final explanation holds the shading effect of the iris responsible. Lambert (1760) first noted that the image of a candle flame, slowly moved toward the pupil from the corneo-scleral limbus, at first did not affect the pupil markedly; but as soon as the tip of the image entered the pupil, a sudden contraction occurred and was followed by oscillations. In 1944, Stern advocated this experiment as a clinical test, whereby the edge of the pupil was grazed by a small point of light, and the pupillary oscillations were counted over a period of time. Later workers reported different oscillation frequencies for normal and for pathological cases. (Campbell & Whiteside, 1950; Wybar, 1952; Stark & co-workers, 1957-1963).

In Fig. 11 such oscillations are shown. They were elicited by light from a Sylvania glow modulator tube, used with a 31 mm condensing lens to form a slightly divergent beam measuring about 20 mm at the level of the subject's cornea (9 inches distant). Intensity was varied by neutral grey filters. It is obvious that extent and rate of the pupillary oscillations differ with different stimulus intensities With weak light the pupillary contraction was followed almost immediately by redilation. The pupil regained its dark-adapted diameter within seconds, and showed no more oscillations than it did in darkness (solid line). In response to brighter light, the first contraction became more extensive and was followed by large, irregular oscillations. After some time, these oscillations became quite shallow while the mean diameter of the pupil enlarged (broken line). When the stimulus was further increased in intensity, the small oscillations became faster and more regular. They were maintained throughout the 2-minute exposure time, even though the mean pupillary diameter enlarged (dash-dot line). Upon stimulation by bright light, the pupil contracted extensively; it remained spastically contracted for a number of seconds, and the small oscillations appeared only gradually, as the eye adapted to light. The initial, maximal constriction was maintained throughout the 2-minute adaptation period (dotted line).

In Fig. 14, the results of a similar experiment are summarized. Pupillary oscillations were recorded for 2-minute adaptation periods over a 9-log unit intensity range. As in the experiment of Fig. 11, only

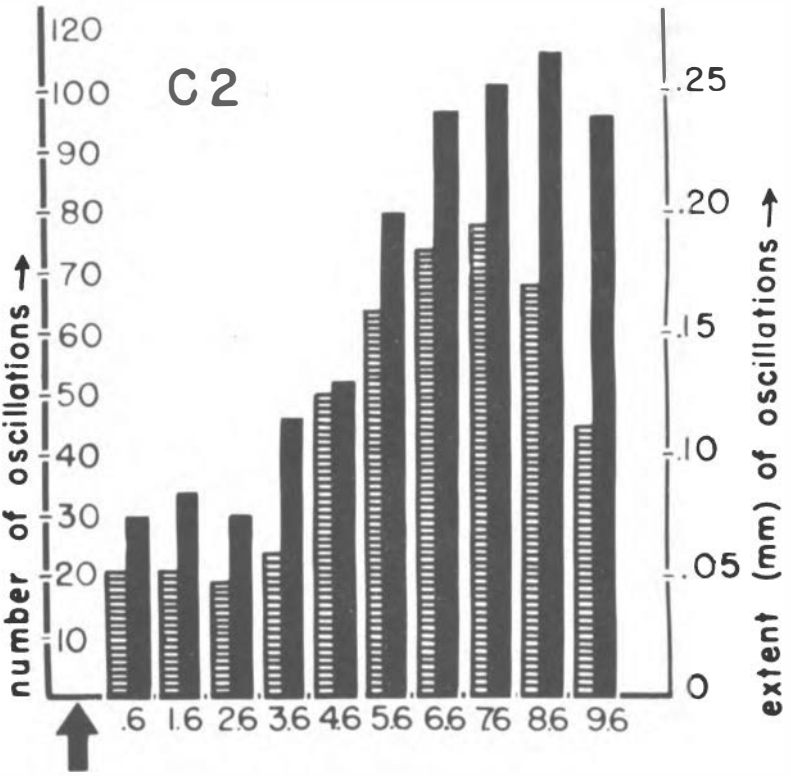

Fig. 14. Extent and frequency of pupillary oscillations in light

Pupillary oscillations recorded from normal subject's right, consensually reacting pupil, with pupil of left, stimulated eye immobilized by cyclogyl.

Abscissa showing light intensity in log units above subject's scotopic visual threshold (marked by arrow); left-hand ordinate and solid columns representing number of pupillary oscillations within 2-minute periods of steady illumination (averaged numbers of 3 experiments per intensity step). Right-hand ordinate and shaded columns showing average extent of same oscillations (in mm).

In dim light the small oscillations were no more frequent or extensive than in equivalent periods in darkness (not shown); they became larger and more numerous with increasing stimulus luminance, until the light intensity exceeded about 8-9 log units above threshold, when they became less extensive and the average frequency within the first 2-minute periods of light dropped somewhat, because very bright light prevents pupillary oscillations in the early period of stimulation (see Fig.11, dotted line).

a few, inextensive pupillary oscillations were found when the stimulus light was weak; in the medium intensity range the movements became more numerous and extensive; finally, during exposure to bright light they became fast, fairly regular, and smaller. The decrease in frequency shown in Fig. 14 for the highest intensity step is only apparent; it is caused by the fact that the pupil does not oscillate at all during the early, spastic phase of the response (see Fig. 11, dotted line).

It is, in the opinion of the author, unlikely that the shading effect of the iris plays a major role in the mechanism of these oscillations, at least in experiments like those just described, in which a fairly large beam of light covered the entire iris. In the experiment of Fig. 14, the stimulated eye had been immobilized by cyclogyl, and the movements were recorded from the consensually reacting opposite pupil. This experiment has been repeated in the same subjects by stimulating either the eye with the normally reacting pupil or the eye with the immobilized pupil, and no difference has been found in the rate and amplitude of the oscillations under these two experimental conditions. These facts do not rule out the possibility that, with a smaller stimulating spot and more elaborate frequency analysis, using a computer and longer stimulation periods, such differences might be found. It should be mentioned, however, that changes in stimulus luminance due to shading by the iris, giving rise to such marked pupillary movements, should be expected to be visible; but in the experience of the author it was precisely in the medium-intensity range, in which the light looked entirely unchanging to the subject, that the pupillary oscillations were most pronounced, while with weak light, which appeared to come and go throughout the 2-minute period, the pupil was stable.

It must be concluded that the mechanism of these movements is yet unexplained. It is possible that the analysis of pupil oscillations under steady illumination may become a useful clinical tool. It is certain, however, that records of frequency and amplitude of such movements without careful control of stimulus intensity are meaningless, both in normal and in pathological cases.

(b) The darkness reflex (symbol d in column O of Table 4B): When one or both eyes have been adapted to light, and when this light is interrupted by a short period of darkness, an interesting tri-phasic pupillary response occurs: during the dark period, the pupil dilates; after the light is re-admitted, it contracts beyond the previous light-adapted diameter, then re-dilates to the pre-stimulatory baseline. This reaction, first observed by Lowenstein (1939; Lowenstein & Givner, 1943), has been named by him the "darkness reflex." It is not identical to the pupillary redilation that follows a short light flash. The conditions differ insofar as, in the case of re-dilation, the eye is adapted to darkness, and the stimulus constitutes a short change to a higher level of illumination, while in the case of the darkness reflex, the eye is adapted to light, and the stimulus is provided by a short change to a lower level of energy.

Clinically, Lowenstein found that the dilation in darkness, the contraction upon re-admittance of light and the final re-dilation to baseline could be altered separately or in certain combinations, depending on the location of the pathological condition within the nervous reflex pathways. These changes are not considered here.

When the adapting light is dim, or when the dark interval is shorter than about 0.3 sec, the first dilation in darkness is missing, while contraction and re-dilation are relatively well preserved.

Kawabata,[7] recording the pupillogram and electro-retinogram simultaneously, found that the dark stimulus elicits a retinal "off"-response, re-admittance of light, an "on"-response. The "on"-wave resembles the usual retinal reactions to stimulation by light, and is much larger than the "off"-wave. If it is assumed that these electrical action potentials parallel the pupillomotor events, it would be easy to understand why the dilation period of the reflex is missing when the adapting light is dim, or when the dark interval is short. In the first case, no effective "off"-discharge would be generated; in the second, the pupillary dilation elicited by the smaller "off"-reaction would be overcome by the contraction elicited by the more powerful "on"-discharge.

The "on"-phase of the darkness reflex is of particular interest because it is undoubtedly due to the fact that the retina, during the short dark interval, gains sufficient sensitivity to respond to the re-appearing, previously adapted light level as to an increment in luminance. Stark, Redhead, and Payne (1961) have determined the interrelation between the duration of the dark interval and the amount by which the re-appearing light may be reduced in order to cause only a small, standardized pupillary contraction, and have found a gain of about 1.5 log units in the sensitivity of the pupillary receptor system within the first 2 sec in darkness. This experiment points to a most fascinating field of application, because it appears possible in this manner to test objectively the adaptive effects of very short dark periods.

(c) The latent period: The question of the latent period of the pupillary contraction to light is one of the most promising unfinished chapters in pupillary physiology. Much effort and ingeniousness were spent by some of the early authors in attempts to measure the latent period (see Listing, 1845; von Arlt, 1869; Chaveau, 1888); but without recording apparatus, the values obtained could not be accurate. Later data, based on experiments with various recording techniques, ranged from 0.17 to more than 0.5 sec. Part of these discrepancies were, of course, based on measuring errors; it should be remembered that not long ago even reasonably accurate recording of the movements of this delicate diaphragm were exceedingly difficult to do. An additional source of discrepancies consisted in the fact, realized only later, that the pupil may, at the moment of light stimulation, happen to be in the

[7] Personal communication, 1959-61.

descending part of a spontaneous contraction. Under such circumstances, the latent period may seem very short. Thus Lowenstein, in early papers, stated that the latent period may drop to as low as 0.06 sec. He has since corrected this error many times in various publications, but, as often happens in such cases, it remained one of his most faithfully quoted statements. A final, more important cause of the disagreements is the fact that the latent period for contraction to light varies with stimulus intensity. From a minimum of about 0.2 sec for very bright light, it may grow to about 0.5 sec near the pupillary threshold. The exact duration of the longest possible latent period in response to dim light has not been established adequately. Data obtained by the author and co-workers were based on averages of reactions which were recorded with a strip chart ink writer. The threshold reflexes of the pupil are so shallow that it is difficult to mark the exact onset of contraction and it is therefore almost certain that the figures thus obtained are slightly higher than the true durations. Hakerem is at present conducting experiments on this problem, using an averaging computer.

As to the shortest possible latent period, the limiting factor is undoubtedly the slowness of the smooth muscle pupillary sphincter. It is not likely that the minimal latent period in mammals will be found to be much shorter than 0.2 sec, because the iris responds after a delay of approximately 0.15-0.2 sec to strong electrical stimulation of the third nerve or the ciliary ganglion (cat, monkey). In birds, with a striated sphincter, the minimal latent period is only about 0.06 sec, proving that, for bright light stimuli, the time delay consumed by the nervous reflex mechanism must be very short indeed.

The most interesting and potentially useful feature of the latent period is its variability. It is affected by changes in the sensory as well as in the motor parts of the reflex arc. On the one hand, according to Lowenstein it is prolonged in cases with lesions in the midbrain or efferent parasympathetic nerve path; it can be altered by the use of drugs, and current work by Feinberg & Podolak indicates a possible age-trend. On the other hand, the inverse relation between the latent period and stimulus intensity makes it appear possible to use the latent period as a measure of the effectiveness of light stimuli. As shown in Fig. 15, individual differences in the reactions to a given stimulus situation are much less marked for the latent period than for the amplitude of the same reactions. The prolongation of the latent period with dim light does not appear to be related primarily to the properties of the effector muscle, since it is almost as pronounced in the pigeon as it is in man (Fig. 16).

Stimulus Area (Spatial Summation)

In clinical examinations of the pupil, the extent of the stimulus area usually has not been considered, and most of the experiments of the

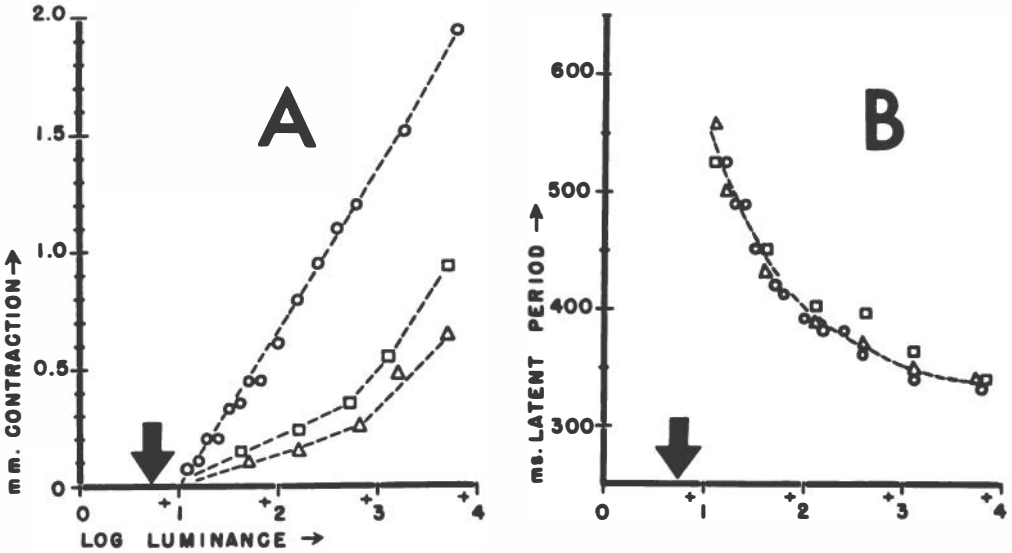

Fig. 15. Extensiveness and latent periods of pupillary reactions to foveal red light flashes in three normal subjects (Fig. 18, Lowenstein, et al., 1964a).

In A, extents of pupillary contractions plotted as ordinate (in mm), and in B, latent periods of same reflexes (in ms), with each symbol representing average of from 8 to 20 reflexes. Stimulus luminance in log units shown by abscissa, where O indicates subject's foveal visual threshold for 1° white light flashes of 1 sec duration; visual threshold for red stimuli (Wratten filter #29) of same area and location marked by arrow.

Three normal subjects were used: (1) a twenty-year old woman with unusually reactive pupils (circles); (2) a twenty-year old man with average pupillary reactivity (squares); (3) a twenty-four year old slightly tense man with somewhat more than average supranuclear inhibition (triangles).

The visual thresholds of the three subjects differed less than 0.1 log unit. Pupillary contractions of subject (1) were up to five times more extensive than those of subject (2), and up to 10 times more than those of subject (3). In contrast, the latent periods of the three subjects agreed well.

interaction of stimulus area and intensity as regards their pupillomotor effectiveness were done by authors primarily interested in problems of physiological optics (Table 5).

The following are the most important results of these experiments:

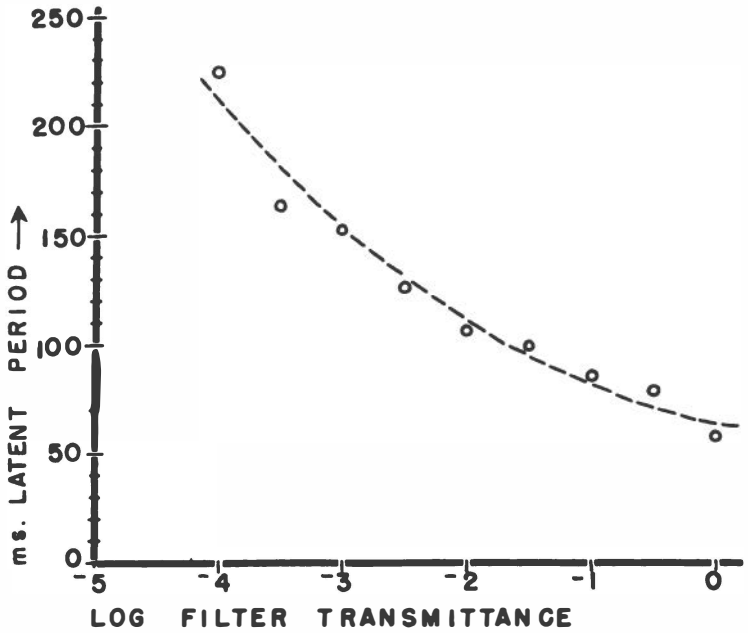

Fig. 16. Latent period of pupillary contractions to light of different intensities in pigeon (Fig. 21, Lowenstein, et al., 1964a)

Average latent periods of pigeon's light reflexes (extents shown in Fig. 2) plotted as ordinate (in ms) against stimulus intensity as abscissa (in terms of transmittance of neutral grey filters used, with O, the maximal available intensity); each symbol represents average of at least 20 reflexes.

Note the short latent period of the pigeon's striated pupillary sphincter muscle when bright light was used, and the lengthening of the latent period with decreasing light intensity (see also Fig. 15).

(1) when a small stimulus field is enlarged, the pupillary threshold is lowered, and

(2) when an already large field is further increased in extent, a further improvement of the responses is found (Abelsdorff & Feilchenfeld, 1904a; Burke, 1963; Ferree, Rand, & Harris, 1933; Hakerem,[8] Schweitzer, 1955-1956);

(3) spatial summation appears to be more pronounced for the pupil than for visual perception: while the pupillary threshold is distinctly higher than the visual threshold for small test patches, the two thresholds become nearly alike when very large stimulus areas are used (Schweitzer, 1955, 1956; Hakerem, 1959-1963; Burke, 1963); and it is common experience that in average room illumination the pupil contracts

[8] Personal communication, G. Hakerem, 1957-1963.

TABLE 5

Area and Retinal Position of Stimuli

Year	Author	Area	Location	Clinical	Experimental	Year	Author	Area	Location	Clinical	Experimental
1760	Lambert	•			•	1934	Luckiesh & Moss	•	•		•
1900	Vervoort	•			•	1936-37	Crawford	•	•		•
1904	Abelsdorff & Feilchenfeld	•	•		•	1938	Elsberg & Spotnitz	•			•
						1938	Talbot	•	•		•
1905	Basler	•			•	1939	Brown & Page	•			•
1907	Hess		•	•	•	1940	Frydrychovicz & Harms		•	•	•
1908	Hess		•	•	•	1943	Bartley	•			•
1909	Hesse		•	•	•	1946	Berens & Zuckerman		•	•	
1909, 13	Behr		•	•		1947	Corrado	•			•
1910	Sachs		•	•		1947	Venco & Marucci		•		•
1913	Schlesinger		•	•	•	1948	Flamant	•			•
1914	Jess		•	•		1949	De Launay		•		•
1914	Schlesinger		•	•	•	1949-54	Harms		•	•	•
1914	Ulbrich		•	•		1950	Sautter	•	•	•	
1914	Walker		•	•		1953	Fry & Allen	•	•		•
1918	Weve		•	•		1954	Fugate	•			•
1919	Weve		•	•	•	1954-55	Du Bois-Poulsen & Loisillier		•	•	•
1922	Vogt		•	•	•						
1926	Holladay	•			•	1955, 56	Schweitzer	•		•	•
1927	Ferree & Rand	•			•	1956	Fugate & Fry	•			•
1929	Barbieri		•	•		1956	Schweitzer & Bouman	•			•
1931, 32	Braun		•	•		1956, 59	Van der Tweel	•			•
1931	Schmeltzer		•	•		1962	Alpern & Campbell	•	•		•
1932	Ferree & Rand	•			•	1963	Burke	•	•		•
1933	Ferree, Rand, & Harris	•			•	1963	Hakerem	•			•
1934	Biffis	•	•	•	•	1963	Lowenstein, Kawabata, & Loewenfeld	•	•		•

when one eye of a subject, previously shaded from the light, is suddenly uncovered so that the light can be seen with both eyes. Under these conditions, there is no sensation of increased brightness.

Retinal Location of Stimuli

1. The literature

In contrast to the lack of interest among clinicians in the extent of the retinal area stimulated, retinal location has been the center of much attention, and a number of instruments were designed to demonstrate "Wernicke's hemianopic pupillary immobility" (Wernicke, 1873; Wilbrand, 1881). Some of these instruments were less complex than the titles of their descriptive articles might lead one to believe, consisting essentially of a light source and simple means for directing a small beam of light into the eye from different directions (lens, pinhole, shade, etc.; Heddaeus, 1893; Fragstein & Kempner, 1899; Kempner, 1899; Wolff, 1900; Stoewer, 1903; Bach, 1904; Bartels, 1904; Friedländer & Kempner, 1904; Veraguth, 1905; Walker, 1914). More elaborate clinical instruments and experiments are listed in Table 5.

The question of the pupillomotor effectiveness of light striking different areas of the retina often circled around the additional question of the identity of the pupillary receptors. The fact that brighter light was needed to elicit a vigorous response from the retinal periphery than from the fovea led to the conclusion that most of the pupillomotor receptors are confined to a relatively small, central retinal area (3-4 mm diameter, according to Hess, 1907). This statement was later interpreted as meaning that the cones alone function as receptors for the pupil, even though it is clear that Hess intended no such implication. The discussion, once opened, flourished in the usual manner, and even today, doubts or a flat denial of a pupillomotor function on the part of the rods are often expressed. It is interesting that among those who have experimented on the subject, these doubts are apparently less common (Table 7). Consideration of this problem will be postponed until the experimental facts pertaining to it have been presented.

TABLE 6

Opinions Expressed about Pupillary Receptors: Rods versus Cones

Year	Author	R	C	Year	Author	R	C	Year	Author	R	C
1900	Abelsdorff	*	*	1934	v. Studnitz	*	*	1957	Bleichert	?	*
1904	Abelsdorff & Feilchenfeld	*	*	1936-37	Steinhardt	*	*	1959	Alpern, Kitai, & Isaacson	*	*
				1939	Brown & Page	-	*				
1905	Basler	*	*	1939-40	Hecht & Pirenne (owl)	*		1959	Lowenstein & Loewenfeld	*	*
1907	Hess	*	*								
1908b	Hess	*	*	1942	Wagman & Gulberg	*	*	1962	Hakerem	*	*
1919	Engelking	*	*					1962	Campbell & Alpern	*	*
1923	Laurens	*	*	1948	Flamant	*	*				
1927	Schlesinger	?	*	1949-54	Harms	-	*	1963	Burke	*	*
1929	Barbieri	*	*	1949	DeLaunay	-	*	1963	Lowenstein, Kawabata, & Loewenfeld	*	*
1933	Ferree, Rand, & Harris	*	*	1953	Fry & Allen	*	*				
				1955, 56	Schweitzer	*	*				
1934	Crawford	*	*	1956	Fugate & Fry	*	*				

Note: R = rods; C = cones.
* = pupillomotor function stated; - = pupillomotor function denied; ? = author was undecided.
b in Year column refers to order in References.

2. Pupillary movements elicited from the fovea and from the retinal periphery

When the eye has been dark-adapted, it is not difficult to obtain pupillary reactions from the retinal periphery. The threshold of these responses is low, even when relatively small stimulus patches are used, and it parallels the visual threshold in the different retinal areas. When light of a color other than red is used, the central scotoma of the dark-adapted eye can be demonstrated, as shown in Fig. 17. This figure also shows that the pupillary threshold reactions cannot be the result of stray light, because the energy needed to obtain contractions by stimuli placed on the blind spot is very much greater than that needed to stimulate adjacent areas of the retina.

TABLE 7

Experiments on Color Sensitivity

Year	Author	Method of Stimulation and Chief Experimental Result
1892	Sachs	color→color or color→grey substitution; light reflected from colored papers; moved new color over adapted color; pupillomotor effectiveness directly related to apparent brightness of color
1893	Sachs	color→color substitution (glass filters in movable frame; intensity varied by grey filters); result same as 1892
1900a	Abelsdorff	color→color substitution (colored filters in movable frame); studied effect of color adaptation in man and animals
1900b	Abelsdorff	color→color or color→grey substitution (prism in modified Helmholtz-König color mixing apparatus; intensity varied by Nichol prism); apparent brightness parallel to pupillomotor effectiveness; found Purkinje shift after light-adaptation
1903	Schäfer	color→grey substitution with spectral colors and color mixtures (Helmholtz color mixing apparatus); some spectral colors more effective than their complimentary colors; others not
1905	Basler	color→color or color→grey substitution (gelatine-glass-liquid filters in movable frame); studied effect of color adaptation; found red more effective in fovea, blue in periphery
1907	Hess	adaptation to spectral colors (Nerst lamp and prism); studied adaptation and spectral sensitivity in day and night birds
1907	Polimanti	color→grey substitution (mirror and spectroscope in double light path); pupillomotor effectiveness of spectral colors parallel to apparent brightness
1908a, b 1910	Hess	spectral colors (Nerst lamp & prism); also colored masks of various shapes; day birds more sensitive in red, cephalopodes and night birds in blue light; color sensitivity in totally color-blind man similar to night birds and to normal, dark-adapted man for dim light; fovea in normal man relatively insensitive to blue light
1913, 14	Schlesinger	intermittent stimulation in different parts of visual field (color filters); selective extinction of reactions to one color need not affect those to a different color
1914, 15	Hess	as 1908-10; also difference thresholds with color and grey filters and wedges; extensive work on normal and color blind man, many animals; results similar to 1908-10; night birds have no Purkinje shift
1922	Engelking	color→color substitution (color wedges in Hess' pupilloscope); determined color sensitivity in a color-blind patient
1923	Laurens	adaptation to equal energy spectrum (Hilger spectrometer, brightness calibrated by distance from tungsten source); determined pupillary effectiveness of colored light in dark-adapted and light-adapted man, pigeon, alligator; established Purkinje shift
1929	Barbieri	color filters in pupil-perimeter; determination of clinical color fields
1939-40	Hecht & Pirenne	step stimuli, large field (tungsten with Wratten filters); determined minimal light of different colors needed to obtain 1/3-1/2 mm contraction in owl; spectral sensitivity curve matched human dim visibility curve
1942	Wagman & Gulberg	step stimuli, large field (tungsten with Wratten filters); determined minimal light of different wave lengths needed to obtain 1/2 mm contraction in dark-adapted human eye; curve matched dim light visibility curve
1955, 58	Schweitzer	intermittent, small test flashes at various retinal sites (tungsten, red or green interference filters); also larger fields, ring-shaped fields, etc.; extensive work on pupillary threshold in dark-adapted eye; found central scotoma with green but not with red light; color sensitivity parallel to scotopic visibility
1959a, b	Lowenstein & Loewenfeld	intermittent stimuli (glow modulator tube, red, green, blue Wratten filters); determined pupillary thresholds in dark-adapted and light-adapted eye
1959	Shakhnovitch	red→blue substitution (filters); found reaction to color change in cat, said to be independent of luminosity
1962b	Alpern & Campbell	color→grey sinusoidal alternation; threshold pupil change as criterion (Hilger-Watts monochromator, rotating polaroid filter in double light path); found mixed cone-rod spectral sensitivity curve for 2° foveal target, which was shifted to purely photopic curve when rods were suppressed by blue background field
1962	Bouma	adaptation to equal energy monochromatic spectrum in photopic brightness range; 4-5 mm pupil contraction as criterion; pupillary spectral sensitivity curve followed scotopic visibility curve
1963	Lowenstein, Kawabata, & Loewenfeld	intermittent stimulation with small test patches in different retinal areas (red, green, blue Wratten filters); compared pupillary threshold reactions and increment curves to visual thresholds and flicker fusion curves

Note: a, b in Year column refers to order in References.

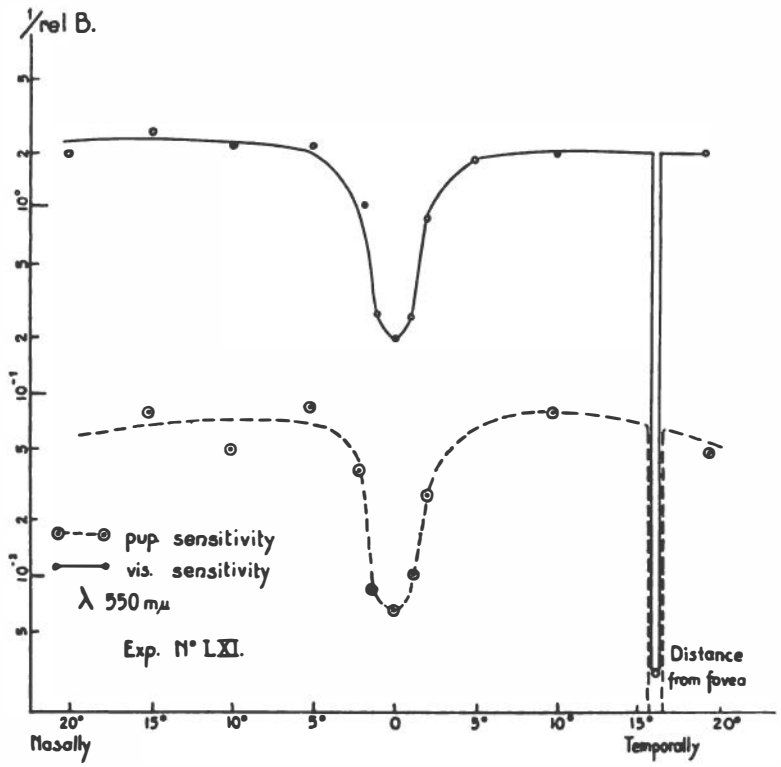

Fig. 17. Pupillomotor and visual sensitivity to green light in fovea and retinal periphery for dark-adapted eye. (Schweitzer, 1956)

Log relative effectiveness of 0.25-sec test flashes of 2° area (tungsten light with rotating shutter and interference filter) represented by ordinate; retinal positions indicated on abscissa. Visual thresholds (solid line) and pupillary thresholds (broken line) are parallel, with pupil about 1.5 log units less sensitive in this experiment (pupillary reactions detected by observation with infrared-sensitive converter-detector; the values for the pupil tend to become somewhat more sensitive when the reflexes are recorded).

Note the central depression for green light, shown in the pupillary reactions as well as for the visual threshold, and the lack of sensitivity at the blind spot.

The question arises as to why so many careful investigators have failed to observe these responses. There are two reasons for the divergent results, namely (a) the differences in the experimental procedure used, and (b) the differences in criteria as to what constitutes pupillary responsiveness.

(a) Influence of experimental procedure: As already described, the pupillary reflexes elicited by dim light are inextensive; they are easily suppressed by antagonistic influences, and are short-lasting even in the presence of continued illumination. When the stimuli are confined to the retinal periphery, the reactions grow only slightly in extent and speed as the light is increased above threshold values (Fig. 18, line of dots). Equal increments in stimulus luminance above threshold cause much greater increments in pupillary activity when the light strikes the fovea (Fig. 18, line of crosses). Finally, the small peripheral reflexes are suppressed more profoundly by adaptation to light than are reflexes elicited by brighter light at the fovea.

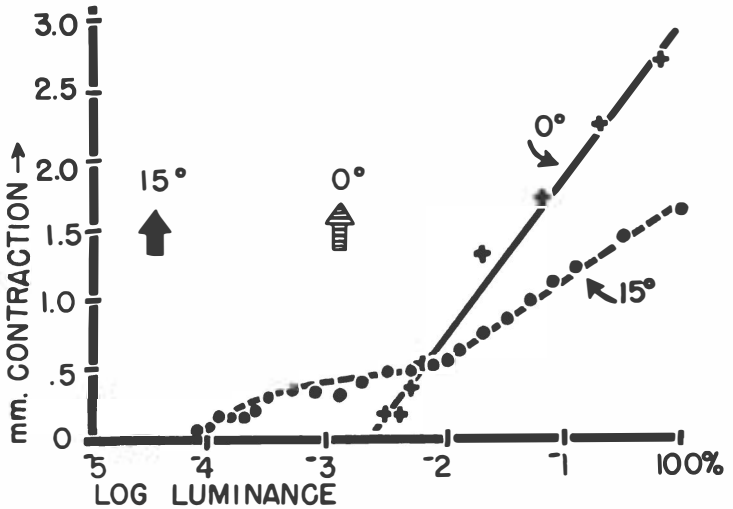

Fig. 18. Increments of pupillary reactivity with increasing light intensity at fovea and in retinal periphery (green light).

Average extent of pupillary contractions plotted (in mm, 12 reactions per intensity step) against stimulus luminance (in arbitrary log units, with 100 per cent maximal intensity available in experiment).

Subject's eyes dark-adapted; stimulus area = 1°; stimulus duration = 1 sec; stimulus position = fovea (0°, crosses), or 15° in temporal retina, horizontally from fovea (dots). Visual thresholds marked by arrows, with shaded arrow indicating foveal, solid arrow peripheral threshold.

With increasing stimulus intensity the pupillary contraction extents rose in a steep slope when the fovea was stimulated (solid line). The reactions elicited 15° peripherally showed a lower threshold than in the fovea, but only small increments to a low plateau, and a second rise when the stimulus luminance exceeded the cone threshold (broken line). The maximal reactions elicited peripherally were less extensive than those obtained at the fovea.

A number of the experiments that resulted in a denial of pupillomotor activity in the retinal periphery were done by the "static" method, that is, the pupillary diameter was measured after the eye was adapted to light of different luminances, and it is clear why no reactions could be found: they had already run their course, and the pupil had returned to its dark-adapted diameter at the time the observation was made. It should be added that the majority of these experiments were done with imperfect dark adaptation. Even "dim" illumination of a subject's eye must obviously be above cone threshold if it is used to render the examined pupil clearly visible to the experimenter (plus the intensity needed to overcome the loss of energy proportional to the square root of the distance between the subject's and the observer's eye).

It is, therefore, reasonable to assume that the small, fleeting, peripheral reflexes were merely suppressed, or escaped observation because they occurred earlier than was expected. Once a doubt is expressed, however, it is surprising how quickly a "small" response may become "negligible," and thence "absent"; and once it is considered absent, there is a tendency to explain it away, should it yet be observed. In the case of the peripheral retinal responses, the contractions, when seen, were thought to be due to stray light scattered by the ocular media, whereby it was not explained why stray light, which must by necessity be less intense than the focused beam, should have been capable of eliciting pupillary reflexes when the stimulus itself was not.

(b) Criteria of pupillary responsiveness: Since the retinal periphery is less efficient than the fovea for the production of extensive pupillary contractions, it appeared as though the pupillomotor representation of the fovea far outweighed that of the periphery, whenever the reflex amplitude was used as a measure of reactivity. Despite their low amplitude, the peripheral reactions are, however, more sensitive than the foveal ones, that is, their threshold is lower. The sensitivity of a retinal element, expressed by the threshold, is thus a quality quite separate from its motor effectiveness, as expressed by the increments in reflex amplitude for light intensities above threshold.

Pupillary reactions are not unique in this respect. For example, when the visual flicker fusion curves are compared with pupillary increment curves, obtained with the same kind and intensity of stimuli, the low threshold and shallow increment curves for the retinal periphery, and the high threshold and steep increment curves for the fovea are very similar for the two functions (Fig. 18, 19).

(c) Pupil perimetry: A number of investigators have made efforts to develop pupil perimeters that would allow the exploration of the visual field by small, well-outlined light patches. There are certain technical difficulties to overcome, but it is hoped that such instrumentation will become practicable, and may allow the objective scanning of the visual field in man and animals, thus opening a most interesting field of future investigation, both clinical and experimental.

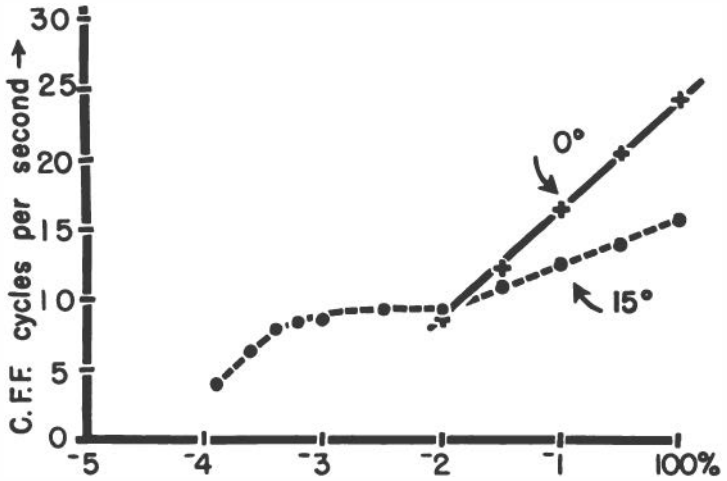

Fig. 19. Increments of critical flicker fusion frequency with increasing light intensity at fovea and in retinal periphery (green light).

Same subject and same apparatus as in Fig. 18, with subject's eye dark-adapted.

Flash duration held constant at 10 ms. Values plotted indicate the lowest rate at which, for each intensity step, 1-sec trains of light flashes were consistently seen as "steady" (not "flickering" Crosses and solid line = foveal stimulation: dots and broken line = stimuli 15° in temporal retina.

Note the parallelism between the flicker fusion increment curves and the pupillary reflex increment curves of Fig. 18.

Stimulus Color

1. The literature

A fascinating group of experiments were concerned with the influence of the wave length of stimulus light upon the pupil (Table 7). It was the purpose of most of these investigations to develop an objective method of testing spectral sensitivity in normal man, color-blind man, and various animals (Table 8).

In the earliest experiments by Sachs (1892), the color of the light was changed by reflecting it from colored papers; soon these were replaced by transmission filters (gelatine, glass, liquid solutions of dyes, colored wedges), or by spectroscopic prisms or color gratings. It is unfortunate that some of the most interesting earlier work (see especially Hess) was done under conditions that cannot be repeated today, because methods of accurate measurement of light intensity and wave length had

not yet been developed. Especially in view of the limited technical possibilities of the time, the ingeniousness and fruitfulness of this work is admirable.

TABLE 8

Experiments on Animals

Cephalopodes:	sepia, eledone	Hess (1910, 14, 15)*0
Teleosts:	eels, other fish	v. Studnitz (1934)=0
Amphibia:	frog	v. Studnitz (1934)=0; Lowenstein & Loewenfeld (1950-60)+=0
Reptiles:	alligator	Laurens (1923)*0
	turtle	v. Studnitz (1934)=0
	lizard	v. Studnitz (1934)*=0
Birds:	pigeon	Abelsdorff (1900a)*0; Hess (1907, 08a, 10, 14b, 15)*0; Laurens (1923)*0; Gundlach (1934)+; Lowenstein & Loewenfeld (1945, 1963)+*0=
	chicken	Hess (1907, 08a)0*; Lowenstein & Loewenfeld (1950)=+0
	magpie, falcon, buzzard	Hess (1908a)0*
	owl	Abelsdorff (1900a)*0; Hess (1907, 08a, 10, 14b, 15)*0; van der Plank (1934)*0; Hecht & Pirenne (1939)*0; Stark et al (1960)=
Mammals:	mouse	Keeler (1927)*0
	rat	Lowenstein & Loewenfeld (1950-55)0=+
	guinea pig	Abelsdorff (1900a)0*; v. Studnitz (1934)0*; Lowenstein & Loewenfeld (1950-55)0+=
	rabbit	Abelsdorff (1900a)0*; Hess (1915)0*; Wagman & Nathanson (1942)0; Lowenstein & Loewenfeld (1950-63)0+=
	cat	Hess (1915)0*; Gundlach (1934)+; Kappauf (1938, 43)0; Shakhnovitch (1959)*; Lowenstein & Loewenfeld (1943-60)0+=
	dog	Hess (1915)0*; Lowenstein & Loewenfeld (1942-50)0+=
	monkey	Hess (1915)0*; Lowenstein & Loewenfeld (1942-60)0+=

Note: Symbols represent functions tested: * = color sensitivity; 0 = light sensitivity; + = speed of movement; = = other.

A method widely used was that of color substitution: after the eye had been adapted to light of one color, the color was changed suddenly, and the luminance of the second color was varied until the sudden change evoked no response, or a small contraction of standardized amplitude. In this manner, the relative physiological effectiveness of the two colors was revealed by the energy needed for each of them to become "pupillomotor equivalent." One color alone could be balanced similarly against neutral grey filters. The method of switching filters consisted most often in mounting them in a movable frame, their edges adjoining, and by flipping the frame back and forth across the stimulus light path. Sudden rotation of a prism was also used for this purpose. Recently, Alpern & Campbell (1962b) used a rotating polaroid filter for slow substitution of lights from a double path. In other experiments, colored light flashes were presented, and the amount of energy needed to cause a pupillary response of predetermined extent (threshold, or higher) was measured, or the amplitude of pupillary reactions that resulted from stimulation by light of various colors but equal energy content was recorded.

2. Pupillary spectral sensitivity

A summary of the results of these experiments follows:

The pupillomotor effectiveness of a colored light stimulus is related to its apparent brightness; for each color, the threshold for pupillary reactions lies slightly above the corresponding visual threshold. This is true for all areas of the retina, and in the dark-adapted as well as the light-adapted eye (Fig. 20). In other words, the Purkinje shift exists for the pupil as well as for visual sensation (Fig. 21).

In the dark-adapted eye, the pupillary spectral sensitivity curve for large stimulus areas agrees well with the human dim-light visibility curve, and with the spectral sensitivity curve for night-birds, with predominantly rod retinae (see especially Hess, 1908a,1910, 1914b, 1915 ; Hecht & Pirenne, 1939-1940; Wagman & Gulberg, 1942; Fig. 22). In the dark-adapted eye, Alpern & Campbell (1962b), using the color substitution technique with fairly bright stimuli, found a mixed cone-rod spectral sensitivity curve, even upon foveal stimulation with small test patches. The authors concluded that the rod-contribution must have been produced by stray light to extra-foveal regions, and, indeed, when the experiment was repeated in the presence of a blue background field, the pupillary spectral sensitivity curve for the foveal stimuli agreed completely with the CIE photopic visibility curve, and with the flicker fusion spectral sensitivity curve obtained from the same subjects under the same experimental conditions (Fig. 23).

In a recent experiment by Bouma (1962), stimuli in the photopic brightness range caused pupillary reactions with a scotopic spectral sensitivity curve. Since Bouma used fairly extensive pupillary contractions as criteria of reactivity, the explanation proposed by Alpern &

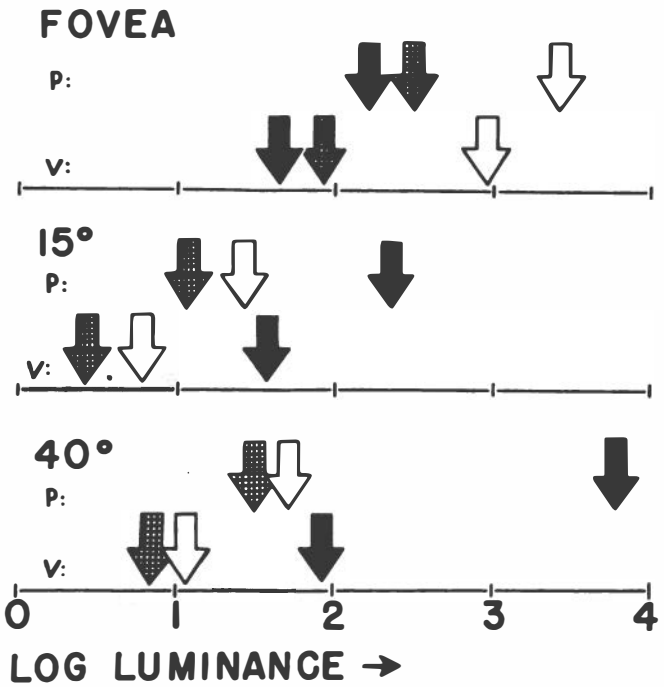

Fig. 20. Visual and pupillary thresholds in different areas of retina

Experiments done after complete dark-adaptation. Subject's left eye stimulated by light flashes of 1° area and 1 sec duration. Stimuli presented at fovea (first line), and 15° or 40° from fovea in nasal field (temporal retina, horizontal meridian, second and third lines, respectively). In each line pupillary thresholds indicated by P, visual thresholds by V; light intensity indicated on abscissa in arbitrary log units, with 4 the maximal intensity available in the experiment. Source = Sylvania glow modulator tube, with flashes elicited by Grass stimulator via constant voltage power supply. Light reflected by circular white cardboard targets placed 98 cm from subject's eye. Wratten filters as follows: red = # 29 (solid arrows); green = # 99 (cross-hatched arrows); blue = # 45 + 47 (white arrows); intensity regulated by neutral grey filters. The #29 Wratten filter is not a pure red; it was chosen nevertheless because it does not overlap with the green filter.
Note the close agreement between pupillary and visual thresholds for all colors and for all retinal locations examined.

Campbell (1962b), namely, that the results were likely to be due to the influence of stray light, appears probable. In Schweitzer's work (1955, 1956), and in the experiments in the author's laboratory with threshold stimuli, stray light probably played no significant role, since the light

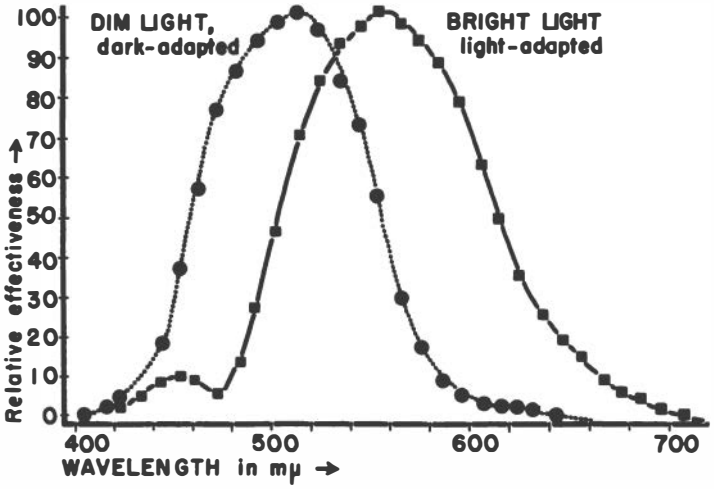

Fig. 21. Purkinje shift in pupillary spectral sensitivity (Laurens, 1923)

Curves constructed from photographic records of pupil size, obtained after 15 minutes of adaptation to darkness or to light of different wave lengths (equal energy stimuli, using tungsten source and Hilger wave length spectrometer).

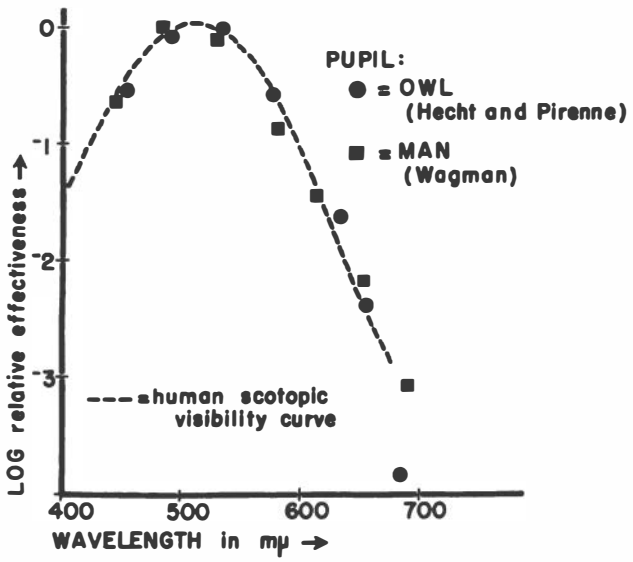

Fig. 22. Pupillary spectral sensitivity curves (re-plotted from Hecht & Pirenne, 1939-40; and Wagman & Gulberg, 1942)

In both experiments curves constructed by measuring energy of light of different wave lengths needed to obtain pupillary threshold reactions (0.3-0.5 mm), with sudden exposure of eye to light, and with relatively large field illuminated (tungsten source and Wratten color filters).

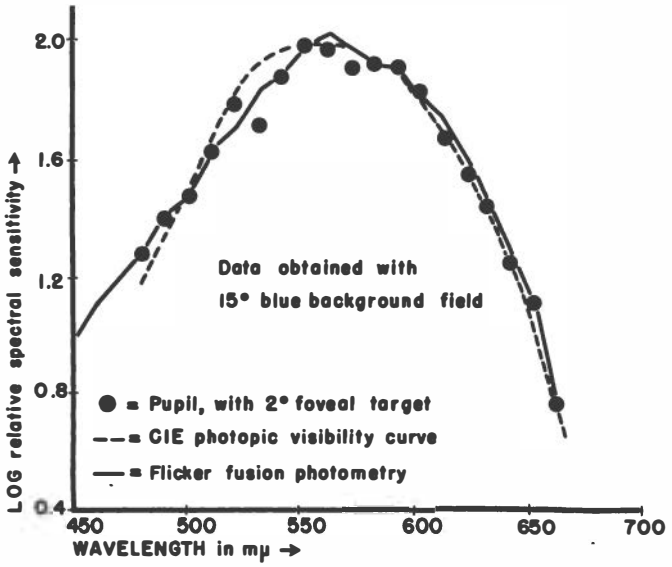

Fig. 23. Foveal pupillary and psychophysical spectral sensitivity curves for two subjects (After Fig. 8, Alpern & Campbell, 1962)

Dots: Mean differential threshold measurements for pupillary reactions to 2-sec test stimuli (2° test patches, centrally fixated, seen against continuous blue background field approximately 15° in diameter—retinal illuminance between 100 and 200 td).

Interrupted line: C.I.E. photopic visibility curve.

Solid line: Mean results of psychophysical measurements of photopic luminosity (flicker fusion photometry) on the same two subjects with the same apparatus. Rods surrounding fovea suppressed by blue adapting field, preventing them from reacting to stray illumination from foveal test lights. Under these conditions foveal pupillary spectral sensitivity curve agreed completely with photopic visibility curve, and flicker fusion spectral sensitivity curve.

flashes used were too weak to elicit pupillary reflexes from the blind spot (Fig. 17). Figure 24 again shows the close agreement between pupillary and visual thresholds, even for blue light at the fovea. When the stimulus luminance was increased, however, the effect of stray light was easily recognized: for equal increments in light intensity, the increases in pupillomotor activity were much steeper for blue, green, or white than for red light. Under the same experimental conditions, the visual flicker fusion curves, which are influenced far less by stray light than is the pupil, were precisely parallel for the four colors (Lowenstein, Kawabata, & Loewenfeld, 1964).

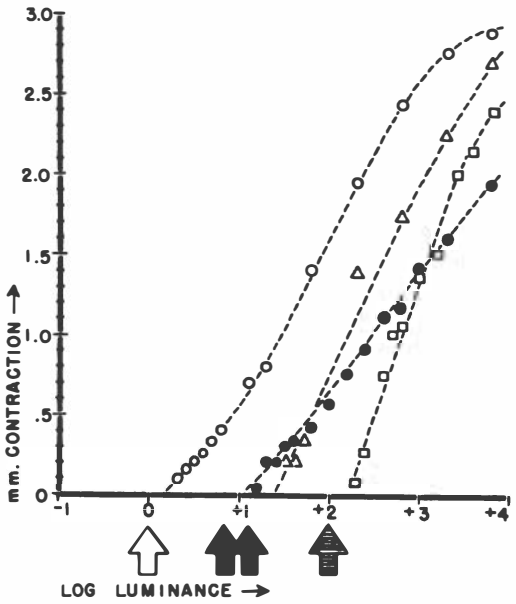

Fig. 24. Extent of pupillary contractions to white, red, green, and blue light stimuli at fovea (Fig. 13, Lowenstein et al., [in press] 1964.

Extent of pupillary contractions plotted as ordinate (in mm) against stimulus luminance as abscissa (in arbitrary log units, with O marking subject's foveal visual threshold to 1-sec white light flashes of 1° area (white arrow)). Foveal visual threshold for red (Wratten filter # 29) shown by black arrow, green (Wratten # 99) by cross-hatched arrow; blue (Wratten #45 + 47) light flashes of same duration and area by shaded arrow.

Pupillary reactions to white light (no filter) indicated by circles, those to red light by dots, those to green light by triangles, and those to blue light by squares. Note the close agreement between pupillary and visual thresholds, and the markedly less steep increment slope for red light than for other lights (cf. also Figs. 18,19).

Day birds such as the pigeon, with predominantly cone retinae, have pupillary spectral sensitivity curves similar to the fovea of the light-adapted human eye, and their pupillary increment curves fail to show the rod-cone break which is typical for the dark-adapted human eye (Tables 7, & 8, & Fig. 2).

In color-blind patients, also, there appears to be close parallelism between the visual and pupillary color responses. Such clinical data are, however, still fragmentary.

It appears, then, that the pupil follows faithfully the visual color sensitivity under all conditions so far examined. This fact opens a large field of most interesting possible applications.

Other Features of Pupillary Reactions to Light

1. Adaptation

(a) Adaptation to darkness: It has already been mentioned that the "dark adaptation" used in pupillary experiments was often far from perfect. In the older work, some kind of illumination was needed to observe the subject's pupil, and even the "infrared" light used since about 1935 for photographic or cinematographic recording of the pupillary responses usually contained some long-wave visible light. Though it was often stated, as it had been at an earlier time about dim white light, that this illumination had only little pupillomotor effect, the results may have differed from those obtained in true darkness. Strictly speaking, then, dark adaptation existed only in those experiments in which the pupillary reactions were recorded by flash photography without other illumination, or were viewed or recorded by infrared-sensitive devices that operated with light beyond the visible spectrum.

(b) Light adaptation: Just as different authors used stimuli of various durations, wave forms, and brightness ranges, of different sizes, shapes, or retinal locations, and of different color, a wide variety of adapting lights were used. The combinations of adapting and stimulating lights are too numerous to be mentioned individually. It should not be forgotten in this connection that all methods in which the "difference threshold" was determined, as well as those in which "static" light stimuli were used, were, in effect, dealing with light-adapted states. In some experiments, pre-adaptation to light, or adaptation to a dim background field, were used to minimize the effects of stray light scattered by the ocular media when a light flash of higher intensity entered the eye. This method was termed "masking technique" (Hesse, 1909; Vogt, 1922; Braun, 1931; Schmelzer, 1931; Biffis, 1934; Fry & Allen, 1953; Fugate, 1954; Alpern & Campbell, 1962b).

The pupillomotor effects of light adaptation were considered generally only in relation to the reduced sensitivity of the retina, or the altered color sensitivity brought about by the adapting light. It should be stressed, however, that light adaptation influences pupillary reactivity by a second, central nervous mechanism (Lowenstein & Loewenfeld, 1961).

In the presence of an adapting light, the supra-nuclear impulses inhibiting the Westphal-Edinger nucleus are reduced, and the functional

state of the parasympathetic motor nucleus is thus altered (cf. above section on Pupillary Reactions to Light—Modifying effects of fatigue and emotional excitement). Depending on the autonomic balance of the individual, this lessening of supra-nuclear inhibition may depress the light reflex, enhance it, or leave it unchanged (Fig. 25).

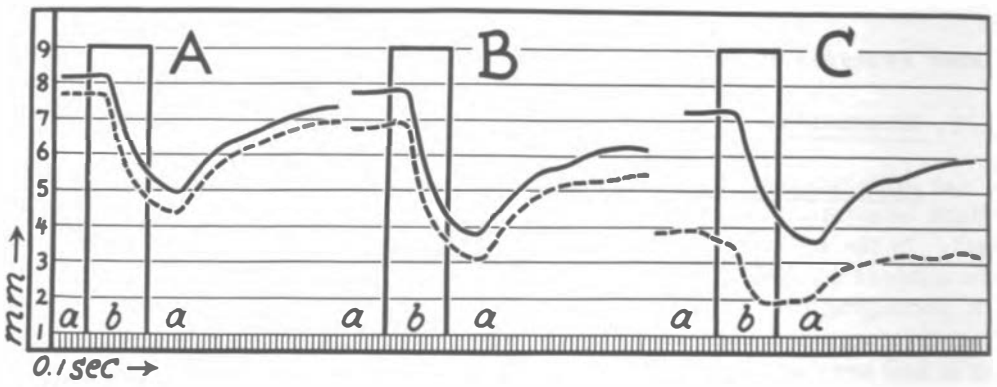

Fig. 25. Effect of dim illumination upon pupillary reaction to light in three normal subjects with different degrees of supra-nuclear inhibition (Fig. 8, Lowenstein & Loewenfeld, 1961).

Pupillary diameter recorded as ordinate (in mm) against time as abscissa (in 0.1 sec units). At a, eyes dark-adapted (solid lines), or adapted to diffuse, blue-green illumination, about 4.5 log units above subject's scotopic visual threshold (broken lines); during periods framed at b, bright, white light flashes presented, approximately 9 log units above absolute visual threshold.

A: The subject was a tense, excitable but otherwise normal 22 year-old woman. The pupil was only slightly smaller after adaptation to dim light than in darkness, and the reflex elicited by the bright light flash was slightly enhanced.

B: The subject was a normal, calm, well-rested 24 year-old woman. The decrease in pupillary diameter after adaptation to dim light was somewhat greater than in subject A, and the light reflex elicited by the bright flash was slightly reduced.

C: The subject was a 36 year-old man, hyper-fatigable because of habitual lack of adequate rest. In darkness his pupillary reflexes remained within normal limits, but adaptation to dim illumination had a profoundly depressing effect: The pupil became quite small, the light reflexes inextensive and pathologic in shape.

When the subject is calm and well rested, adaptation to dim background illumination causes the pupil to become slightly smaller than in darkness, while the light reflexes, elicited by standardized light flashes, are unchanged or slightly diminished (Fig. 25B). When the subject is tired, the same background light has a profoundly depressing effect: the pupil becomes quite small, and reflexes to standard light stimuli inextensive and pathological in shape (Fig. 25C). When the subject is tense, or emotionally excited, the pupils are large in darkness, and remain large in dim light. In such subjects the background field may enhance the contractions evoked by the standard light flash (Fig. 25A).

The central nervous nature of these changes is proven by the fact that they can be obtained also by exposing the opposite, non-stimulated eye to dim light.

In experiments in which the eye is adapted to light, it is necessary to consider these central nervous effects. Even weak background light may alter the reflexes considerably, whereby opposite changes may occur in different subjects.

2. Effect of the entrance pupil

Since the luminosity of a beam of light entering the eye is affected by the size of the entrance pupil, investigations were done to test the effect of different pupil sizes upon visual functions. These papers, in which the pupil was considered exclusively in its role as a component in the optical system of the eye, have been excluded from this review.

In a number of experiments efforts were made to eliminate the effects of variations of the entrance pupil. The means used were:

(1) immobilization of the pupil of the stimulated eye, most often by cycloplegic drugs, and occasionally by miotics;
(2) small artificial pupils close to the stimulated eye; and
(3) optical means, that is, placing the focus of the stimulating light beam in the plane of the subject's pupil. (For the latter two methods, careful immoblization of the subject's head is, of course, essential).

3. Binocular interaction

Several kinds of studies fall into this category: (a) Galen, in the second century A.D., used a clinical test that has enjoyed wide popularity throughout the centuries. With the patient facing a source of light, first one eye was covered, and then the other, while the first eye was exposed to the light. Whenever vision was impaired in one eye, the pupil would be larger when it was opened, and smaller when its healthy fellow-eye was exposed. Galen believed the difference to be due to some defect that interfered with the normal flow of "vital spirits" from the brain through

the hollow optic nerve to the eye; vision was impaired because less of the vital energy was available to illuminate the outside world. Some centuries later it was recognized that the change in pupillary size is due to the difference in afferent conduction from the two eyes. Kestenbaum (1928-1929) has attached the name of "pseudo-anisocoria" to this phenomenon, but since the pupils actually are not unequal at any time, it is the author's opinion that this term is unfortunate. Recently, Leavatin (1959) has advocated a modification of this test, as the "swinging flashlight test", that is, using a flashlight that is moved from one eye to the other.

(b) Summation of afferent impulses from the two eyes has been found to exist, within the limits of mechanical possibility: the pupil was found to respond to the total light energy stimulating the two eyes unless the light was so intense that unilateral stimulation alone resulted in maximal constriction (Silberkuhl, 1896; Abelsdorff & Feilchenfeld, 1904; Weiler, 1905; Blanchard, 1918; Reeves, 1918-1920; Luckiesh & Moss, 1934b; Bartley, 1943; Thompson, 1947; Venco & Marucci, 1947; Flamant, 1948; Kawabata[9]).

(c) "Retinal rivalry" has been reported to affect the pupil, so that a larger percentage of near-threshold stimuli resulted in a pupillary contraction when the stimulated eye was in the dominant phase that when it was in the inhibited phase (Nicolai, 1929; Bárány & Halldén, 1948; Wirth, 1952). These experiments were, however, done without records of the pupillary movements; in view of the great difficulty in judging accurately the small, variable pupillary threshold responses, especially in dim light, the question cannot be considered as settled.

(d) Similar difficulties attend pupillary investigations on amblyopic patients. Some authors described good pupillary reactions in amblyopes: Harms (1949) and Dolénék, Křistek, Němec, & Komenda (1962) reported reduction in pupillomotor activity). Harms stated that in cases of unilateral amblyopia both pupils enlarged whenever the patient fixed with the amblyopic eye, and became smaller when he fixed with the normal eye. Since, however, the fovea is much more efficient for pupillary contraction than the extrafoveal retina, some means would have to be provided in such experiments to assure exact positioning of the stimulating light spot on the retina, in order to rule out the possibility that the change might be caused by a difference between the effects of foveal and of eccentric fixation.

---

[9] Personal communication, H. Kawabata, 1959-1960.

The Pupillary Reaction to Near Vision

As in the sections on the reactions to light, the pupillary reaction to near vision is considered in its physiological aspects only, and work dealing with the optical effects of pupil size during near vision has been excluded from this review.

In Table 9, the publications available to the author have been listed. In contrast to the many aspects of light reactions, not much can be said about this literature. The greater part of the discussions have revolved around the question of whether the pupillary contraction depends on convergence or on accommodation. These discussions are still current, even though it has been established that any one of the three functions can be abolished without interfering with the others. Thus, convergence or accommodation may be eliminated selectively by the use of prisms or lenses. Clinical cases with isolated impairment or loss of pupillary contraction, accommodation, or convergence are not too uncommon, and in experiments on animals, isolated pupillary constriction, accommodation of the lens, and contraction of the internal rectus muscle were obtained by electrical stimulation in the cortex, the oculomotor nuclear complex, or the efferent third nerve. These facts lead to the conclusion that the nervous impulses that cause accommodation, convergence, and pupillary constriction must arise from different cell groups within the third nerve nucleus, and travel via separate fibers to their effector muscles, whereby the paths for the ciliary muscle and the iris sphincter undergo synapses in the ciliary ganglion.

The theory has been proposed that the pupillary fibers for near vision do not synapse in this ganglion while those for the light reflex do, thus explaining the isolated loss of the pupillary light reflex in the presence of unimpaired pupillary contraction to near vision in the Argyll Robertson syndrome (Naquin, 1954). This theory is disproven by the fact that in monkeys, retrobulbar injection of a ganglion-blocking agent such as nicotine entirely abolishes the pupillary contractions elicited by intracranial stimulation of the third nerve with strong currents (Loewenfeld, 1958).

Accommodation, convergence, and pupillary contraction are associated movements, and are not tied to one another in the manner usually referred to by the term "reflex". They are controlled, synchronized, and associated by supranuclear connections, and are not caused by one another.

As a final point, it must be remembered that the pupillary reaction to near vision is subject to the same central nervous inhibitory and sympathetic antagonistic influences as are the contractions to light. The extent of the reactions may, therefore, vary from one moment to the other. Just as for the light reflex, these variations have given rise to some unusual statements in the literature. For example, von Graefe's

TABLE 9

Pupillary Movements and Near Vision

Year	Author	Experiments on Man: Lenses	Prisms	Fusion	Timing	Other	Clinical	Animals	Findings and Conclusions
1619	Scheiner					*			first to describe pupillary contraction to near vision
1659	Plempius					*			similar description as Scheiner's
1780	Olbers					*			measured pupil contraction with accommodation method of Lambert
1821, 51	Weber	*				*			near vision contracts pupil even if object is darker; accommodation alone does not cause miosis, convergence does
1835	Plateau					*			learned to accommodate without converging: pupil contracted
1853	Cramer	*							accommodative tension without convergence may contract pupil
1853	De Ruiter	*							accommodation alone may contract pupil
1854	von Graefe							*	reported observation of Müller: in dog, pupil dilates upon near vision
1856	von Graefe						*		case with complete extraocular paralysis; vision perfect; pupil immobile to light but contracted well to near vision; concl.: pupil reaction does not depend on extraocular movements; probably midbrain lesion
1864, 65	Donders	*	*						pupil may contract with accommodation alone or with convergence alone
1866	Trautvetter							*	repeated test on dog and cat; same result for dog (dilation); cat uncooperative
1868	Hering			*					entoptic images fused without convergence→pupil contraction; concl.: accommodation alone may cause contraction, but the three movements are associated, not interdependent
1869	von Arlt				*				pupil contraction occurs later than accommodation
1869	Le Conte					*			learned to accommodate without converging→pupil constricted; concl.: pupil is associated with accommodation but may also constrict with strong convergence alone
1870	Adamük							*	obtained associated pupil contraction, movement of globes in & down, from anterior midbrain of dog; pupil may contract with accommodation in absence of convergence
1871	Adamük & Woinow							*	measured depth of anterior chamber, lens curvature (dog); electrical stimulus to efferent nerves
1873	Coccius	*							accommodation alone and convergence alone may contract pupil
1874	Kreuchel (& Mulder)					*			studied effect of muscarine on accommodation and pupil
1876	Drouin					*			pupil and accommodation are associated but not dependent on one another

TABLE 9 (Cont'd)

Year	Author	Experiments on Man: Lenses	Prisms	Fusion	Timing	Other	Clinical	Animals	Findings and Conclusions
1878	Hensen & Völckers							*	obtained isolated accommodation, pupil constriction, contr. medial rectus, from floor of Sylvian aqueduct (dog); after death, extraocular reactions to brain stimuli elicited 15 min. longer than pupil and accommodation
1880	Angelucci & Aubert				*				measured speed of pupil and of movement of Purkinje images: pupil was slower
1888	Donders (2nd ed.)	*	*						neither iris nor accommodation are dependent on convergence
1892	Borthen	*	*				*		case with absent light reflex, good accommodation, pupil contraction only with convergence; concl.: pupil is relatively independent of accommodation
1893	Du Bois-Reymond & Greeff					*			near vision effort in total darkness (flash photograph): pupil contracted
1898	Heine				*			*	in birds, pupil contraction faster than accommodation (electrical stimulus efferent nerves)
1898	Hess & Heine							*	dog, cat, rabbit, even when young, have poor accommodation
1898	Ovio					*			tested pupil, accommodation, convergence with one or both eyes open; concl.: pupil associated with both accommodation and convergence, depends on distance of vision
1900	Vervoort			*					pupil does not contract to accommodation in absence of convergence
1902,03	Marina							*	exchanged internal and external recti in monkeys: pupil contraction with convergence post-operative = with contraction of external recti; concl.: no rigid connection in nervous centers
1903	Friberger				*				measured speed of pupillary movements associated with convergence and accommodation
1904	Bach					*	*		cases with (a) complete loss of accommodation, (b) paralysis of internal rectus, (c) unilateral amblyopia or loss of eye: pupil near vision reaction normal; concl.: accommodation, pupil, convergence are associated movements but not dependent on one another
1905	Moderow					*			analysis of literature; concl.: convergence is, but accommodation is not associated with pupil
1905	Ovio								not read by reviewer 1963
1905	Wlotzka			*					accommodation alone: pupil immobile; concl.: pupil, accommodation both depend on convergence
1908	Kanngiesser	*				*			pupil contraction with accommodation alone; atropine affected accommodation longer than pupil
1908	Lohmann					*	*		accommodation changed without convergence; case with post-diphtheric loss of accommodation; concl.: pupil contraction is synergic co-movement with accommodation and convergence
1909	Magitot					*			pupil contraction works in 5th foetal month, accommodation only months after birth

TABLE 9 (Cont'd)

Year	Author	Experiments on Man: Lenses	Prisms	Fusion	Timing	Other	Clinical	Animals	Findings and Conclusions
1912	Hesse						*		cases with extraocular paralysis could not converge: pupil contraction with accommodation
1912	Isakowitz						*		critique of Hesse: absence of convergence movement does not prove absence of convergence impulse
1920	Pick			*					8 diopters accommodation without convergence: pupil immobile; pupil is synergic co-movement
1920	Sattler						*		in high, uncorrected myopes pupils contract when eyes converge without accommodation
1922	Caspary & Goeritz			*					obtained changes in accommodation without pupil contraction; concl.: pupil tied to convergence, not to accommodation; normally, the three functions occur together
1926	Holladay		*						pupils contract to forced convergence = chief cause of near vision contraction
1928-29	Kestenbaum & Eidelberg	*	*				*		diverse cases, quoted second-hand; concl.: accommodation and pupil work together only in presence of convergence; pupil = associated movement (with convergence)
1930, 31	Gualdi	*	*						accommodation alone does not affect pupil, convergence alone does
1936	Schubert & Burian			*					find reflex to fusion, independent of convergence or accommodation
1937	Haessler					*			tested near vision in near-darkness (luminous dial): pupil contracted
1943	Bender & Weinstein							*	obtained isolated contraction internal rectus, miosis, accommodation by electrical stimulation in third nerve nuclear complex (monkey)
1945	Fry					*			complex apparatus, allowing independent control of convergence and accommodation; concl.: pupil, accommodative vergence and accommodation are associated movements; influence of fusional convergence questionable
1949	Knoll					*			complex apparatus; pupil constricted with accommodation and accommodative vergence; in some subjects pupil also constricted with fusional convergence
1949	Marg & Morgan					*			complex apparatus; found linear relation between pupil diameter and (1) accommodation, (2) accommodative vergence, and (3) fusional convergence; latter is minor in some subjects; possibly an influence of psychic awareness of nearness; under normal conditions pupil reflex is essentially elicited by accommodation
1950a	Marg & Morgan					*			psychic proximity factor influenced pupil in only 1 of 10 subjects; pupil reaction elicited by accommodation; vergence elicited by accommodation, does not occur alone under normal conditions
1950b	Marg & Morgan			*		*			no pupillary effects of fusion found, independent of convergence-accommodation

TABLE 9 (Cont'd)

Year	Author	Experiments on Man: Lenses	Prisms	Fusion	Timing	Other	Clinical	Animals	Findings and Conclusions
1951	Renard & Masonnet-Naux	*	*				*		pupil contraction is not reflex but associated movement (with convergence)
1956	Lowenstein						*	*	obtained isolated accommodation, contraction internal rectus, miosis by electrical stimulation of 3rd nerve; case with present light reflex, absent near vision contraction OD, absent light reflex, present near vision contraction OS
1956, 60a 61	Shakhnovitch				*	*			records eye movements and pupil together; convergence movement is complete before end of latent period for pupil
1958, 59	Jampel							*	studied supranuclear control of ocular movements in monkey
1961	Alpern, Mason, & Jardinico					*			complex apparatus; found linear relation between accommodative vergence and pupil, curvilinear relation between accommodation and pupil; discrepancy thought to be due to limitations of amplitude of accommodation imposed by lens
1961	Samojloff, Sokolova, & Shakhnovitch					*			pupillary reaction symmetrical when only one eye converges (uncentered target)
1924-65	Lowenstein						*		diverse cases: isolated accommodation paralysis, Adie's syndrome with or without tonic accommodation, loss of pupil contraction with preserved accommodation and/or convergence

report of a finding by Müller (1854) is still soberly quoted today (Smythe, 1958) to the effect that in the dog, in contrast to other mammals, the pupil dilates upon near vision and contracts upon far vision. But the visual target provided for the dog was a piece of meat or sausage. Trautvetter (1866), who repeated the experiment with similar results, described how the dog, having been starved for two days, "followed the sausage with the most desirous of glances" [10]. Obviously, the dog must have been under more than visual stimulation as the deliciously fragrant

[10] "...Ich griff sogar zu künstlichen Mitteln, um die Thiere zu zwingen, ihre Augen für die Nähe und Ferne einzustellen, und liess zu diesem Zwecke einen jungen Hund und eine Katze zwei Tage hungern; dann band ich den Hund auf das Brett und indem ich selbst die Linsenbilder beobachtete, liess ich einen Gehülfen nach Kommando ein Stück Wurst der Nase des Hundes nähern und dann wieder von derselben entfernen ... Das Thier verfolgte die Wurst während der ganzen Zeit des Versuches mit den lüsternsten Blicken...Bei der Katze, der zum Accommodationsgegenstand eine lebende Maus diente, misslang der Versuch, da sie, wohl ihrer tückischen Natur wegen, sehr nachlässig accommodierte..."

TABLE 10

More Elaborate Experimental Designs

Year	Author	Chief Purpose of Design
1869	von Arlt	time pupillary light reflex characteristics
1880	Angelucci & Aubert	time movements of pupil and Purkinje images
1893	Sachs	test color sensitivity
1894	Greeff & Du Bois-Reymond	relate pupil size to stimulus luminance
1897	Garten	record pupillary dilation after withdrawal of light
1900b, c	Abelsdorff	test color sensitivity
1900	Vervoort	test relations between pupil, accommodation, and convergence
1903	Friberger	measure time characteristics of pupillary movements
1903	Schäfer	test color sensitivity
1904	Abelsdorff & Feilchenfeld	test pupil response to stimulus luminance and area
1905	Basler	test color sensitivity
1907	Hess	explore retinal areas (pupil perimeter)
1907	Polimanti	test color sensitivity
1907	Schlesinger	fine pupillary thresholds to white or colored stimuli
1908a	Hess	test color sensitivity in birds
1908b	Hess	find response to alternate stimulation of different retinal areas
1910	Hess	test color sensitivity in animals
1913	Schlesinger	objective perimetry (peri-pupillometer)
1914-16	Hess	test difference threshold (white or colored light)
1918	Blanchard	study retinal sensitivity (brightness, contrast, etc.)
1919	Engelking	test pupillary threshold
1918, 20	Reeves	study rate, extent of pupil contraction and dilation
1923	Laurens	test spectral sensitivity (photopic and scotopic)
1923	Gradle & Eisendraht	study speed of pupillary contraction to light
1926	Holladay	study reactions to glaring light
1926-65	Lowenstein	study effects of stimulus luminance, duration, frequency
1929	Barbieri	perimetry (pupil perimeter with colors or white light)
1929, 30	Stiles	study effect of glare on brightness difference threshold

TABLE 10 (Cont'd)

Year	Author	Chief Purpose of Design
1932	Gradle & Ackerman	study speed of pupillary redilation after light stimuli
1933	Ferree, Rand & Harris	determine effectiveness of very large adapting fields
1933-35	Machemer	study dynamics of pupillary reflexes to bright light
1934	Biffis	test sensitivity of different retinal areas
1934	Luckiesh & Moss	determine effects of stimulus area and luminance
1936-37	Crawford	determine effects of stimulus area and luminance
1938, 43	Kappauf	study brightness sensitivity in cat
1938	Talbot	find influence of stimulus intensity, area, duration
1939	Brown & Page	record pupillary dilation after withdrawal of light
1940	Frydrychovicz & Harms	objective perimetry (pupil perimeter)
1939-40	Hecht & Pirenne	determine spectral sensitivity in owl
1942a	Bartley	record reactions to light flashes at different rates
1942	Wagman & Gulberg	determine pupillary spectral sensitivity (scotopic)
1942	Wagman & Nathanson	study effect of stimulus luminance in man and rabbit
1943	Bartley	test stimulus luminance, area, binocular interaction
1945	Fry	study relation of pupil, accommodation, convergence
1948	Bárány & Halldén	study retinal rivalry
1948	Flamant	test effect of stimulus luminance for very large field
1948	Spring & Stiles	test effect of light entering the eye via different areas of the pupil
1949	De Launay	study effect of stimulus luminance
1949-54	Harms	objective perimetry (pupil perimeter)
1949	Knoll	relate pupil changes, accommodation, convergence
1949, 50	Marg & Morgan	test relations of pupil, accommodation, and convergence
1950	Campbell & Whiteside	record pupillary oscillations in steady light
1951-54	Cüppers	relate pupillary reactions to retinal sensitivity
1953	Alpern & Benson	show directional sensitivity of pupil receptors
1953	Fry & Allen	study pupil responses to light flashes of different luminance, area, duration, retinal location
1954	Young & Biersdorf	record pupillary reactions to light and darkness
1954	DuBois-Poulsen & Loisillier	explore retinal areas (dark-adapted eye)

TABLE 10 (Cont'd)

Year	Author	Chief Purpose of Design
1955, 56	Schweitzer	study pupil threshold of dark-adapted eye (various areas, durations, colors, retinal positions of stimuli)
1956	Fugate & Fry	study pupillary movements to glaring light
1956	Hopkinson	study pupillary reactions to glaring light
1956	Van der Tweel	study effects of stimulus luminance, rate, wave form
1957	Bleichert & Wagner	record pupil responses to sinusoidal light stimuli
1957	Shakhnovitch	record pupillary and eye movements during reactions to light and to near vision
1957	Stark & Sherman	servo-analysis of pupillary reactions (frequency)
1957	Stegemann	servo-analysis (sinusoidal light stimuli)
1958	Samojloff & Shakhnovitch	explore different retinal areas (objective perimetry)
1958-60	Shakhnovitch	record pupillary and eye movements during near vision
1958	Stark & Campbell	servo-analysis of pupil oscillations in steady light
1958	Stark & Cornsweet	servo-analysis of pupil oscillations in steady light
1959	Alpern, Kitai, & Isaacson	study dark-adaptation of pupillomotor receptors
1959	Lowenstein & Loewenfeld	study pupil threshold (light- and dark-adapted eye)
1959	Samojloff	objective perimetry
1959	Shakhnovitch	study color sensitivity in cat
1959	Stark	servo-analysis of pupil reactions (stimulus frequency)
1959	Stark & Baker	servo-analysis of pupillary movements in steady light
1960b	Shakhnovitch	objective perimetry
1961	Alpern, Mason, & Jardinico	test relations between pupil, accommodation, convergence
1961	Samojloff, Sokolova, & Shakhnovitch	record eye movements and pupillary changes during near vision and other eye movements
1962a	Alpern & Campbell	determine photopic pupillary spectral sensitivity
1962b	Alpern & Campbell	study pupil during dark-adaptation after bright light
1962	Bouma	determine pupillary spectral sensitivity (photopic)
1963	Burke	relate visual and pupillary thresholds
1963	Feinberg & Podolak	determine latent periods of light reflex
1964	Lowenstein, Kawabata, & Loewenfeld	relate visual and pupil thresholds, visual flicker fusion, and pupillary incremental behavior

target slowly approached his eyes. The importance of these mechanisms for work in which the pupil is used as an indicator, especially when the experiments are time-consuming, cannot be stressed too much.

As a diagnostic tool for the neurologist and ophthalmologist, the pupillary near-vision response is less reliable than the light reflex because of its subjective features. When the pupillary near-vision contraction is poor or absent it is often not possible to be sure that the patient actually made a satisfactory effort of near vision. The reaction is important diagnostically when it is more extensive than the contraction to light, that is, in the Argyll Robertson syndrome and in "Adie's" syndrome.

Conclusions

The controversies that have clouded a clearer understanding of the pupillary receptor and near-vision mechanisms have had their origin mainly in (a) the difficulties in observing an organ as small and as mobile as the iris, especially in dim light; (b) differences in experimental procedure, that is, the stimuli and state of adaptation used in different investigations; and (c) differences in criteria used to determine pupillary responsiveness. Despite all these divergencies, an impressive number of experimental facts now available furnish convincing support for the assumption that, at the level of the retinal receptors, pupillary and visual afferent impulses arise from the same structures. The following are the most important findings:

(1) In the normal, dark-adapted human eye

(a) small pupillary contractions can be obtained with stimulus intensities below the photopic range;

(b) the pupillary threshold is lower at the parafovea and the retinal periphery than at the fovea;

(c) the pupillary threshold is lowered, and the contractions enhanced, when a small stimulus field is enlarged, and also when an already large field is further increased in extent;

(d) the pupillomotor effectiveness of colored stimuli is related to their apparent brightness, with the peripheral retina far more sensitive to white, green, or blue light than to red light; in other words, the pupillary spectral sensitivity curve for large fields resembles closely the human scotopic visibility curve.

(2) Totally color-blind patients, and patients who have lost all their visual field except for a small, peripheral area may have extensive pupillary reflexes.

(3) Animals with predominantly rod retinae, such as the owl and the rat, have sensitive pupillary responses, whereby the owl's pupillary spectral sensitivity curve is very similar to that of the human dark-adapted eye.

(4) In the normal, light-adapted human eye

(a) the pupillary threshold is much higher than after dark adaptation;

(b) the retinal periphery is no longer more sensitive than the fovea;

(c) compared to the conditions after dark adaptation, red light has gained in effectiveness; in other words, the Purkinje shift exists for the pupil; and for small, centrally fixated fields, the pupillary spectral sensitivity curve agrees with the CIE photopic visibility curve and with the spectral sensitivity curve obtained by flicker fusion photometry under the same experimental conditions.[11]

(5) Animals with predominantly cone retinae, such as the pigeon or chicken, have vigorous pupillary reflexes, and these animals are more sensitive to red light and less sensitive to blue light than is the owl.

(6) When the stimulus intensity is increased above threshold values, the pupillary reflexes increase in amplitude. The reflex increments show behavior very similar to that of the increments in critical flicker fusion frequency: the pupillary and flicker fusion increment curves run parallel for stimuli of the same color and retinal location.

In view of all these many kinds of functional parallelism between pupillary reflexes and subjective visual phenomena, it appears impossible, in the author's opinion, to uphold the theory of the existence of separate, specialized, pupillary receptors. This assumption would require the existence of a complex arrangement of at least two pairs of separate but closely related retinal elememts: a set of "visual rods" and "visual cones", and a second set of "pupillary rods" and "pupillary cones" that would mirror accurately the foveal and peripheral thresholds, the color sensitivity, and the incremental behavior of the visual cells. In addition, there is no reason why one should assume a double set of sensory elements in the eye, any more than one assumes a double set of auditory receptors for the appreciation of sound and for reflex movements elicited by sound, or a double set of temperature-or pain-receptors for sensory perception and for reflex adjustments.

---

[11] In such experiments, the effect of stray light on the sensitive peripheral retina must be reduced by adaptation or by pre-adaptation to a background field.

Pupillary reactions to light are very sensitive in the fovea as well as in the retinal periphery, even when small stimulus areas are used. In response to bright light, distinctive kinds of pupillary behavior are found, according to the conditions of adaptation, and the intensity, duration, wave form, and frequency of the stimuli.

Pupillary movements can be measured accurately in intact, conscious animals or man, without operative procedure of any kind. Because of their objective and functionally unequivocal nature, it is hoped that they may become increasingly useful indicators of retinal activity, as more refined and reliable instrumentation becomes available.

As to the pupillary contraction to near vision, the persistent questions about its dependence on accommodation or on convergence appear outdated, since it is clear that it can take place in the absence of either of these functions. Normally, convergence, accommodation, and pupillary constriction are associated movements, brought into play by supranuclear mechanisms. Details of their normal interrelation, and of deviations from this normal correlation in pathological cases, might be clarified by simultaneous recording with the new electronic devices now available.

BIBLIOGRAPHY[12]

* Abelsdorff, G. Zur Erforschung des Helligkeits- u. Farbsinnes bei Menschen u. Thieren. (Verh. Physiol. Ges. Berlin 23. Feb.) Arch. Anat. Physiol., (Physiol.) 1900, 561-562. (a)

* Abelsdorff, G. Ueber die Möglichkeit eines objektiven Nachweises der Farbenblindheit. Arch. Augenheilk., 1900, 41, 155-162. (b)

* Abelsdorff, G. Die Änderungen der Pupillenweite durch verschiedenfarbige Belichtung. Z. Psychol. Sinnesorg., 1900, 22, 81-95. (c)

* Abelsdorff, G., & Feilchenfeld, H. Über die Abhängigkeit der Pupillarreaction von Ort und Ausdehnung der gereizten Netzhautfläche. Z. Psychol. Sinnesorg., 1904, 34, 111-131. (a)

* Abelsdorff, G., & Feilchenfeld, H. Erwiderung auf die vorstehenden Bemerkungen von Dr. H. Wolff. Z. Psychol. Physiol. Sinnesorg., 1904, 36, 98. (b)

* Adamük, E. Über die Innervation der Augenbewegungen. Centralbl. f.d. med. Wiss., 1870, 65-67.

* Adamük, E., & Woinow, M. Über die Pupillenveräderung bei der Accomodation. v. Graefe's Arch. Ophthal., 1871, 17,1, 158-168.

/ Alpern, M. Photopupillary kinetics in normal man. Fed. Proc., 1961 (March), 20.

* Alpern, M., & Benson, D. J. Directional sensitivity of the pupilomotor photoreceptors. Amer. J. Optom., 1953, 30, 569-580.

[12] Symbols:
* = The original text was read in its entirety;
# = abstracts or quotations by other authors (authors quoted are indicated);
/ = not read by reviewer July 1963.

All citations, unless otherwise indicated, are completely referenced within this Bibliography under the name of the individual author(s). When this usual publication information was lacking, source was verified and is identifiable as stated in Index catalog list. All dissertations of foreign source listed herein (except those of American universities) are available from the National Library of Medicine, Bethesda, Md.

* Alpern, M., & Campbell, F. W. The behavior of the pupil during dark adaptation. Proc. Physiol. Soc., 1962, 28-29, 1-2. (a)

* Alpern, M., & Campbell, F. W. The spectral sensitivity of the consensual light reflex. J. Physiol., 1962, 164, 478-507. (b)

* Alpern, M., Kitai, S., & Isaacson, J. D. The dark adaptation process of the pupillomotor photoreceptors. Amer. J. Ophthal., 1959, 48, Pt. 2, 583-593.

* Alpern, M., Mason, G. L., & Jardinico, R. E. Vergence and accommodation. V. Pupil size changes associated with changes in accommodative vergence. Amer. J. Ophthal., 1961, 52, 762-767.

* Angelucci,—., & Aubert, —. Beobachtungen über die zur Akkomodation des Auges und die zur akkomodativen Krümmungsveränderung der vorderen Linsenfläche erfordenlichen Zeiten. Pflüger's Arch. f.d. ges. Physiol., 1880, 22, 69-86.

* v. Arlt, Jr., F. Beitrag zur Kenntniss der Zeitverhältnisse bei den Bewegungen der Iris. v. Graefe's Arch. Ophthal., 1869, 15, 294-317.

* Aubert, H. Physiologische Optik. In Graefe-Saemisch Handb. ges. Augenheilk. (1st ed.), 1876, Vol. 2. Pp. 453, 457, 470.

* Bach, L. Das Verhalten der Pupillen bei der Konvergenz und Akkomodation. Zeit. f. Augenheilk., 1904, 12, 725-729.

* Bach, L. Pupillenlehre. Anatomie, Physiologie und Pathologie. Methodik der Untersuchung. Berlin: Karger, 1908.

* Baker, F. H. Pupil response to short-duration pulses. MIT: Res. Lab. Electronics, Quart. Prog. Rep., 1962(April), No. 65, 251-257.

* Bárány, E., & Halldén, U. Phasic inhibition of the pupil during retinal rivalry. J. Neurophysiol., 1948, 11, 25-30.

* Barbieri, A. El campo visual luminoso y el reflejo pupilar. La perimetria objetiva. Su importancia clinica. Un nuovo perimetro pupiloscópico. Arch. Oftalm., Buenos Aires, 1929, 4, 618-638.

* Barkan, O. Differential pupilloscopy. Arch. Ophthal., 1922, 51, 29-39.

* Bartels, —. Zur Methode der Pupillenuntersuchung bei Gasglühlicht. Z. Augenheilk, 1904, 11, 445-449.

* Bartley, S. H. A factor in visual fatigue. Psychosom. Med., 1942, 4, 369-375.

* Bartley, S. H. Some parallels between pupillary "reflexes" and brightness discrimination. J. exper. Psychol., 1943, 32, 110-122.

* Basler, A. Über die Pupillarreaktion bei verschiedenfarbiger Belichtung. Nach gemeinsam mit Frau S. Höfer (Leipzig) ausgeführten Untersuchungen. Pflüger's Arch. ges. Physiol., 1905, 108, 87-104.

* Becker, W. Statistiche Untersuchungen der Pupillenweiten in Abhängigkeit von der Lichtintensität. Z. Biol., 1957, 109, 81-85.

* Behr, C. Zur topischen Diagnose der Hemianopsie. v. Graefe's Arch. Ophthal., 1909, 70, 340-402.

* Behr, C. Zur Physiologie und Pathologie des Lichtreflexes der Pupille. v. Graefe's Arch. Ophthal., 1913, 86, 468-513.

* Behr, C. Die Lehre von den Pupillenbewegungen. In Graefe-Saemisch Handbuch der ges. Augenheilk. Vol. II, 3rd ed. Berlin: Springer, 1924.

* Bender, M. B., & Weinstein, E. A. Functional representation in the oculomotor and trochlear nuclei. Arch. Neurol. Psychiat., 1943, 49, 98-106.

* Biffis, A. Ricerche topografiche sulla sensibilità retinica, par il riflesso fotomotore della pupilla. Ann. Ottal., 1934, 62, 665-694.

* Blanchard, J. The brightness sensibility of the retina. Phys. Rev., 1918, Ser. 2, 11, 81-99.

* Bleichert, A. Die Lichtkontraktion der Pupille als Regelvorgang. v. Graefe's Arch. Ophthal., 1957, 159, 396-410.

* Bleichert, A., & Wagner, R. Über den Frequenzgang der Pupillenreaktion auf Licht. Z. Biol., 1957, 109, 281-296.

* Bömer, M. Über die praktische Verwendbarkeit des Sanderschen Pupilloskopes. Klin. Mbl. Augenheilk., 1933, 90 (N.F. 55), 207-210.

* Bordier, H. De l'acuité visuelle. Mém. Soc. phys. nat. Bordeaux, 1892-1893, (Séance 15 juin 1893) 4s 4, 1-156.

* Borsotti, I. Indagini pupillografiche su alcuni particolari aspetti fisiologici del riflesso fotomotore mediante cinematografia a luce ordinaria. (Nota prev.) Boll. Soc. med.-chir., Pavia, 1939, 53, 943-961.

* Borthen, L. Die topisch-diagnostichen Verhältnisse bei einseitiger isolirter reflectorischer Pupillenstarre. Klin. Mbl. Augenheilk., 1892, 30, 121-134.

* Bouma, H. Size of the static pupil as a function of wavelength and luminosity of the light incident on the human eye. Nature, 1962, 193, 690-691.

* Braun, G. Ein neues Hemikinesimeter. Klin. Mbl. Augenheilk., 1931, 87, 441-450.

* Braun, G. Ein neues Hemikinesimeter. Klin. Mbl. Augenheilk., 1932, 88, 61-62.

* Broca, A., & Laporte, F. Étude des principales sources de lumière au point de vue de l'Hygiène de l'oeil. (Extr. Bull. Soc. int. électriciens, juin) Ann. d'oculist, 1908, 151, 190-218.

* Broca, A., Jouaust, de La Gorce, & Laporte, F. Étude des nouvelles lampes électriques luminescentes. Action sur l'oeil du rouge extrême et de l'ultraviolet. (Extr. Bull. Soc. int. électriciens, fev.) Ann. d'oculist, 1914, 151, 273-285.

* Brown, R. H., & Page, H. E. Pupil dilation and dark adaptation. J. exper. Psychol., 1939, 25, 347-360.

* Budge, J. Ueber die Bewegungen der Iris, für Physiologen und Ärzte. Braunschweig: F. Vieweg u. Sohn, 1855.

* Bujadoux, A. & Gourevitch, F. Les troubles du pré-Argyll-Robertson (De la réflexométrie pupillaire). Presse méd., 1937, 45, 550.

* Bujadoux, A., & Kofman, T. Un nouveau réflexomètre pupillaire. Bull. Soc. franç. d'Ophthal., Paris, 1933, 46, 243-249. (46 Congr., 26-29 juin, 1933)

* Bumke, O. Beiträge zur Kenntnis der Irisbewegungen. I. Der galvanische Lichtreflex (Vorläufige Mitteilung). Centralbl. f. Nervenheilk. & Psychiat., 1903, 62, 447-451.

* Bumke, O. Die Pupillenstörungen bei Geistes- und Nervenkrankheiten. Jena: Fischer, 1904.

/ Burian, H., & Schubert, G. Das Wesen der Naheinstellungsreaktion der Pupillen. v. Graefe's Arch. Ophthal., 1936, 136, 377-386.

* Burke, D. W. A comparison of pupillary and visual thresholds. Dissertation, Univer. Minn., 1963.

* Campbell, F. W., & Alpern, M. Pupillomotor spectral sensitivity curve and color of the fundus. J. optical Soc. Amer., 1962, 52, 1084.

* Campbell, F. W., & Whiteside, T. C. D. Induced pupillary oscillations. Brit. J. Ophthal., 1950, 34, 180-189.

* Caspary, H., & Goeritz, C. Die Synergie von Akkomodation und Pupillenreaktion. Pflüger's Arch. f.d. ges. Physiol., 1922, 193, 225-230.

* Chaveau, A. Sur le méchanisme des mouvements de l'iris. J. de l'Anat. et de la Physiol., 1888, 24, 193-200. Also, C.R. Soc. Biol., 1888, 14, 352.

* Clynes, M. Computer dynamic analysis of the pupil light reflex: a unidirectional rate sensitive sensor. London: 3rd Int. Conf. med. Electronics Rep., 1960, 356-358.

* Clynes, M. Unidirectional rate sensitivity: a biocybernetic law of reflex and humoral systems as physiologic channels of control and communication. (Pavlovian Conf. Monogr. on Higher Nervous Activity) Ann. N.Y. Acad. Sci., 1961, 92: 946-969.

Coccius, E. A. De Pupillenreactie by Accomodatie en Convergentie. Dissertation, Univer. Leiden, 1899. Cited by H. Vervoort, 1900; A. Fuchs, 1903; K. Weiler, 1910.

* Cohn, H. Ueber das Photographieren des Auges. Centralbl. f. prakt. Augenheilk, 1888, 12, 65-67.

* Corrado, M. Influenza dell' estensione dello stimulo luminoso sul potere riflessogeno pupillomotore della retina (curva riflessometrica pupillomotoria). Ann. Ottal. clin. Ocul., 1947, 73, 171-182.

* Crawford, B. H. Dependence of pupil size upon external light stimulus under static and variable conditions. Proc. Roy. Soc., Ser. B., 1936-1937, 121, 376-395.

Cramer, A. Het accomodatie-vermogen der Ogen. Harlem: de erven Loosjes, 1853. Cited by H. Vervoort, 1900; F. C. Donders, 1888; G. Braun, 1931.

* Cüppers, C. Die fortlaufende Registrierung der direkten und der konsensuellen Pupillenreaktion. v. Graefe's Arch. Ophthal., 1954, 155, 588-616.

* Cüppers, C., & Graff, Th. Über ein neues Gerät zur stetigen Beobachtung und Aufzeichnung des normalen und pathologischen Pupillenreflexes (Ein Beitrag zur Frage der objektiven Perimetrie). Klin. Mbl. Augenheilk., 1951, 110, 189-194.

* Cüppers, C., & Wagner, E. Zur pharmacologischen Beeinflussung der Netzhautfunktion. Klin. Mbl. Augenheilk., 1951, 118, 208-230.

* De Groot, S.G., & Gebhard, J. W. Pupil size as determined by adapting luminance. J. opt. Soc. Amer., 1952, 42, 492-495.

* De Launay, J. A note on the photo-pupil reflex. J. opt. Soc. Amer., 1949, 39, 364-367.

De Ruiter, G. C. P. Onderzoekingen over de werking van Atropa Belladonna op de iris (Trans., Diss. Phys. med. de actione Atropae | Belladonna in iridem. Dissertation, Univer. Utrecht, 1853). Nederl. Lancet, 1853-1854, 3, 433-472. Cited by F. C. Donders, 1888; G. Braun, 1931.

* Dolének, A., Kristek, A., Nemek, J., & Komenda, S. Über Veränderungen der Pupillenreaktion nach erfolgreicher Amblyopiebehandlung. Klin. Mbl. Augenheilk, 1962, 141, 353-357.

* Donders, F. C. On the anomalies of accommodation and refraction of the eye. The new Sydenham Soc., London, 1864, Vol. 22, 573-583.

Donders, F. C. Reflexiebeweging der beide Pupillen bij het invallen van Licht aan eene Zijde. Nederl. Arch. voor Geneesk., 1865, 106. Cited by H. Vervoort, 1900; F. von Arlt, Jr., 1869; K. Weiler, 1910.

* Donders, F. C. Die Anomalien der Refraktion und Akkommodation des Auges. (2nd ed.) Wien: W. Braumüller, 1888.

* Drischel, H. Über die Dynamik des Lichtreflexes der menschlichen Pupille. I. Mitt. Der normale Reflexablauf nach kurzdauernder Belichtung und seine Variabilität. Pflüger's Arch. ges. Physiol., 1957, 264, 145-168. (a)

* Drischel, H. Untersuchungen über die Dynamik des Lichtreflexes der menschlichen Pupille. II. Mitt. Dynamische Typologie des normalen Lichtreflexablaufes unter dem Einfluss vegetativer Pharmaca. Pflüger's Arch. ges. Physiol., 1957, 264, 269-290. (b)

* Drischel, H. Experimentelle Untersuchungen über den Lichtreflex der menschlichen Pupille nach kurzdauerndem Lichtreiz. Klin. Mbl. Augenheilk., 1957, 131, 740-755. (c).

* Drouin, A. Note pour démontrer qu'il n'y a pas de rapport direct entre l'état d'accommodation de l'oeil et le diamètre de la pupille. C. R. Soc. Biol., 1876, T3, 6th sér., 199-205.

Dubois-Poulsen, F., & Loisillier, M. Un appareil utilisant les convertisseurs d'infrarouges pour l'étude de la pupille dans l'obscurité absolue. (Soc. d'Ophtal. Paris 18. déc.) Bull. Soc. Ophtal., France, 1954-1955, 150-154. Also, Zbl. Ophthal., 1955-56, 66, 137-138.

* Du Bois-Reymond, Cl., & Greeff, R. Über Pupillenstudien. (Berl. Ophthal. Ges. 15, Juni, 1893) Centralbl. Augenheilk., 1894, 18, 171-173.

* Dupont, M. Instruments pour provoquer et mesurer le réflexe pupillaire. (Soc. Neurol. 15 Mai) Rév. gén. Ophtal., 1902, 21, 515-516. (a)

* Dupont, M. Excitateur de la pupille pour la recherche du réflexe lumineux. C. R. Soc. Biol., 1902, 54, 1366-1368. (b)

* Eckhard, C. Beiträge zur Geschichte der Experimentalphysiologie der motorischen Nerven des Auges. Vol. 11, Giessen: Emil Roth, 1885. Pp. 115-218.

* Elsberg, C. A., & Spotnitz, H. Relation between area and intensity of light and size of pupil, with formulas for pupillary reactions. Bull. neurol. Inst., N.Y., 1938, 7, 160-169.

* Engel, S. Widerstandspupilloskop. Ein neuer Apparat zur Messung der motorischen und optischen Unterschiedsempfindlichkeit. Arch. Augenheilk., 1930, 103, 657-664.

* Engelking, E. Der Schwellenwert der Pupillenreaktion und seine Beziehungen zum Problem der pupillomotorischen Aufnahmeorgane. Z. Sinnephysiol., 1919, 50, 319-337.

* Engelking, E. Vergleichende Untersuchungen über die Pupillenreaktion bei der angeborenen totalen Farbenblindheit. Klin. Mbl. Augenheilk., 1922, 69, 177-188.

* Feldmann, J. B. Improved illuminator and pupillometer. Arch. Ophthal., 1933, 9, 974-976.

* Ferree, C. E., & Rand, G. Instrument for measuring breadth of the pupil. Amer. J. Psychol., 1937, 38, 292-293.

* Ferree, C. E., & Rand, G. Relation of size of pupil to intensity of light and speed of vision and other studies. J. exper. Psychol., 1932, 15, 37-55.

* Ferree, C. E., Rand, G., & Harris, E. T. Intensity of light and area of illuminated field as interacting factors in size of pupil. J. exper. Psychol., 1933, 16, 408-422.

* Fick, A. Über die chromatische Abweichung des menschlichen Auges. v. Graefe's Arch. Ophthal., 1856, 2,2, 70-76.

* Flamant, Francoise. Variation du diamètre de la pupille de l'oeil en fonction de la brillance. Rev. d'opt. thèoret. et instr., 1948, 27, 751-758.

* Fragstein, —., & Kempner, —. Pupillenreaktionsprüfer. Klin. Mbl. Augenheilk., 1899, 37, 243.

Friberger, R. Om mätning af pupillens vidd. Dissertation, Univer. Uppsala, 1903. Cited in Jber. Leist. Ophthal., 1903, 34, 68-70.

* Friedländer, R., & Kempner, —. Beitrag zur Kenntnis der hemianopischen Pupillenstarre. Neurol. Zentralbl., 1904, 23, 2-8.

* Fry, G. A. The relation of pupil size to accommodation and convergence. Amer. J. Optom., 1945, 22, 451-465.

* Fry, G. A., & Allen, M. J. Effect of flashes of light on night visual acuity. Part II. Ann Arbor, Mich.: AF-NRC Vision Comm. Rep., 1953.

* Frydrychovicz, G., & Harms, H. Das pupillomotorische Perimeter. (Ber. 53. deutsch. Ophthal. Ges. Dresden, August 5-7) Zbl. Ophthal., 1940, 45, 326; 650. (a)

* Frydrychovicz, G., & Harms, H. Objektive Perimetrie. (Ber. 53. Verh. deutsch. Ophthal. Ges. Dresden, August 5-7) Zbl. Ophthal., 1940, 45, 614-615. (b)

* Frydrychovicz, G., & Harms, H. Ergebnisse pupillomotorischer Untersuchungen an Gesunden und Kranken. (Ber. 53. Verh. deutsch. Ophthal. Ges. Dresden, August 5-7) Zbl. Ophthal., 1940, 45, 615. (c)

* Fuchs, A. Die Messung der Pupillengrösse und Zeitbestimmung der Lichtreaktion der Pupillen bei einzelnen Psychosen und Nervenkrankheiten. Jahrbücher f. Psychiat., 1903, 24, 326-458.

* Fugate, J. M. A masking technique for isolating the pupillary response to focused light. J. opt. Soc. Amer., 1954, 44, 771-779.

* Fugate, J. M., & Fry, G. A. Relation of changes in pupil size to visual discomfort. Ill. Eng., 1956, 51, 537-549.

Galenus (Galen), C. (131-200, approx.). Opus de usu partium corporis humani etc. Transl. by Daremberg, Ch.: Oeuvres anatomiques, physiologiques et médicales de Galien, traduites sur les textes imprimés et manuscripts, accompagnées de sommnaires, de notes, de planches et d'une table de matières, précédées d'une introduction ou étude biographique, litéraire et scientifique sur Galien. Paris: J.-B. Baillière, 1854, 1856, 2 vols.

* Garten, S. Beiträge zur Kenntnis des zeitlichen Ablaufes der Pupillenreaktion nach Verdunkelung. Pflüger's Arch. ges. Physiol., 1897, 68, 68-94.

* Gasteiger, H. Klinische Beobachtungen über die Ausdehnung des pupillomotorisch wirksamen Bezirkes der Netzhaut. Arch. Augenheilk., 1934, 108, 553-558.

* Gifford, R., & Mayer, L. L. Clinical use of Sander pupilloscope. Arch. Ophthal., 1931, 6, 63-69.

* Gorham, J. The pupil-photometer. Proc. Roy. Soc., London, 1884, 37, 425-426.

* Gradle, H. S., & Ackerman, W. Reaction time of normal pupil; second communication. AMA Transactions, Sect. Ophthal., 1932, 342-348.

* Gradle, H. S., & Eisendraht, E. B. Die Reaktionszeit der normalen Pupille. Vorläufige Mitt. Mbl. Augenheilk., 1923, 71, 311.

* von Graefe, A. Das Verhalten der Pupillen am Hund bei der Accomodation in der Nähe (Observation by A. Müller) v. Graefe's Arch. Ophthal., 1854, 1,1, 440.

* von Graefe, A. Pathologisches zur Accommodationslehre. v. Graefe's Arch. Ophthal., 1856, 2,2, 299-319.

* Groethuysen, G. Über die Beziehungen zwischen motorischer und optischer Unterschiedsempfindlichkeit bei normalen und krankhaften Zuständen des Sehorgans. Arch. Augenheilk., 1921, 87, 152-188; 88; 83-115.

Gualdi, V. Contributo sperimentale allo studio della reazione pupillare alla convergenza (Nota preventiva). Atti Congr. Soc. Ital. di Oftal., Roma, 1930. Cited by V. Gualdi, 1931. (a)

* Gualdi, V. La reazione della pupilla alla convergenza (Revisione critica degli studi sull'argomento e stato attuale della conoscenza scientifica del fenomeno: reazione pupillare alla accomodazione-convergenza). Lettura oftal., 1930, 7, 205-226.

* Gualdi, V. Richerche sperimentali e osservazioni cliniche sul comportamento e sul meccanismo della reazione pupillare alla convergenza. Boll. d'oculistica, Florence, 1931, 10, 806-855.(b)

/ Gundlach, R. H. The speed of pupillary contraction in response to light in pigeons, cats, and humans. J. genet. Psychol., 1934, 44, 250-253.

* Haessler, H. F. Near reaction of the pupil in the dark. Arch. Ophthal., 1937, 18, 796-801.

* Harms, H. Grundlagen, Methodik und Bedeutung der Pupillenperimetrie für die Physiologie und Pathologie des Sehorgans. v. Graefe's Arch. Ophthal., 1949, 149, 1-68.

* Harms, H. Hemianopische Pupillenstarre. Klin. Mbl. Augenheilk., 1951, 118, 133-147. (a)

* Harms, H. Objektive Kontrolle von Gesichtsfeldstörungen. 57. Zus. dtsch. Ophthal. Ges., Heidelberg, 1951, 245-251. (b)

* Harms, H. Neue Methoden der Perimetrie. In: Zeitfragen der Augenheilk. Leipzig: Georg Thieme, 1954.

* Hartinger, H. Pupillenweiten. Z. Ophthal. Opt., 1937, 25, 1-7.

* Hecht, S., & Pirenne, M. H. Sensibility of the nocturnal long-eared owl in the spectrum. J. gen. Physiol., 1939-1940, 23, 709-717.

* Heddaeus, E. Über hemiopische Pupillenreaction. Dtsch. med. Wschr., 1893, 19, 748-751.

* Heine, L. Physiologisch-anatomische Untersuchungen über die Accomodation des Vogelauges. v. Graefe's Arch. Ophthal., 1898, 45, 469-496.

Helmbold, —. Zur Prüfung der Pupillarreaktion. Med. Klinik, 1911, No. 47. Cited in Neurol. Zbl., 1912, 428 (Tobias).

* Hensen, V., & Völckers, C. Über den Ursprung der Accomodationsnerven, nebst Bemerkungen über die Function der Wurzeln des Nervus oculomotorius. v. Graefe's Arch. Ophthal., 1878, 24, 1-26.

Hering, E. Die Lehre vom binocularen Sehen. Leipzig: W. Engelmann, n.d. Cited by V. Gualdi, 1931; E. Wlotzka, 1905; W. Lohmann, 1908. Also in C. A. Raddle: Spatial sense and movements of the eye.* Trans., n.d., no title of original text.

* Hess, C. Untersuchungen über die Ausdehnung des pupillomotorisch wirksamen Bezirkes der Netzhaut und über die pupillomotorischen Aufnahmeorgane. Arch. Augenheilk., 1907, 58, 182-205.

* Hess, C. Untersuchungen über das Sehen und über die Pupillenreaction von Tag- und von Nachtvögeln. Arch. Augenheilk., 1908, 59, 143-167. (a)

* Hess, C. Zur Physiologie und Pathologie des Pupillenspiels. Arch. Augenheilk., 1908, 60, 327-389. (b)

* Hess, C. Neue Untersuchungen über den Lichtsinn bei wirbellosen Tieren. Pflüger's Arch. ges. Physiol., 1910, 136, 282-367.

* Hess, C. Vorführung eines Apparates für Pupillenuntersuchungen. (34. Vers. Rhein.-Westfäl. Augenärzte Köln) Zbl. ges. Ophthal., 1914-1915, 1-2, 434. (a)

* Hess, C. Neue Versuche über Lichtreaktionen bei Tieren und Pflanzen. Münch. med. Woch., 1914, 61, No. 27, 1489-1492. (b)

* Hess, C. Messende Untersuchungen zur vergleichenden Physiologie des Pupillenspiels. v. Graefe's Arch. Ophthal., 1915, 90, 382-393.

* Hess, C. Das Differentialpupilloskop. Eine Methode zur messenden Bestimmung von Störungen des Pupillenspiels. Arch. Augenheilk., 1916, 80, 213-228.

* Hess, C., & Heine, L. Arbeiten aus dem Gebiet der Akkomodationslehre. IV. Experimentelle Untersuchungen über den Einfluss der Akkomodation auf den intraoculaten Druck, nebst Beiträgen zur Kenntnis der Akkomodation bei Säugetieren. v. Graefe's Arch. Ophthal., 1898, 46, 2, 243-276.

* Hesse, R. Studien über die hemiopische Pupillenreaktion und die Ausdehnung des pupillomotorischen Bezirkes der Netzhaut. Klin. Mbl. Augenheilk., 1909, 47 (N.F.7), 33-55.

* Hesse, R. Über die Verengerung der Pupille beim Nahesehen. Klin. Mbl. Augenheilk., 1912, 50 (N.F. 13), 740-745.

Himly, K. Ophthalmologische Beobachtungen und Untersuchungen: 1801; 47. Cited by J. Budge, 1855; C. Eckhard, 1885.

* Hirschberg, J. Geschichte der Augenheilkunde. In Graefe-Saemisch Handbuch der Augenheilk. Berlin: 1908-1918. 15 vols.

* Holladay, L. L. The fundamentals of glare and visibility. J. opt. Soc. Amer., 1926, 12, 271-319.

* Hopkinson, R. G. Glare discomfort and pupil diameter. J. opt. Soc. Amer., 1956, 46, 649-656.

* Hübner, A. H. Beschreibung eines Apparates zur Untersuchung der Pupillen nebst Bemerkungen über einige Pupillenreaktionen. Monatsschr. Psychiat., 1907, 22, 15-20.

* Isakowitz, J. Einige Bemerkungen zu der Arbeit von Dr. Robert Hesse "Über die Verengerung der Pupille beim Nahesehen." Klin. Mschr. Augenheilk., 1912, 50,2, 228-230.

* Jampel, R. S. A study of convergence, divergence, pupillary reactions and accommodation from faradic stimulation of the macaque brain. J. comp. Neurol., 1960, 115, 371-397.

* Jampel, R. S. Representation of the near-response on the cerebral cortex of the macaque. Amer. J. Ophthal., 1959, 48, Pt. 2, 573-582.

* Kadlecová, V. The pupillomotorial adaptation of the eye. Ophthalmologica, (Basel) 1960, 140, 379-387. (a)

/ Kadlecová, V. (Objective adaptometry by control of the pupillary reaction.) In Czech. Čs. Oftalmol., 1958, 14, 85-91. Cited in Ophthal. Lit., 1958.

/ Kadlecová, V. (The influence of pre-adaptation on pupillomotor adaptation.) In Czech. Čs. Oftalmol., 1960, 16, 241-246. Cited in Ophthal. Lit., 1960. (b)

/ Kadlecová, V. (Second bend in the course of the sensory and pupillomotor adaptation curve.) In Czech. Sbor Jék., 1960, 62, 189-192. Cited in, Ophthal. Lit., 1960. (c)

Kadlecová, V. (The effect of dazzling on sensory and pupillomotor adaptation of the eye.) In Czech. Čs. Oftal., 1961, 17, 410-412. Summary by author in English.

* Kadlecová, V.; & Peleška, M. (Infrascopic examination of the diameter of the pupil in darkness adaptation; infrascopic pupillometry.) In Czech. Čs. Oftal., 1955, 11, 4-5.

Kadlecová, V., & Peleška, M. (The pupillary diameter in light and dark in various age categories.) In Czech. Čs. Oftal., 1957, 13, 278-282. (See author's summary in English.) Cited in Zbl. ges. Ophthal., 1958, 73, 255.

* Kanngiesser, F. Licht und Konvergenzmiosis, zwischen der Atropin- und Eserinwirkung auf Iris und Ciliarmuskel, nebst Bemerkungen über die Form der Pupille. Dissertation, Univer. Marburg, 1908. Wiesbaden: Bergmann, 1908. Also, Arch. Augenheilk., 1909, 63, 78-88.

* Kappauf, W. E. The size of the cat's pupil as a function of stimulus brightness. Psychol. Bull., 1938, 35, 719.

* Kappauf, W. E. Variation in the size of the cat's pupil as a function of stimulus brightness. J. comp. Psychol., 1943, 36, 125-230.

* Kawabata, H. Electroretinogram and pupillogram. Comparison of the two methods, based on simultaneous recording of retinal potentials and pupillary movements. Paper presented at Assoc. res. Ophthal. Eastern Section. Amer. J. Ophthal., 1961. (Abstract)

/ Keeler, C. E. Le réflexe irien à la lumière chez la souris à rétine sans batonnets. C. R. Soc. Biol., 1927, 96, 1, 10. (Ref.: Jber. Ophthal., 1927)

* Kempner, —. Neues Instrument f.d. Prüfung d. hemianopischen Pupillenreaktion. (Ber. Verh. 9. Int. Ophthal. Congr. Utrecht.) Beilageheft, Zeitschr. f. Augenheilk., 1899, 2,23.

* Kestenbaum, A., & Eidelberg, L. Konvergenzreaktion der Pupille und Naheeinstellung. v. Graefe's Arch. Ophthal., 1928-1929, 121, 166-212.

* Kleefeld, G. Pupillométrie physiologique et pathologique. Une nouvelle méthode de mesuration du réflexe photomoteur de la pupille. Ann. d'oculist, 1921, 158, 4-43; 262-304.

* Knoll, H. A. Pupillary changes associated with accommodation and convergence. Amer. J. Optom., 1949, 26, 346-356.

* Koch, R. Ein einfaches Pupilloskop. Münch. med. Wschr. (Feldärzt. Beilage II), 1916, 1607-1608.

* Kofman, T., & Bujadoux, A. Le réflexomètre pupillaire (presentation de l'appareil). Les résultats de la réflexométrie dans l'étude du réflexe photomoteur normal. C. R. Soc. Biol., Paris, 1922, 186, 1165-1166; 1166-1167.

* Kofman, T., & Bujadoux, A. Recherches sur la réflexométrie pupillaire normale et pathologique. Ann. d'oculist, 1923, 160, 943-961.

* Kreuchel, V. Over de werking van muscarine op de accommodatie en de pupil. Ned. Gasthuis voor Ooglijdes, Utrecht, 1874, 36-52. Cf. also, Über die Wirkung des Muscarins auf Akkomodation und Pupille., v. Graefe's Arch. Ophthal., 1874, 20, 135-150.

* Krusius, F. F. Über ein Unocularpupillometer. Arch. Augenheilk., 1907, 57, 97-100.

* Krusius, F. F. Über ein Biocular-Pupillometer. Neurol. Zentralbl., 1908, 154-157.

* Lambert, J. H. Photometria sive de mesura et gradibus luminus, colorum et umbrae, 1760. In E. Audig (Ed. & Trans.) Photometria. Leipzig: W. Engelmann, 1892. Ch. 2. Experimentelle und theoretische Bestimmung der Beziehungen zwischen der Öffnung der Pupille, der subjektiven Helligkeit und der Grösse der Lichtquellen.

* Landolt, M. Suggestions on methodical examination of the pupils. Amer. J. Ophthal., 1920, 3, 81-87.

* Lans, L. J. Diamètre pupillaire. (Xe Congr. int. d'ophtal.) Rev. gén. d'Ophthal., 1899, 18, 475-476.

* Lans, L. J. Ueber Pupillenweite. Arch. Anàt. Physiol. (Physiol.), 1900, 79-102.

* Laurens, H. The relative physiological value of spectral lights. III. The pupillomotor effects of wave-lengths of equal energy content. Amer. J. Physiol., 1923, 64, 97-119.

Le Conte, J. On some phenomena of binocular vision. Amer. J. Sci. & Art, 1869, 47, 68-77. Cited by G. A. Fry, 1945; E. Marg & M. W. Morgan, Jr., 1949.

* Lehrfeld, L. Quantitative pupillary light reflex. Amer. J. Ophthal., 1928, 11, 897-898.

/ de Leonibus, F. Richerche di pupillometria nella visione del vincino. Ann. Ottalm., 1949, 75, 231-238.

* Levatin, P. Pupillary escape in disease of the retina or optic nerve. Arch. Ophthal., 1959, 62, 768-779.

Listing, J. B. Beitrag zur Physiologischen Optik. Besonderer Abdruck aus d. Göttinger Studien, 1845, 27,28. Cited by C. Eckhard, 1885; A. Drouin, 1876; H. Aubert, 1876.

Lodato, G. Pupilloscopy and adaptometry. Arch. di Ottal., 1934, 41, 306. Also, Amer. J. Ophthal., 1935, 18, 572. (Abstract, H. D. Scarney)

* Loewenfeld, Irene E. Über die Aufzeichnung des Pupillenspiels und die nervöse Steuerung dar Pupillenreflexe. v. Graefe's Arch. Ophthal., 1956, 157, 628-655.

* Loewenfeld, Irene E. Mechanisms of reflex dilation of the pupil. Historical review and experimental analysis. Doc. Ophthal., 1958, 12, 185-448.

* Loewenfeld, Irene E. The iris as pharmacologic indicator. I. Effect of physostigmine and of pilocarpine on pupillary movements in normal man. Arch. Ophthal., 1963, 70, 42-51.

* Lohmann, W. Über die Frage: Konvergenz- oder Akkomodations-Verengerung der Pupille bei der Naheinstellung? Vers. d. Ophthal. Ges. Heidelberg, 1908, 264-277.

* Lowenstein, O. Der Psychische Restitutionseffekt. Das Prinzip der psychisch bedingten Wiederherstellung der ermüdeten, der erschöpften und der erkrankten Funktion. Basel: Benno Schwabe, 1937.

* Lowenstein, O. Les troubles du réflexe pupillaire à la lumière dans les affections syphilitiques du système nerveux central. Paris: Doin & Cie, 1939.

* Lowenstein, O. The Argyll Robertson pupillary syndrome. Mechanism and localization. Amer. J. Ophthal., 1956, 42, 2, 105-121.

* Lowenstein, O. Electronic pupillography. Why, how and when? Eye, ear, nose & throat monthly, 1959, 38, 549-550.

* Lowenstein, O., & Givner, I. Pupillary reflex to darkness. Arch. Ophthal., 1943, 30, 603-609.

* Lowenstein, O., & Loewenfeld, Irene E. Mutual role of sympathetic and parasympathetic in shaping of the pupillary reflex to light. Arch. neurol. Psychiat., 1950, 64, 341-377.

* Lowenstein, O., & Loewenfeld, Irene E. Types of central autonomic innervation and fatigue. Arch. neurol. Psychiat., 1951, 66, 580-599.

* Lowenstein, O., & Loewenfeld, Irene E. Disintegration of central autonomic regulation during fatigue and its reintegration by psychosensory controlling mechanisms. J. nerv. ment. Dis., 1952, 115, 1-21; 121-145.

* Lowenstein, O., & Loewenfeld, Irene E. Electronic pupillography. A new instrument and some clinical applications. Arch. Ophthal., 1958, 59, 352-363.

* Lowenstein, O., & Loewenfeld, Irene E. Scotopic and photopic thresholds of the pupillary light reflex in normal man. Amer. J. Ophthal., 1959, 48,2, 87-98. (a)

* Lowenstein, O., & Loewenfeld, Irene E. Influence of retinal adaptation upon the pupillary reflex to light in normal man: Part I: Effect of adaptation to bright light on the pupillary threshold. Amer. J. Ophthal., 1959, 48,2, 536-549. (b)

* Lowenstein, O., & Loewenfeld, Irene E. Influence of retinal adaptation upon the pupillary reflex to light in normal man. Part II: Effect of adaptation to dim illumination upon pupillary reflexes elicited by bright light. Amer. J. Ophthal., 1961, 51,4, 644-654.

* Lowenstein, O., & Loewenfeld, Irene E. The sleep-waking cycle and pupillary activity. Ann. N.Y. Acad. Sci., 1964, 117: 142-156.

* Lowenstein, O., Feinberg, R., & Loewenfeld, Irene E. Pupillary movements during acute and chronic fatigue. A new test for the objective evaluation of tiredness. Invest. Ophthal., 1962, 2,2, 138-157.

* Lowenstein, O., Kawabata, H., & Loewenfeld, Irene E. The pupil as indicator of retinal activity. Amer. J. Ophthal. 1964, 57, 569-596.

* Luckiesch, M., & Moss, F. K. Size of pupil as possible index of ocular fatigue. Amer. J. Ophthal., Ser. 3, 1933, 16, 393-396.

* Luckiesch, M., & Moss, F. K. A correlation between pupillary area and retinal sensibility. Amer. J. Ophthal., Ser. 3, 1934, 17, 598-601. (a)

* Luckiesch, M., & Moss, F. K. Area and brightness of stimulus related to the pupillary light reflex. J. opt. Soc. Amer., 1934, 24, 130-134. (b)

* Lythgoe, R. G. Med. Res. Comm. Special Report #173: Reports of the Committee upon the physiology of vision. 1932.

* Machemer, H. Beiträge zur Physiologie und Pathologie der Pupille. Klin. Mbl. Augenheilk., 1933, 91, 302-316.

* Machemer, H. Beiträge zur Physiologie und Pathologie der Pupille. II. Mitt. Über den Ablauf des normalen Lichtreflexes. Klin. Mbl. Augenheilk., 1935, 94 (N.F. 59), 305-319.

* Machemer, H. Beiträge zur Physiologie und Pathologie der Pupille. III. Mitt. Die Latenzzeit des Lichtreflexes der normalen menschlichen Pupille. Klin. Mbl. Augenheilk., 1941, 106, 385-389.

* Magitot, A. L'apparition précoce du réflexe photomoteur au cours du développement foetal. Ann. d'oculist, 1909, 141, 161-181.

* Magitot, A. L'iris. Paris: Doin, 1921.

* Magitot, A. Physiologie oculaire clinique. Paris: Masson, 1946.

* Marg, E., & Morgan, M. W. Jr. The pupillary near reflex. The relation of pupillary diameter to accommodation and the various components of convergence. Amer. J. Optom., 1949, 26, 183-198.

* Marg, E., & Morgan, M. W. Jr. The pupillary fusion reflex. Arch. Ophthal., 1950, 43, 871-878. (a)

* Marg, E., & Morgan, M.W. Jr. Further investigation of the pupillary near reflex. The effect of accommodation, fusional convergence and the proximity factor on pupillary diameter. Amer. J. Optom., 1950, 27, 217-225. (b)

/ Marina, A. Über die Pupillenreaktion bei der Konvergenz. Neurol. Zbl., 1902, 21, 980.

* Marina, A. Über die Contraction des Sphincter iridis bei der Convergenz und die Seitenbewegungen der Bulbi. Zeitschr. f. Nervenheilk., 1903, 24, 274-284.

* Mazzucconi, M. La riflessometria pupillare con l'apparecchio Kofman & Bujadoux modificato. Ann. di Ottalm., 1925, 53, 808-813.

* Mehrtens, H. G., & Barkan, O. The use of the pupilloscope in neurology. Cal. St. J. Med., 1923, 21, 13-14.

* Meineri, L. Pupilloscopio differnziale di Hess. Giorn. di Med. milit., 1927, 75, 593-606.

* Moderow, F. Das Verhalten der Pupillen bei der Konvergenz und Akkomodation. Dissertation, Univer. Marburg, 1905. Leipzig: A. Hoffman, 1905.

* Modonesi, F. Contributo alla seminologia pupillare con presentazione ed illustrazione di un nuovo apparecchio "Il Pupilloscopio" e i suoi vantaggi. Bull. della Sci. med., Bologna, 1929, Vol. 101, 133-155.

* Moon, P., & Spencer, D. E. On the Stiles-Crawford Effect. J. opt. Soc. Amer., 1944, 34, 319-329.

* Morone, G. Richerche pupillografiche nell'abbagliamento. Boll. d'Oculist., 1948, 27, 639-652.

* Naquin, H. Argyll Robertson pupil following Herpes Zoster Ophthalmicus. With remarks on the efferent pupillary pathways. Amer. J. Ophthal., 1954, 38, Pt. 1, 23-31.

* Nayrac, P., & Franchomme, J. Un procédé de mesure numérique du réflexe photomoteur. Echo méd. du Nord, 1937, 7, 405-413.

Nicolai, G. F. Erfahrung mit Pupillenmessung. Rev. Asoc. méd. Argent., 1929, 221-267. Cited in Zbl. Ophthal., 1930, 22, 375. (Abstract)

Olbers, —. De mutationibus oculi internis. Dissertation, Univer. Göttingen, 1780. Cited by H. Aubert, 1876; M. Landolt, 1920; A. Fuchs, 1903.

Ovio, G. Sui movimenti pupillari. (15th Congr. dell'Ass. Oftalm. Ital.) Annali di Ottalm., 1898, 28, 89. (Abstract) Cited in Jber. Ophthal., 1898, 29. (Abstract, Schenk)

* Ovio, G. Movimenti pupillari, intensità luminosa, accomodazione. Annali di Ottalm., 1905, 34, 102-146.

Ovio, G. Ueber den Pupillenerweiterungskoeffizienten (19th Vers. ital. Ges. Ophthal., Parma, 1-4 Oct.) Zeitschr. Augenheilk., 1908, 19, 77-78. (Abstract)

* Petersen, P. Die Pupillographie und das Pupillogramm. Eine methodologische Studie. Acta Physiol. Scand., 1956, 37, Suppl. 125.

Phillips, L. R. Some factors producing individual differences in dark adaptation. Proc. Roy. Soc., London, Ser. B, 1939, 127, 405-424. Cited by N. M. J. Schweitzer, 1955.

* Pick, —. Konvergenz- oder Akkomodationsbewegungen. (Verein d. Augenärzte v. Ost- u. West-Preussen, Sitz. 28. Febr., Königsberg i. Pr.) Zeitschr. f. Augenheilk., 1920, 44, 329. (Abstract)

* Piltz, J. Ein neuer Apparat zum Photographieren der Pupillenbewegungen. Neurol. Zentralbl., 1904, 17, 18, 801-811; 853-857.

Plateau, —. L'Institut, J. gén. des Soc. et Traveaux sci. de la France et de l'Etranger, 1835, No. 103. Cited by F. Moderow, 1905; E. Wlotzka, 1905; V. Gualdi, 1931.

Plempius, V. F. Ophthalmographia, sive tractatio de oculo. 3rd ed. Lovanii: Nempaei, 1659. Cited by C. Eckhard, 1885; J. Budge, 1855; J. Hirschberg, 1908-1918.

* Polimanti, O. Sulla Valenza motoria della pupilla. Arch. di Ottlam., 1907, 14, 85-93, also, Arch. ital. de Biol., 1907, 47, 400.

* Poursines, Y. Nouvel appareil pour la recherche du réflexe pupillaire. L'isophote de Walter. Marseille méd., 1932, 69^2, 320-324.

* Reeves, P. Rate of pupillary dilation and contraction. Psychol. Rev., 1918, 25, 330-340.

* Reeves, P. The response of the pupil to various intensities of light. J. opt. Soc. Amer., 1920, 4, 35-43.

* Renard, G., & Massonnet-Naux, —. La synergie pupillaire à la convergence. Arch. d'Ophthal., 1951, N.S. 11, 137-145.

* Sachs, M. Über den Einfluss farbiger Lichter auf die Weite der Pupille. Pflüger's Arch. ges. Physiol., 1892, 52, 79-86.

* Sachs, M. Eine Methode der objektiven Prüfung des Farbensinnes. v. Graefe's Arch. Ophthal., 1893, 39, Pt. 3, 108-125.

* Sachs, M. Zum Nachweis der hemiopischen Pupillarreaktion. Pflüger's Arch. ges. Physiol., 1910, 136, 402-411.

* Samojloff, A. J. Die Lokalpupillographie bei Sehbahnenläsionen. Zeit. arztl. Fortbildung, 1959. (Ber. 3. Tag. Augenärzte DDR, Dresden, 16-18 April)

* Samojloff, A. J., Sokolova, O. N., & Shakhnovitch, A. R. (Pupillographic method in the study of the act of convergence.) Biofizika, 1961, 6. In Russian. Biophysics, Royer & Roger, Inc. Amsterdam: Elsevier Publishing Co., 1961. (Trans. in English)

* Samojloff, A. J., & Shakhnovitch, A. R. (A new method of local pupillography and its applications in physiology and in the clinic.) In Russian. Vestnik Akad. Med. Nauk., SSSR, 1958, 13, 47-58.

* Sander, E. Über quantitative Messung der Pupillenreaktion und einen in der Praxis hiefür geeigneten einfachen Apparat. Klin. Mbl. Augenheilk., 1929, 83, 318-322.

/ Santamaria, —. Le oscillazioni pupillari consecutive al riflesso fotomotore. Il Policlinicio, Ser. Prat., 1926, 145.

Sattler, C. H. Zwei Fälle von chronischer progressiver Ophthalmoplegie. Vorhandene Lichtreaktion bei fehlender Konvergenzreaktion. Deutsch. med. Woch., 1920, 40, 793.

* Sautter, H. Ein neues Gerät zum Nachweis der hemianopischen Pupillenstarre (Hemikinesimeter). Ber. D. Ophthal. Ges., 1950, 55, 380-382.

* Schadow, —. Beiträge zur Physiologie der Irisbewegung. v. Graefe's Arch. Ophtal., 1882, 28, 3, 183-200.

* Schäfer, G. Über die Untersuchung auf Anisocorie ohne Pupillenstarre. Dissertation, Univer. Giessen, 1899. Altona: Hammerich & Lesser, 1899.

* Schäfer, G. Wie verhalten sich die Helmholtzschen Grundfarben zur Weite der Pupille? Z. Psychol. Physiol. Sinnesorg, 1903, 32, 416-419.

* Scheiner, C. Oculus, hoc est: fundamentum opticum, in quo ex accurata oculi anatome, abstrusarum experimentiarum sedula pervestigatione, etc. Oeniponti, D. Agricolam, 1619.

* Schirmer, O. Untersuchungen zur Physiologie der Pupillenweite. v. Graefe's Arch. Ophthal., 1894, 40, 8-21.

* Schirmer, O. Zur Methodik der Pupillenuntersuchung. Deutsch. med. Woch., 1902, 218-221. (a)

* Schirmer, O. Noch einmal die Methodik der Pupillenuntersuchung. Deutsch. med. Woch., 1902, 13, 412. (b)

* Schlesinger, E. Pupillometer. Med. Klin., 1907, 3, 205-206.

* Schlesinger, E. Über den Schwellenwert der Pupillenreaktion und die Ausdehnung des pupillomotorischen Bezirkes der Retina. Untersuchungen auf Grund einer neuen Methodik. Deutsch. med. Woch., 1913, 39, No. 4, 163-165.

* Schlesinger, E. Demonstration eines Pupillenmessapparates. (Berl. Ges. Psychiat. Nervenkrankh. 15. Juni) Neurol. Centralbl., 1914, 33, 863 (Summary by author)

* Schlesinger, E. Ein neuer Apparat zum Studium der Physiologie und Pathologie des Pupillenreflexes (Peripupillometer). Zeitschr. f. Augenheilk., 1927, 62, 96-97.

* Schmelzer, H. Eine einfache Untersuchungsmethode auf hemianopische Pupillenstarre mittels der Spaltlampe. Klin. Mbl. Augenheilk., 1931, 87 (N.F. 52), 200-203.

* Schober, H. Akkomodation, Konvergenz und Pupillenweite. Mschr. Feinmechanik & Optik, 1953, 70, 135-136.

* Schubert, G., & Burian, H. Die Fusionsreaktion, eine bisher unbekannte Reaktion der Pupille. Pflüger's Arch. ges. Physiol., 1936, 238, 184-186.

* Schweitzer, N. M. J. Threshold measurements on the light reflex of the pupil in the dark-adapted eye. Dissertation, Univer. Utrecht, 1955. S'Gravenhage: H. Junck, 1955.

* Schweitzer, N. M. J. Threshold measurements on the light reflex of the pupil in the dark-adapted eye. Doc. Ophthal., 1956, 10, 1-78.

* Schweitzer, N. M. J., & Bouman, M. A. Threshold measurements on the light reflex of the pupil. Ophthalmologica, 1956, 132, 286-288.

* Schweitzer, N. M. J., & Bouman, M. A. Differential threshold measurements on the light reflex of the human pupil. Ophthalmologica, 1958, 135, 298-300.

* Shakhnovitch, A. R. (Cinematographic investigation of orienting and defensive pupillary reflexes.) In Russian. Akademia Nauk SSSR. Probl. physiol. Optics, 1958, 12, 175-180. (b)

* Shakhnovitch, A. R. (Concerning the method of investigation of color vision in animals.) In Russian. Akademia Nauck (SSSR) Biophysics, 1959, 4, 367-371. Summary in English.

* Shakhnovitch, A. R. (On the principle of scanning the pupil.) In Russian. Akademia Nauk SSSR, 1960, 5, 494-496. (a)

* Shakhnovitch, A. R. (Hemianopic pupillary reactions in disorders of the optic tract at different levels.) In Russian. Vop. Neirokhir., 1960, 24, 20-24. (b)

* Shakhnovitch, A. R., & Shakhnovitch, V. R. (Scanning pupillograph.) In Russian. Vop. Neiokhir., 1961, 25, 57-59.

Shakhnovitch, V. R. (A method of cinematographic recording of pupil reflexes and its diagnostic significance.) In Russian. Bjull. eksper.

Biol. i Med., 1957, 105-108. Summary in English. Cited in Zbl. ges Ophthal., 1958, 73, 254.

* Shakhnovitch, V. R. (Cinematographic investigation of pupillary reaction to convergence.) In Russian. J. Physiol. USSR, 1958, 44, 170-172. (a)

* Silberkuhl, W. Untersuchungen über die physiologische Pupillenweite. v. Graefe's Arch. Ophthal., 1896, 42, 3, 179-187.

* Smythe, R. H. Veterinary ophthalmology. Baltimore: Williams & Wilkins, 1958.

* Sommer, R. Verbesserter Pupillenmessapparat mit Messung von Reiz und Wirkung. (Vers. südwestdtsch. Nervenärzt. Frankfurt a.M. 12.Nov.) Münch. med. Woch., 1899, 1657.

* Spring, K. H., & Stiles, W. S. Variation of pupil size with change in the angle at which the light stimulus strikes the retina. Brit. J. Ophthal., 1948, 32, 340-352.

* Stark, L. Biological rhythms, noise and asymmetry in the pupil-retinal control system. Ann. N. Y. Acad. Sci., 1962, 98, 1096-1108. (a)

* Stark, L. Environmental clamping of biological systems: pupil servomechanism. J. opt. Soc. Amer., 1962, 52, 925-930. (b)

* Stark, L. The effect of drugs on the transfer function of the human pupil system. MIT: Res. Lab. Electronics, Quart. Prog. Rep., 1963, No. 68.

* Stark, L., & Baker, F. Stability and oscillations in a neurological servomechanism. J. Neurophysiol., 1959, 22, 156-164.

* Stark, L., Campbell, F. W., & Atwood, J. Pupil unrest: an example of noise in a biological servomechanism. Nature, 1958 (Sept.), No. 4639, 857-858.

* Stark, L., & Cornsweet, T. N. Testing a servoanalytic hypothesis for pupil oscillations. Science, 1958 (March), Vol. 127, 588.

* Stark, L., Redhead, J., & Payne, R. C. Asymmetrical behavior in pupil system. MIT: Res. Lab. Electronics, Quart. Prog. Rep., 1961, No. 61.

* Stark, L., & Sherman, Ph. M. A servoanalytic study of consensual pupil reflex to light. J. Neurophysiol., 1957, 20, 17-25.

* Stark, L., Van der Tweel, H., & Redhead, J. Pulse response of the pupil. Acta physiol. Pharmacol. Neerl., 1962, 11, 235-239.

* Stegemann, J. Über den Einfluss sinusförmiger Leuchtdichtenänderungen auf die Pupillenweite. Pflüger's Arch. ges. Physiol., 1957, 264, 113-122.

Steinhardt, J. Discrimination in the human eye. I. The relation of $\Delta I/I$ to intensity. J. gen. Physiol., 1936-1937, 20, 185-209. Cited by G. A. Fry & M. J. Allen, 1953.

* Stern, H. J. Simple method for early diagnosis of abnormalities of pupillary reaction. Brit. J. Ophthal., 1944, 28, 275-276.

* Stiles, W. S. The effect of glare on the brightness difference threshold. Brit. Dept. Sci. Ind. Res.: Illum. res. tech. Paper, 1929, No. 8.

* Stiles, W. S. The scattering theory of the effect of glare on the brightness difference threshold. Proc. Roy. Soc. London B, 1930, 105, 131-146.

* Stiles, W. S., & Crawford, B. H. The luminous efficiency of rays entering the eye pupil at different points. Proc. Roy. Soc. London B, 1933, 112, 428-450.

* Stoewer, —. Ein Fall von Sehnervenatrophie bei Diabetes nebst Bemerkungen über Pupillenreaktion bei Durchleuchtung der Sklera. (Rhein. Westf. Augenärzt. Vers. Nov. 6) Klin. Mbl. Augenheilk., 1903, 41, 97-100.

* v. Studnitz, G. Pupillarreaktion und Helligkeitswahrnehmung. Naturwiss., 1934, 61, 627-633.

* Talbot, S. A. Pupillography and the pupillary transient. Dissertation, Harvard Univer., Cambridge, 1938. (a)

* Talbot, S. A. Cinematography of the pupil. Amer. J. Physiol., 1938, 123, 200. (b)

* Tange, R. A. Die normale Pupillenweite nach Bestimmungen in der Poloklinik. Dissertation, Univer. Amsterdam, 1901. Also, Arch. f. Augenheilk., 1903, 49-61.

* Thomson, L. C. Binocular summation within the nervous pathways of the pupillary light reflex. J. Physiol., 1947, 106, 59-65.

* Toulant, P. Le réflexe pupillaire à la lumière ultraviolette. (39th Congr.) Soc. franç. d'Ophtal., 1926, 155-159.

* v. Trautvetter, D. Über den Nerv der Accomodation. v. Graefe's Arch. Ophthal., 1866, 12, 95-149.

* Troelstra, A., Zuber, B. L., Simpson, J. I., & Stark, L. Pupil variation and disjunctive eye movements as a result of photic and accommodative stimulation. MIT: Res. Lab. Electronics, Quart. Prog. Rep., 1963, No. 69, 250-253.

* Tschirren, B. Die fortlaufende Registrierung des Pupillenreflexes. Helv. Physiol. Acta, 1947, 5, C57-C58.

Ulbrich, H. Instrument zur Prüfung der hemiopischen Pupillenreaktion. (Wien. Ophthal. Ges. 9. Feb) Klin. Mbl. Augenheilk., 1914, 536. Cited by C. Behr, 1924.

* Van der Tweel, L. H., & van der Gon, D. The light reflex of the normal pupil of man. Acta Physiol. Parmacol. Neerl., 1959, 8, 52-88. (English version of thesis, L. H. Van der Tweel, 11 July 1956)

* Venco, L. & Marucci, L. Rilievi pupillografici sul riflesso alla luce e dall'oscuramento in condizioni fisiologiche. Ann. di Ottalm. Clin. Ocul., 1947, 73, 486-494.

* Veraguth, —. Zur Prüfung der Lichtreaktion der Pupille. Neurol. Zentralbl., 1905, 24, 338-343.

* Veraguth, —. Zur Fage nach dem pupillomotorischen Feld der Retina. Neurol. Zentralbl., 1908, 27, 402-404.

* Vervoort, H. Die Reaction der Pupille bei der Accomodation und der Convergenz und bei der Belichtung verschieden grosser Flächen der Retina mit einer constanten Lichtmenge. v. Graefe's Arch. Ophthal., 1900, 49, 2, 348-374..

* v. Vintschgau, M. Zeitbestimmungen der Bewegung der eigenen Iris. Pflüger's Arch. ges. Physiol., 1881, 26, 324-390.

* v. Vintschgau, M. Weitere Beobachtungen über die Bewegungen der eigenen Iris. Pflüger's Arch. ges. Physiol., 1882, 27, 194-196.

* Vogt, A. Ein neues Hemikinesimeter. (Ges. Schweitz. Augenärzt. 15, Schaffhausen) Klin. Mbl. Augenheilk., 1922, 69, 119.

* Wagman, I. H., & Gulberg, J. E. The relationship between monochromatic light and pupil diameter. The low intensity visibility curve as measured by pupillary movements. Amer. J. Physiol., 1942, 137, 769-778.

* Wagman, I. H., & Nathanson, L. M. Influence of intensity of white light upon pupil diameter of the human and of the rabbit. Proc. Soc. exper. Biol., 1942, 49, 466-470.

Walker, C. B. Further observations on the hemiopic pupillary reaction obtained with a new clinical instrument. J. AMA, 1914, 63, 846-851. Cited by C. Behr, 1924.

* Walter, A. Isophote, pour le recherche du réflexe pupillaire. Gaz. d'hôp., 1933, 106, 76-77.

Weber, E. H. Tractatus de motu iridis. Lipsiae: Glückii, 1821.

Weber, E. H. Additamenta ad tractatum de motu iridis. Pars I. Lipsiae: 1823.

Weber, E. H. Annotationes anatomicae et physiologicae. Programma collecta. Fas. III. Summa doctrinae de motu iridis. Lipsiae: 1851. Cited by J. Budge, 1855; C. Eckhard, 1885; V. Gualdi, 1931; J. Hirschberg, 1908-1918; A. Drouin, 1876; E. Marg & M. W. Morgan, Jr., 1949; F. E. Donders, 1888; H. Vervoort, 1900; G. A. Fry, 1945.

* Weiler, K. Demonstration eines neuen Pupillenmessapparates. III. Jahresvers. (Verein Bay. Psychiat. München, June 1905) Neurol. Centralbl., 1905, 24, 682-683.

* Weiler, K. Untersuchungen der Pupille und der Irisbewegungen beim Menschen. Zeitschr. ges Neurol. Psychiat., 1910, II, 101-274.

* Wernicke, C. Ueber hemiopische Pupillenreaktion. Fortschr. Med., 1873, 1,2, 49-53.

* Weve, H. Vorrichtung zur Untersuchung der hemiopischen Pupillarreaktion. Klin. Mbl. Augenheilk., 1918, 61, 140.

* Weve, H. Zur Physiologie des Lichtreflexes der Pupille. v. Graefe's Arch. Ophthal., 1919, 100, 137-156.

* Wilbrand, H. Ueber Hemianopsie und ihr Verhältniss zur topischen Diagnose der Gehirnkrankheiten. Berlin: Hirschwald, 1881.

* Wilbrand, H., & Saenger, A. Die Neurologie des Auges. Vol. 7. Die Erkrankungen der Sehbahn vom Tractus bis in den Cortex. Die homonyme Hemianopsie, nebst ihren Beziehungen zu den anderen cerebralen Herderscheinungen. Wiesbaden: J. F. Bergmann, 1917.

* Wirth, A. Comportamento del riflesso pupillare fotomotore nell' antagonismo binoculare dei colori. G. Ital. Oftal., 1952, 5, 22-29.

* Wlotzka, E. Die Synergie von Akkomodation und Pupillenreaktion. Pflüger's Arch. ges. Physiol., 1905, 107, 174-182.

* Wolff, H. Über Pupillenreaktionsprüfung mit Berücksichtigung der Refraktion des untersuchten Auges sowie über eine zentrale und periphere Pupillenreaktion, nebst Angabe eines neuen Instrumentes. Berl. klin. Wochenschr., 1900, No. 28, 613-615.

* Wolff, H. Über die Abnahme der Pupillenreflexempfindlichkeit der Netzhaut vom Zentrum nach der Peripherie. Z. Augenheilk., 1904, 12, 644-650. (a)

* Wolff, H. Bemerkungen über die Arbeit "Über die Abhängigkeit der Pupillarreaktion von Ort und Ausdehnung der gereizten Netahautfläche" von Dr. G. Abelsdorff u. Dr. H. Feilchenfeld in Bd. 34 dieser Zeitschrift. Z. psych. Physiol., Sinnesorg, 1904, 36, 93-97. (b)

* Wybar, K. C. Ocular manifestations of disseminated sclerosis. Proc. Roy. Soc. Med., 1952, 45, 315-320.

* Young, F. A., & Biersdorf, W. R. Pupillary contraction and dilation in light and darkness. J. comp. physiol. Psychol., 1954-1955, 47, 264-268.

* Zeldenrust, E. L. K. Über die Chronaxie des Lichtreflexes der Pupille. Arch. Augenheilk., 1931, 104, 585-593.

THE FUSION REFLEX

Kenneth N. Ogle
Mayo Clinic and Mayo Foundation

From earliest times, man has been puzzled over one of the amazing facts of vision: namely, that whereas he has two eyes he experiences generally only a single perception of space. Speculation as to the reason for this phenomenon had been made long before anything was known about the neuro-anatomical structures of the visual pathways. Most popular of these speculations was that one or the other of the uniocular images was alternately suppressed. This notion was thought to be reinforced to some extent by the experiments with retinal rivalry.

Leaving aside these speculations, however, it is now usually said that the neural excitations from the images on the two retinas "fuse"— the process involved is called fusion, and takes place in the occipital cortex of the brain. The term fusion sometimes carries other connotations, but here it is used only to convey the idea that when both eyes enter the visual act with appropriate fixation of both eyes, the observer perceives singly. (This terminology will be used herein without implying any notions as to the exact nature of the process.)

It is the neuro-anatomy of the visual processes, of course, which makes this fusion possible and which provides the basis for it, but this cannot be the cause of fusion. Fusion cannot be just a complete unification of the excitations from the two eyes alone, either, for one must assume that the integrity of both images is always maintained.

To provide for this sensory aspect of fusion all movements of the two eyes must be executed and coordinated in the interest of maintaining single vision, and especially for fusion of the images of the fixation object. Eye movements made to preserve single vision are known as fusional movements. To be precise, therefore, the fusion reflex is actually a reflex concerned with the motor control of the eyes in order to preserve the interests of the fusion of the images of the object fixated.

At the outset, to understand the phenomenon of the fusion of the images from the two eyes, one must be familiar with the principles of corresponding retinal points and of Hering's law of identical visual directions, which define corresponding retinal points. Only through these can one have a similar topographical representation of visual space from the

optical images that fall on the two retinas. In this representation there must be a common point of fixation of the two eyes, the images of which fall on the foveas of the two eyes. The neural excitations from any pair of these points give rise to the same subjective visual direction.

The study of the fusion processes in general has proven difficult. As in the study of any natural phenomenon, however, insight is gained into the phenomenon only with respect to those procedures with which it can be changed. Present knowledge of the fusion reflex has come through the following:

1. forced changes in convergence of the eyes—horizontally and vertically, and changes in a cyclotorsion or "twisting" of the images about the anterior-posterior axes of the eyes;

2. studies of the above changes with modification of the visible patterns;

3. anomalies of fusion found in subjects with impaired binocular vision (mostly with strabismus);

4. studies of physiologically "perceived" double images.

Consider the following simple and perhaps trite experiment (Fig. 1). While fixating a point on a chart across the room, suddenly interpose before one eye an ophthalmic prism of, say, three prism diopters, base-out. Instantly, one sees two charts which appear to move toward one another, the speed of movement seeming to increase as the separation of the two decreases. Suddenly, the two charts appear to coalesce—only one chart is seen. A person watching during this time can readily verify that the eye behind the prism has turned inward—the convergence of the eyes has been increased. One eye still fixates the chart, but the other fixates the displaced image of the chart produced by the prism. This experiment demonstrates the phenomenon designated as the compulsion-to-fusion reflex. If the images are widely separated immediately after the prism is inserted, the observer may be able to exert a certain degree of voluntary control over the movement of the two half-images. However, if the separation is small the fusional movements under ordinary conditions are involuntary and compulsive, that is, can seldom be changed at will.

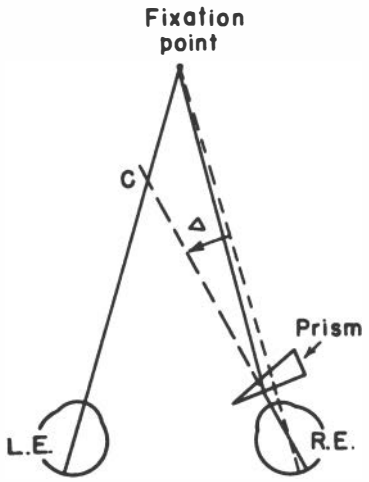

Fig. 1. Simple experiment to demonstrate phenomenon of compulsion to fusion.

When the images come together at the end of a fusional movement, the sensation of the observer is that the two seem to lock together. It is this sensation that probably gave rise to the term fusion. All subsequent fixation eye movements to different parts of the charts are precisely coordinated movements, and bifoveal single vision is maintained. Coordinated eye movements such as these are not, however, a property of fusion per se. When an occluder is placed before one eye so that binocular perception is prevented, the eye movements are still more or less coordinated, that is, said to be concomitant, although, because of the usual oculomoter imbalance of the subject, both eyes are not directed to the same point on the chart. The fusion reflex, therefore, adds something new in that, in the interest of single vision, innervations to the extra-ocular muscles of the two eyes are directed to the same point, or nearly so.

The phenomenon of the compulsion to fusion just demonstrated has led to many notions about fusion. Of particular interest is the strength of this compulsion for fusional eye movements, and even the speed with which the coordinated eye movements can lead to a resumption of single binocular vision (Brecher, 1954). One hopes for some kind of a measure of this reflex, for it probably varies among individuals and might serve a clinical purpose. Certainly the ophthalmologist often finds persons, many with strabismus, who have impediments to binocular vision of several types, and also who, under suitable conditions, can see both half-images.

There are patients for whom the images in the two eyes cannot be made to appear superposed. As attempts are made to cause the image from one eye to pass over the image of the other eye in a stereoscope or haploscope by control of target positions, the two images first appear double-crossed and then double-uncrossed. The subject is unable to see both images at the same time in the same direction. In these instances there is almost a repulsion, or a negative compulsion reflex to fusional movements.

There is also the baffling problem presented by the person with one eye habitually misdirected, the other eye being called the sighting eye. The misdirected eye sees the image of the object fixated by the sighting eye by peripheral vision, but oddly perceives that object in the same or nearly the same visual direction as does the fovea of the fixating eye. Usually, but not in all instances, the two eyes are relatively concomitantly coordinated. Generally, there is reason to believe that, despite the fact that visual direction of the squinting eye is similar to that for the sighting eye, true fusional movements cannot usually be demonstrated.

Finally, there are subjects whose ability to maintain binocular vision is very tenuous. Small changes in convergences introduced by prisms of low deviating power before one eye cause a doubling of the images. Or small changes in ophthalmic lenses before the eyes may cause doubling. In these individuals fatigue may also readily give rise

to diplopia. Can it be said that the strength of the compulsion for fusional movements in these individuals is weak?

The phenomenon found in the individuals with strabismus is evidence that a functioning of the normal neuro-anatomical structures of the visual processes to the occipital cortex is a prerequisite for true fusion and fusional movements.

To find a measure of the reflex compulsion for fusional eye movements, an attempt is usually made to force a change in the normal pointing of the eyes, that is, to force a change in the convergence of the eyes while keeping the stimulus to accommodation constant. These changes can be produced by artificial means, such as by ophthalmic prisms before the eye, or by the use of such instruments as the haploscope. Usually one seeks to find the greatest change in convergence (the magnitude of prism power) that can be produced just before diplopia or double images are perceived. The larger the range of this convergence-divergence change, the greater is said to be the strength of the reflex compulsion for fusional eye movements. However, in this procedure one must consider the role played by an increasingly embarrassed relationship between the accommodation and convergence of the two eyes, which may be a governing factor. Perhaps, mechanical limitations may also be imposed by the properties of the extra-ocular muscles themselves.

The essence of the sensory aspects of fusion lies in there being in the visual field similar contours, for the fusion compulsion strives to keep the cortical excitations arising from images of these contours unified by appropriate innervations to the extrinsic muscles of the two eyes. The importance of contours cannot be over-emphasized. In Fig. 2 are shown illustrations of certain kinds of contours that might be used in a stereoscope. Where contours are identical, fusion—unitary perception—of both images easily occurs. One can verify that both eyes are involved in the visual act by the use of check marks (the dot and cross).

In the third set, the line viewed by the left eye is wider than that viewed by the right, but the contours of the edges are similar. When viewed in the haploscope it can be seen that the narrow line appears to "stick" to either the right edge or the left edge of the wider line; which edge it sticks to depends on the direction of the oculomotor imbalance, the heterophoria of the observer. Thus, one cannot say that the image of the thin line fuses with that of the wide, only that the images of one or the other of the similar contours fuse.

If circles of unequal size are presented, again one edge of the smaller circle usually appears to "stick" to one edge of the larger. Which side of the larger again depends on the direction of the oculomotor imbalance under the conditions of observation.

Defective but partially similar contours may also be sufficient for fusion and for controlling the oculomotor adjustments of the eyes.

However, if the contours are very dissimilar either the images appear to move randomly, or, as is more probable, to move to the phoria position, or there occurs the familiar phenomenon known as retinal rivalry. Even in these circumstances, there tends to be a marked persistence of the visibility of the contours from both eyes, or more often a random alternation of perception of the dissimilar contours.

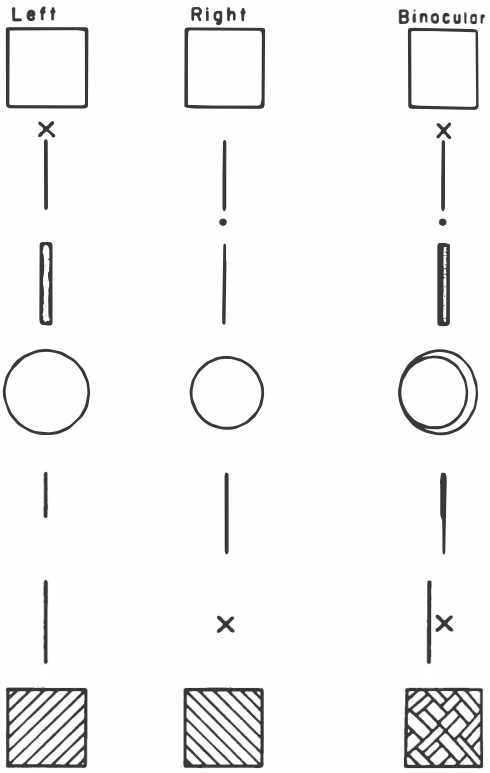

Fig. 2. Types of contours that do and do not provide fusion.

Small wheel-like rotations of the eyes about their lines of fixation—anterior-posterior axes of the eyes—are called cyclotorsional movements. These movements can and do occur constantly in the normal use of the two eyes so as to maintain single binocular vision. These movements then are called cyclofusional movements (Ogle & Ellerbrock, 1946). Cyclofusional movements occur more readily when the visible contours are oriented more or less vertically than when the contours are oriented nearly horizontally.

It can be said that the fusional movements of the two eyes provide bifoveal fixation on the object of interest. However, one must distinguish between bifoveal fixation brought about by the fusion reflex and the so-called fixation reflex, which is a monocular phenomenon. Bifoveal fixation with fusion is not the result of two monocular fixation reflexes acting at the same time, for it can be shown readily that images of contours that fall on the peripheral parts of the retinas of the two eyes are sufficient to control the pointing of the eyes through the fusing of these images (Burian, 1939). In the absence of foveal stimuli, prism vergences of the eyes wholly from peripheral stimuli can be demonstrated easily. Displaced peripheral contours, if sufficiently plentiful, can cause a doubling of non-displaced contours seen only foveally.

In most demonstrations of the compulsion for fusional movements, a large number of contours in a single vertical plane are commonly used.

When a prism is placed before one eye large and equal disparities are introduced between the images of all the contours on the surface. The disparities of the images of all the contours, therefore, provide the innervations for the fusional eye movements. The character of the fusional movements in the sense of their compulsive attribute and the speed of the recovery will be influenced by the number and complexity of the contours on this screen. The strength of the fusion compulsion as measured by prisms certainly is less for a point of light in a dark room than for the details on a wall chart.

In the binocular vision of one's normal surroundings, however, the point of fixation may be in the midst of a larger number of objects in the field of view at different distances (Fig. 3). The images in the two eyes of those objects more distant than the fixation point will be uncrossed and disparate; the images of those nearer than the fixation point will be crossed and disparate. One would expect these disparities also to provide stimuli for fusional movements. That these movements do not occur is usually attributed to the role of attention given to the point of interest. If the attention is suddenly given to a second object, it is thought that the fusional movements of the eyes necessary to fix bifoveally this second object then act as a reflex movement. These movements have been said to be initiated by psycho-optical stimuli (Hofmann, 1925).

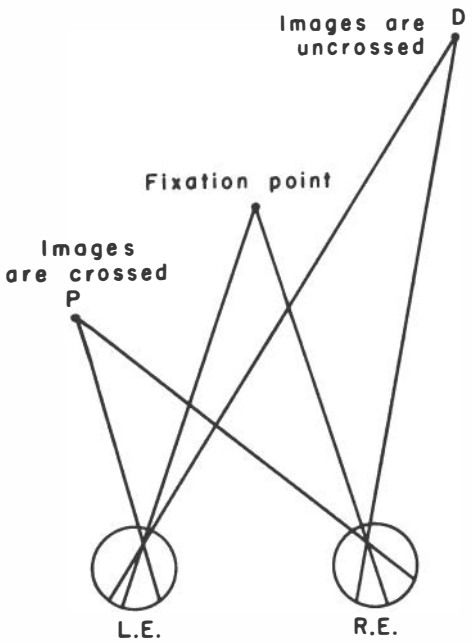

Fig. 3. When eyes fixate near object, images of other objects at different distances in field of view will be disparate.

The fusional movements associated with the vertical diplopia caused by the introduction of a vertical disparity by ophthalmic prisms placed base-down or base-up before an eye are thought to be purely reflex movements. Cyclofusional movements that occur naturally when objects fixated are inclined to the visual plane are thought to be reflex movements also. Under these conditions it is thought that psycho-optical stimuli arise only from the horizontal disparities.

The sensory aspects of fusion and the initiation of fusional movements for objects spatially distributed involve another well-known phenomenon (Fig. 4). If two parallel horizontal lines are presented in a stereoscope to each of the eyes,

it is found that the separation of the lines on one of the targets can be increased or decreased by a small amount before the moved line is perceived double, that is, before three lines are perceived. The magnitude of the change in separation is greater than the sum of the widths of the two lines, and, hence, cannot be a function only of visual resolution. The range in which this separation can be changed is a measure of Panum's fusional area in the vertical meridian. The difference in separation just as doubling appears is usually expressed as the angle subtended at the eye expressed in minutes of arc. Similarly, in the horizontal meridian a range can be found within which single binocular vision is reported. This range is a measure of Panum's fusional area in the horizontal meridian. The experiment is more difficult to perform in the horizontal meridian because the moved line with respect to its mate in the other eye will appear to move in stereoscopic depth. Within the ranges of separation described here, one may say the images are fused in spite of the fact that, except for some one separation, the images must be disparate. In the horizontal meridian these disparate images can be not only the stimulus for stereoscopic depth perception but also potential stimuli for fusional movements.

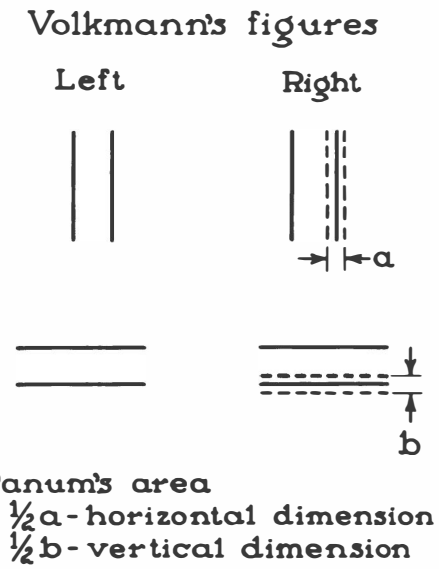

Fig. 4. Haploscopic figures used to demonstrate Panum's areas of fusion in vertical and horizontal meridians.

In normal surroundings, say, with a fixation on a near object (Fig. 5), because of Panum's fusional areas, only objects lying in a certain region would have images in the two eyes that would fall within the region of binocular single vision. All other objects that lie outside these areas would have disparate images and should be seen double. However, generally one is unaware of this doubling, unless attention is called to it, because of a kind of suppression, although it is just as probable that the subject ignores the confusion of images. In spite of the fact that one is not consciously aware of the doubling, the question is whether the disparities between the images do not still act as potential stimuli for fusional movements when attention is directed to any other object. It is also true that for disparities within certain limits that are larger than the horizontal dimension of Panum's area, stereoscopic depth of the images is readily perceived; this implies a similar type of interaction between the excitations from the half-images in the visual cortex (Ogle, 1952a; 1952b).

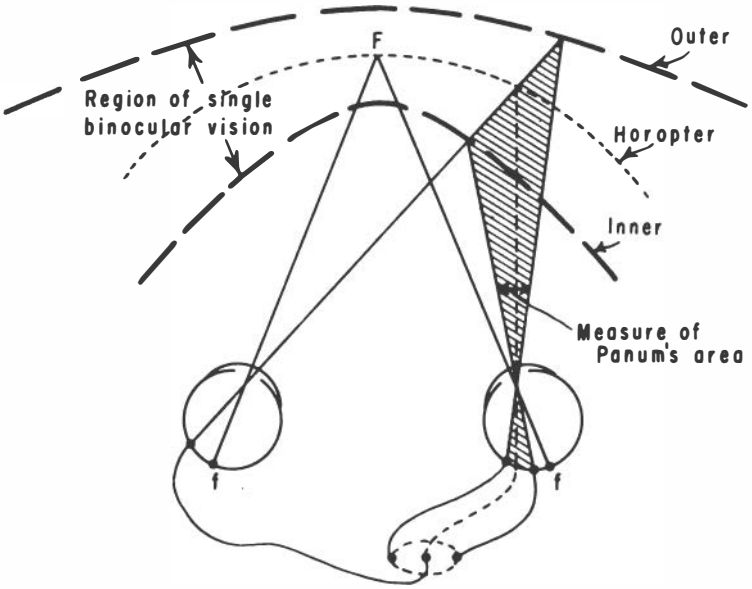

Fig. 5. Schematic illustration of region of binocular single vision due to existence of Panum's areas.

According to presently accepted notions, when the eyes first fixate a distant object and then a near object, a change in convergence of the eyes is necessary if there is to be bifoveal fixation. The question is: Where do the innervations arise for this change in convergence of the eyes, and how much of this convergence is due to the compulsion-to-fusion reflex? Except in subjects with large oculomotor imbalances, the part of the total convergence change due to fusional movements may be quite small. This magnitude would vary among individuals. The greater part of the change in convergence comes from the accommodative-convergence synkinesis, together, perhaps, with the somewhat controversial psychological influence of the awareness of distance of the objects fixated. The so-called fusional convergence then makes up only for the residual convergence needed for fusion of the object fixated. One would expect that if the subject were orthophoric, that is, had no motor imbalance for objects at the two distances, no fusional convergence whatever would be needed, though sensory fusion of the images would, of course, be maintained. The fusional convergence is needed, therefore, only where an oculomotor imbalance (or heterophoria) between the eyes exists. Why oculomotor imbalances exist at all is not clear. They may often be due in part to the so-called tonic factors, uncorrected refractive errors, low accommodative-convergence ranges, perhaps psychological factors, et cetera.

When binocular vision is prevented by a suitable occluder before one eye, for a given point of fixation by the other, and thus a given stimulus to accommodation, the occluded eye turns to a position such that no

imbalance exists between the tensions of the extra-ocular muscles, or better, an equilibrium exists in those tensions. The angle through which the eye has turned from pointing to the fixation point can be measured, for example, by using a Maddox rod as the occluder, which at the same time forms a streak image of the fixation point. By also introducing prisms of various strengths before the eye, the image of this streak can be made to appear in the same visual direction as the fixation point. The strength of the prisms used then measures the angle—the phoria. This angular deviation is said to be a measure of the heterophoria, and it is assumed also to be a measure of the oculomotor imbalance when fusion is maintained.

At the request of the chairman of this symposium, a method is briefly described here for obtaining a measure of the oculomotor imbalance when fusion of the images and normal convergence are maintained, and when both eyes are under the same stimulus to accommodation. This method rests on the fact that, because of the existence of Panum's fusional areas, it is not necessary that the centers of both foveas be directed exactly upon the point of fixation. Thus, if an oculomotor imbalance exists for a given fixation on a given target, it is possible for the eyes actually to overconverge (Fig. 6), or underconverge by a very small angle in the

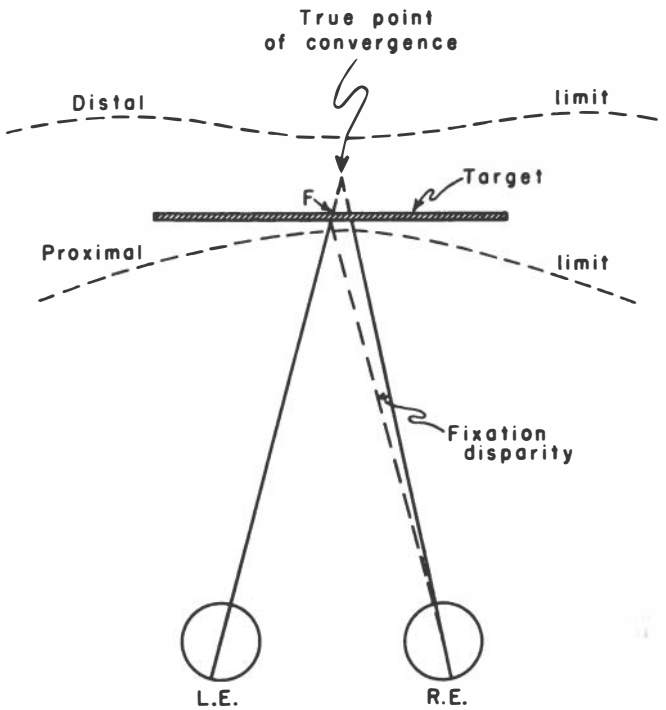

Fig. 6. Schematic illustration of how, under influence of convergent oculomotor imbalance, eyes will actually overconverge by a small angle, and yet images of target fixated will be seen single.

direction of the oculomotor imbalance, namely, an esophoria, or an exophoria, respectively (Fig. 7). This small angular error in convergence is called fixation disparity, because, when first discovered in horopter experiments using the nonius technique, it was clear that the images of the fixation point were actually disparate when the experimenter was heterophoric (Ogle, 1958; 1962).

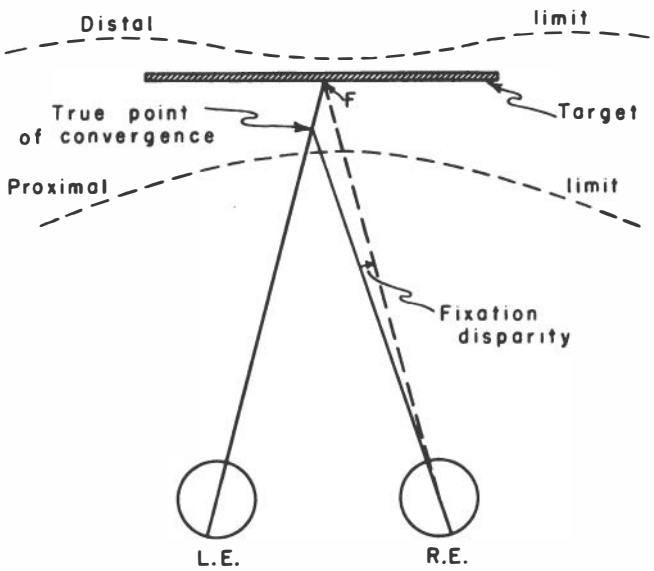

Fig. 7. Schematic illustration of how, under influence of divergent oculomotor imbalance, eyes will actually underconverge by a small angle, and yet images of target fixated will be seen single.

To perceive this small angle of overconvergence or underconvergence, it is necessary only to present details near or at the fixation point, the images of which cannot be fused, and each of which, therefore, would be perceived in the primary uniocular visual direction of each eye separately (Fig. 8). Experiments have shown that if an oculomotor imbalance is present these dissimilar details will appear displaced in spite of fusion, whether these details are seen foveally with peripherally fused images, or extrafoveally with fusion for the images of a fixation object. In a recent study, the angle of fixation disparity has been demonstrated and measured objectively.

To measure subjectively the small angle of fixation disparity, it is necessary only to design an instrument so that one of the two nonius lines can be displaced laterally with respect to the other, until the subject reports that the two nonius lines appear in the same visual direction (Fig. 9). The actual displacement is then expressed in minutes of arc corresponding to the angle subtended by the separation of the two lines at the eyes.

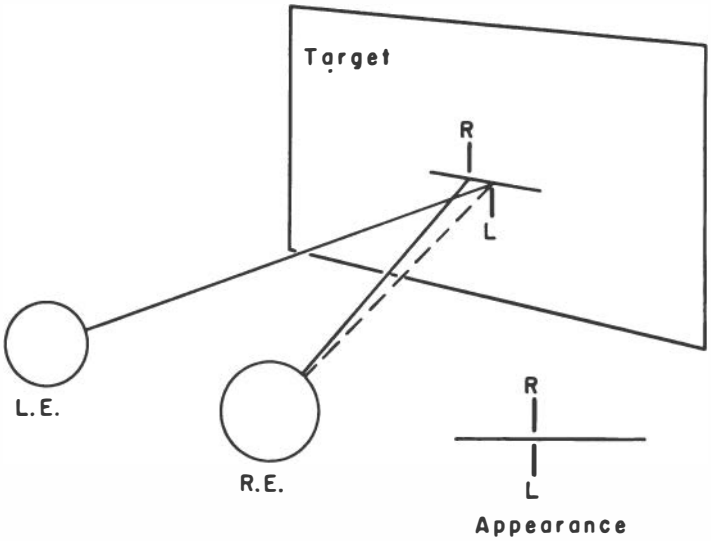

Fig. 8. Type of target used to demonstrate fixation disparity.

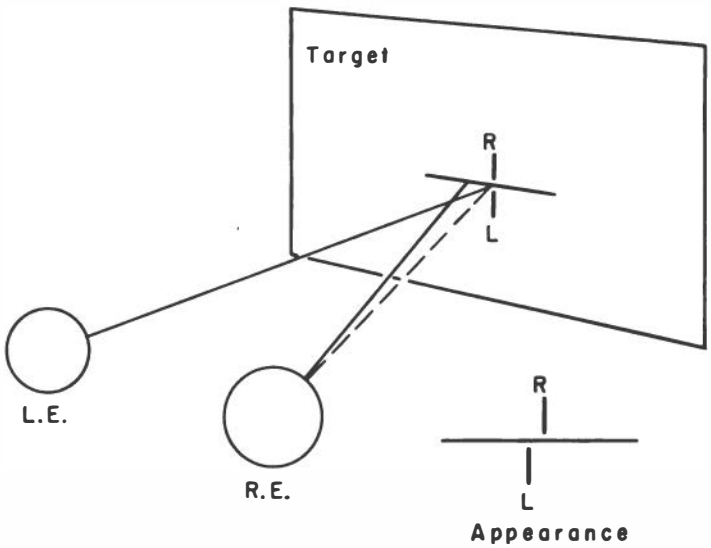

Fig. 9. Type of target, in which lower nonius line can be displaced horizontally, used to measure fixation disparity.

Of special interest are the studies that show the manner in which fixation disparity changes as the oculomotor imbalance between the two eyes is artificially changed by prisms or by ophthalmic lenses. In either case, the relationship between the accommodation and the convergence is altered with prisms by changing the stimulus to convergence (Fig. 10), with lenses by changing the stimulus to accommodation (Fig. 11). The pattern of response of the fixation disparity measurements to these changes varies among subjects.

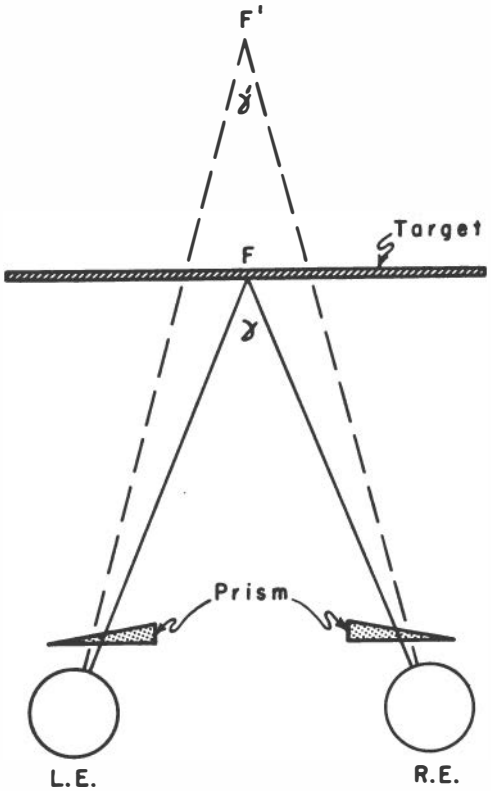

Fig. 10. For target at given observation distance, prisms base-in before eyes reduce angle of convergence of eyes, and thus alter status between accommodation and convergence.

Figure 12 illustrates typical data for a subject measured for both distant vision and near vision (Ogle & Prangen, 1951). The abscissa of this graph corresponds to the prismatic deviation (in prism diopters) introduced: to the right of the origin prisms base-out, which necessitates an increased convergence, and to the left of the origin prisms base-in, which necessitates a decreased convergence of the eyes if fusion is to be maintained. On the ordinate are plotted the measured angles of fixation disparity: above the origin for an overconvergence of the eyes, i.e., an esodisparity (crossed), and below the origin for an underconvergence, an exodisparity (uncrossed)—all in minutes of arc. When prisms are placed before the eyes base-in to cause a decreased convergence an esodisparity is induced, as though the eyes resisted the forced decrease in convergence. When prisms are placed before the eyes base-out to necessitate an increased convergence an exodisparity is induced, as though the eyes resisted the forced increase in convergence. Using the technique of obtaining measurements of fixation disparity by alternately placing prisms of increasing power base-in and then base-out before the eyes, by short exposures of the movable nonius test line, and by not prolonging the

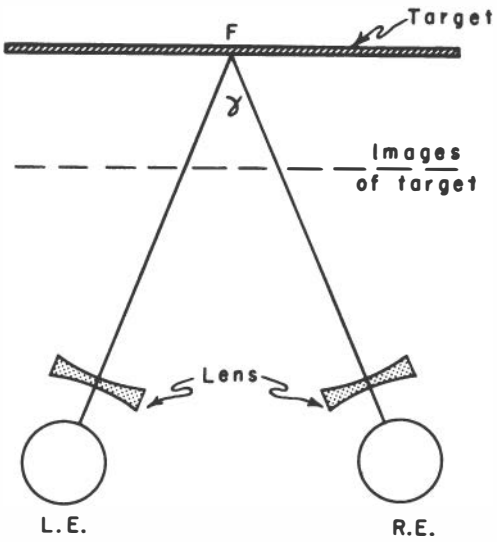

Fig. 11. For target at a given observation distance, ophthalmic lenses of minus power before eyes cause increase in stimulus to accommodation, again altering status between accommodation and convergence.

period of time used for the measurement, one obtains data that can be fitted by a smooth curve. At certain limits of prismatic power the disparity becomes large, and diplopia results, usually dramatically, for any further increase in prismatic deviation. These limits correspond to the usual prism vergences.

For distant vision the subject whose data are shown here is virtually orthophoric, but for near vision there is a large exodeviation of 16 minutes of arc. The point where the curve crosses the abscissa indicates the prism power for which the oculomotor imbalance has been reduced to zero. This particular prism power would be comparable to the measurement of the heterophoria obtained with disassociated vision. In the near graph, then, the equivalent phoria is about 13 prism diopters base-in—an exophoria.

The fixation disparity will also change when lenses are introduced before the eyes to alter the stimulus to accommodation, and thus to alter the accommodation-convergence relationship as shown in the central graph of Fig. 13. On this graph the abscissa corresponds to the lens power in diopters, minus lenses to the right (because there would then be an increased stimulus to accommodation), and plus lenses to the left (there would be a decreased stimulus to accommodation). The range of lens powers that can be used is usually more limited than for prisms.

If one plots the prism power that produces the same fixation disparity as does a given change in the stimulus to accommodation, one

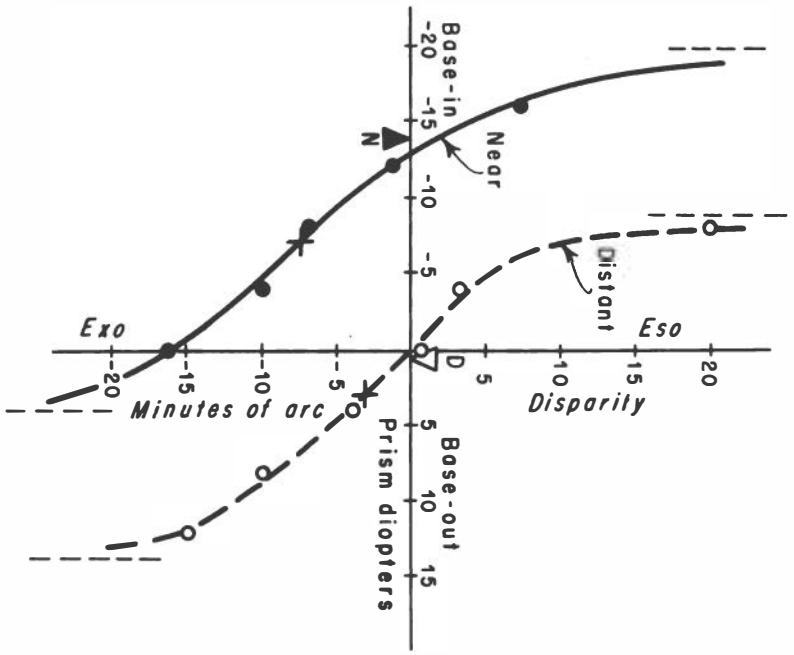

Fig. 12. Two sets of data for distant and near observation distances. Near set shows equivalent phoria of -13 prism diopters.

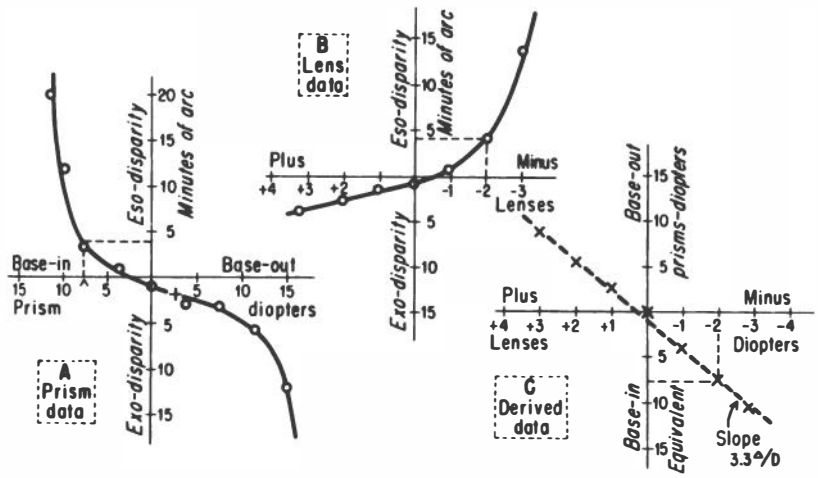

Fig. 13. Sets of data showing change in fixation disparity with both prisms and lenses, and derived graph giving relation between change in prism vergence and change in stimulus to accommodation.

almost invariably obtains derived data that fall on a straight line. The slope of this line is the accommodative-convergence/accommodation ratio (Ogle & Martens, 1957).

It is not desirable to go further here with the phenomenon of fixation disparity. However, on the basis of these studies it may be assumed that the fixation disparity is a measure of the oculomotor imbalance while sensory fusion is maintained and both eyes respond to the same stimulus to accommodation. This measure, then, tells how the oculomotor imbalance changes when changes are made either with prisms or with ophthalmic lenses. It would be concomitantly a measure of the strength of the innervations that must be supplied to the extra-ocular muscles of the eyes to provide the fusional convergence necessary for binocular vision to be maintained on the object fixated.

One might consider the slope of the tangent to the curve at any point as an inverse measure of the strength of the fusion compulsion reflex at that point.

In conclusion, this paper has presented an over-simplified discussion of these topics:

1. the difficulty of determining the exact nature of fusion;

2. the relationship between the fact of sensory fusion and the reflex nature of the innervations to the extra-ocular muscles necessary to maintain sensory fusion;

3. the demonstration of the reflex compulsion for fusional movements that will maintain sensory fusion, but that in normal surroundings may be due to psycho-optical stimuli;

4. the role of sensory fusion of disparate retinal images brought about by Panum's areas;

5. the difficulties of obtaining a measure of the reflex compulsion to fusional movements to preserve sensory fusion;

6. the role of fusional convergence to overcome oculomotor imbalances;

7. finally, the phenomenon of fixation disparity used as a method of measuring, on the one hand, the degree of oculomotor imbalance with fusion maintained, and, on the other hand, the strength of the innervations to the fusional processes to maintain sensory fusion.

References

Brecher, G. A. Quantitative studies of binocular fusion. Amer. J. Ophth., 1954, 38, 134-141.

Burian, H. M. Fusional movements; role of peripheral retinal stimuli. Arch. Ophth., 1939, 21, 486-491.

Hofmann, F. B. Physiologische optik (Raumsinn). In A. Graefe & T. Saemisch, Handbuch der gesamten Augenheilkunde. (2nd ed.) Berlin: Julius Springer, 1925. Vol. 3, Ch. 13.

Ogle, K. N. Disparity limits of stereopsis. Arch. Ophth., 1952, 48, 50-60 (a).

Ogle, K. N. On the limits of stereoscopic vision. J. exp. Psychol., 1952, 44, 253-259 (b).

Ogle, K. N. Fixation disparity and oculomotor imbalance. Amer. Orthoptic J., 1958, 8, 21-36.

Ogle, K. N. The optical space sense. In H. Davson (Ed.), The eye. New York: Academic Press, 1962, Vol. 4.

Ogle, K. N., & Ellerbrock, V. J. Cyclofusional movements. Arch. Ophth., 1946, 36, 700-735.

Ogle, K. N., & Martens, T. G. On the accommodative convergence and the proximal convergence. AMA Arch. Ophth., 1957, 702-715.

Ogle, K. N., & Prangen, A. deH. Further considerations of fixation disparity and the binocular fusional processes. Amer. J. Ophth., 1951, 34(2), 57-72.

VESTIBULAR MECHANISMS AND VISION[1]

Earl F. Miller II and Ashton Graybiel
U. S. Naval School of Aviation Medicine, Pensacola

This report summarizes briefly the results of some investigations carried out at the U. S. Naval School of Aviation Medicine dealing with the vestibular and visual systems under the influence of unusual gravitational-inertial force environments (GIFE). The initial stimulus for these researches stemmed from the need to evaluate the role of the GIFE in causing disorientation in pilots; now, space flight has provided an added impetus. It was learned early that exposure to unusual force environments greatly affected the flyer through the sensory receptors in his vestibular organs, and through them visual mechanisms, and that, in turn, vision and the visual environment also affected the responses to stimulation of the vestibular organs. Thus, exposure to angular acceleration, a physiological stimulus to the semicircular canals, resulted in apparent movement of an object which was fixed in relation to the observer. This has been termed the oculogyral illusion, and its form bears a definite relation to the pattern of angular acceleration. Unusual patterns evoked bizarre effects. The Coriolis phenomenon may be regarded as a special instance of the oculogyral illusion in response to simultaneous rotation of the head about two axes which generates a Coriolis acceleration. Ocular nystagmus may be an associated response to angular and Coriolis accelerations and, when prominent, contributes to the illusion.

When a person is exposed to linear acceleration with a change in direction of the resultant force relative to himself, he not only feels that he is being tilted, but he also perceives an apparent displacement of objects in the visual field which tend to accord with the new direction of the mass acceleration. The visual component has been termed the oculogravic illusion which has quite different characteristics from the oculogyral or Coriolis illusions. An associated phenomenon is ocular counterrolling which is manifested to a greater degree than when a person simply tilts with respect to the gravitational upright.

---

[1]This research was conducted under the sponsorship of the Office of Life Science Programs, National Aeronautics and Space Administration (Grant R-47). Opinions and conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

Simultaneous exposure to linear and angular acceleration alters the responses in a characteristic manner, suggesting a close functional relationship between the two vestibular organs. Positional nystagmus, and positional alcohol nystagmus may be dependent on this relationship.

In carrying out the experiments, an attempt was made to simulate the unusual force environments in the laboratory, but in the case of weightlessness it was necessary to go aloft. It was relatively easy to control vision and the visual environment, and it was possible to control the inputs from the semicircular canals and the otolith apparatus by the use of subjects who had lost the function of the canals and, probably, also of the otoliths. The investigations sought to exploit these vestibulo-visual phenomena: (a) in testing the function of the semi-circular canals and the otolith organs; (b) in using these phenomena as indicators in the investigation of different psychophysiological mechanisms including adaptation; and (c) in attempting to show how these mechanisms are affected under the unusual force environments to which man may be subjected in an aircraft or space vehicle.

Otolith Organs and Vision

Linear acceleration, considered the adequate stimulus to the macular end organs, can be varied to evoke changes in overt behavior by repositioning the head (actually the otolith organs themselves) with respect to gravity, moving it in a circular path at a constant rate, or in a rectilinear path at an accelerating rate. Direction of the stimulus force is controlled by orienting the head with respect to the resultant gravitational-inertial force, which varies in magnitude as a function of velocity. Normal gravitational acceleration can be counteracted completely or partially within the earth's gravitational field by Keplerian trajectory flight maneuvers. The otolith organs of humans can be probed remotely by linear acceleration in a way analogous to the direct mechanical stimulation of these organs in animals. It is possible to apply forces of various magnitudes in specific directions relative to the anatomical spatial arrangement of the otolith organs within the skull; the mode of action and role in perception of the otolith organs can then be determined indirectly by measuring external changes such as occur in ocular counterrolling and egocentric visual localization. Subjects with known labyrinthine defects offer a means of evaluating the extent to which extra-labyrinthine factors are involved in these external signs of inner ear function.

Counterrolling

When certain experimental procedures are followed, the conjugate rolling movement of the eyes around their lines of sight opposite to the lateral inclination of the head is generally held to be a direct reflex originating in the otolith organ. The distinct advantage of having an external indicator of otolith activity which is not under voluntary control has been

outweighed in the past by the great difficulty in obtaining precise measurements of the rolling movements. Throughout the long colorful history of counterrolling studies, several methods of measuration have been used (Miller, 1962). All have as a common basis the selection of anatomical landmarks on the eye to establish a reference plane containing the line of sight for specifying the rotation of the eye around its line of sight. The most accurate of these older methods yielded a measuring error which was large even in relation to the maximum amount of counterrolling, in some cases less than six degrees (°), that can be evoked by head inclination.

A method involving photography of natural landmarks on the iris was devised to meet the requirement of greater precision in measurement. A solution to the problem of measuring very small amounts of movement of these landmarks was found in simple magnification. In this procedure, the film image of the entire eye is enlarged over 300 times the actual eye size by projection onto a distant screen. Measurement of angular torsional movement around the center of the pupil is then accomplished by superimposing upon each test image in succession a second projected image of the subject's eye serving as a standard of comparison. More complete details of this measuring technique have been published (Miller, 1962). It is sufficient for this discussion to point out that a high degree of accuracy and reliability in measurements (= ± 5 minutes [min] of arc) is possible with this procedure.

Normal subjects. Counterrolling measurements using the photographic technique have been made on several normal individuals tilted in 25° steps up to ± 75° from the gravitational vertical (Miller & Graybiel, 1962a). Each of these subjects revealed a qualitatively similar counterrolling response (Fig. 1) to head inclination, but quantitatively there were interindividual differences. There were also significant right-left differences in some individuals but not in others. A more extensive study (Miller, 1962) was also conducted in which measurements were made at every 15° within the frontal, sagittal, and two intermediate planes. Maximal compensatory torsional eye movement was found in the frontal plane, somewhat less in the intermediate planes, and none at all in the sagittal plane.

The absence of appreciable counterrolling when the head is tilted in its sagittal plane does not justify any inference that compensatory eye reflexes arising in the otolith organs do not exist when tilting in this plane. On the contrary, there is evidence that the eyes move reflexly in a vertical direction directly counter to the fore-and-aft tilting of the head. In the counterrolling experiments, innervation to elevate or depress the eyes was compensated by counter-fixational innervation. Counterrolling was always found to occur (Fig. 2) opposite to the lateral component of head tilt and to increase fairly rapidly up to maximum at a head inclination between 60° and 90°. From this point on counterrolling decreased but at a lesser rate than it increased, reaching about zero when

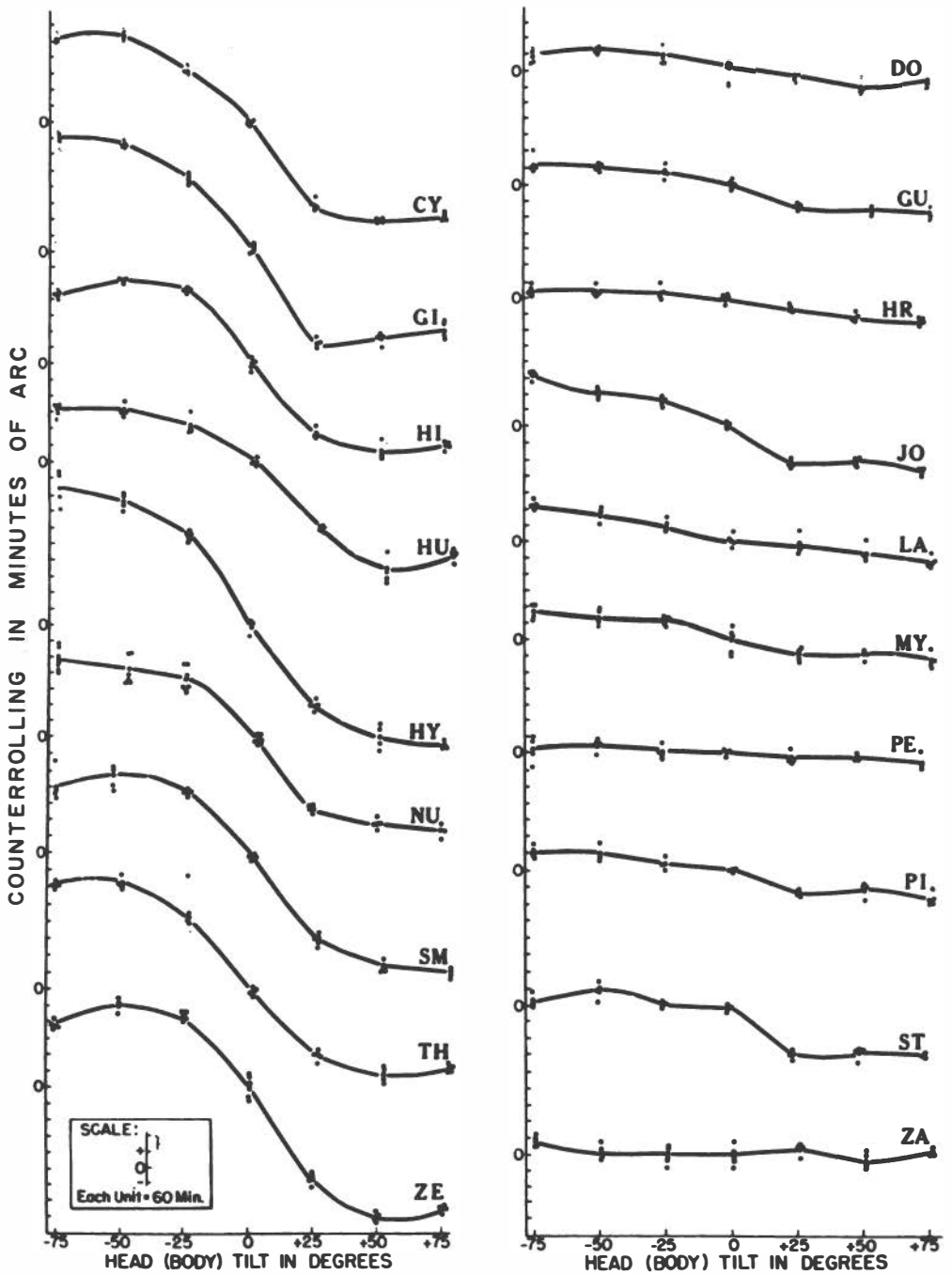

Fig. 1. Mean counterrolling values plotted as function of leftward and rightward tilt (left column: normals; right column: labyrinthine-defective (L-D) subjects; closed circles average values in minutes of arc; open circles: values for different trials at given body position).

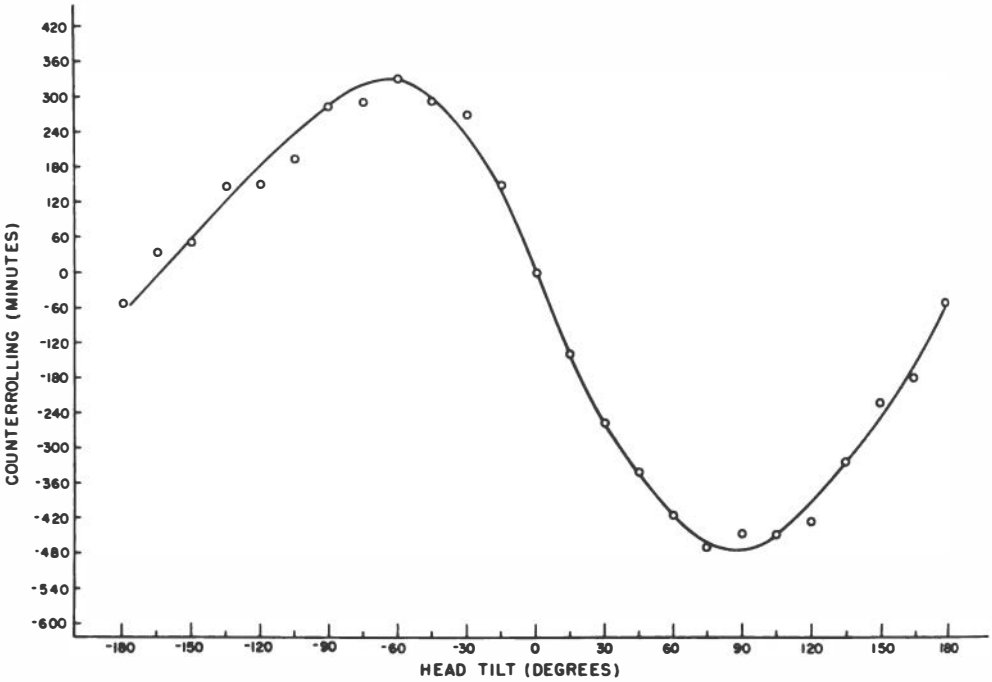

Fig. 2. Counterrolling (average values) as function of lateral head tilt.

the head was positioned vertically downward. The curve in Fig. 2 represents the average of several values obtained at each position for each head position. A considerable amount of variability among individual measurements far greater than the measuring error has been found in almost every subject tested, indicating that a certain amount of physiological unrest also exists with respect to the antero-posterior axis of the eye. This variability has been observed by several authors using various measuring techniques.

By the use of counterrolling and known anatomical data a theory ("inward shearing") was developed in an attempt to explain the mechanism of otolith stimulation. It was proposed that each of the otolith organs (utricles and saccules) can be stimulated physiologically only by a shearing force applied inwardly, i.e., toward the median sagittal plane. This unidirectional response, furthermore, reaches its maximum when the direction of the force (gravity) is parallel to the individual macular planes. In its active zone the response of each otolith, as indicated by counterrolling movements, appears to vary as a cosine square function of the angular displacement of the inward direction of the macula from the force of gravity. If the response were proportional to the gravity component in the inward direction of the macula, then the response would be proportional to the cosine of this displacement. But this simple relationship did not conform to the findings. The structure of the otolith organ apparently is such as to dampen the effect of gravity (G) in yielding the cosine square

function. A more complete discussion of these factors has been presented elsewhere (Miller, 1962). An important aspect of the general theory is the assumption that the saccules, like the utricles, act as gravireceptors and, when activated, contribute a smaller, yet significant effect upon counterrolling. There are several studies that would tend to support the supposition that the saccule functions as an equilibrial organ.

Labyrinthine-defective subjects. The photographic technique is particularly useful in measuring smaller-than-normal amounts of counterrolling that are found in individuals with disease or otherwise damaged vestibular organs. Investigators with less sensitive measuring devices had the difficult task of differentiating between a relatively large measuring error and a possible small residuum of otolith function. Information gained from precise measurements of otolith organ activity is needed to evaluate completely the inner ear organ triad and would complement the now routine audiometric and caloric irrigation tests of the other two auricular organs. If counterrolling, as has been assumed, is a specific indicator of otolith activity, then the level of function should be revealed in the character of the counterrolling response. In order to examine this theory, ten deaf subjects with bilateral loss of the semicircular canals were used as subjects for counterrolling measurements (Miller & Graybiel, 1962a). As can be seen in Fig. 1, these labyrinthine-defective (L-D) subjects did not disclose the characteristic pattern found in normal subjects in most instances. The magnitude of the response was in all cases less than in a comparable normal group. In some instances, there was no definite evidence of counterrolling; in others, it was limited to one direction of tilt; and in still others there was a small but regular dependence of counterroll with the successive increase in bodily tilt. The highly significant differences between the normal and L-D groups must have been due to loss of function of the auricular sensory organs. More specifically, since there is no evidence that the counterrolling reflex is released by the organ of Corti, and insufficient evidence that it originates in the semicircular canals, but good evidence that it is released by the otoliths, it was concluded that the reduction in counterrolling in these cases was the result of injury to the otoliths. Interindividual differences in the L-D group are best explained by the presence of some residual otolith function. It was proposed that a single index—counterrolling (CI)—calculated as one-half of the difference between the greatest maximum roll associated with leftward and rightward tilt be used to describe the functional status of the otolith organs for a given individual.

Effect of change in gravitational inertial force environments. Counterrolling can also serve as an indicator of the effect of physiological deafferentation of the otolith organs brought about by eliminating or reducing the gravitational inertial force environment. The counterrolling response of six normal and six L-D subjects was measured at five different tilt positions under zero G, 1/2 G, and standard G conditions. The average results of the normal and L-D groups are portrayed in Fig. 3. In the case of the normal subjects otolith activity as indicated

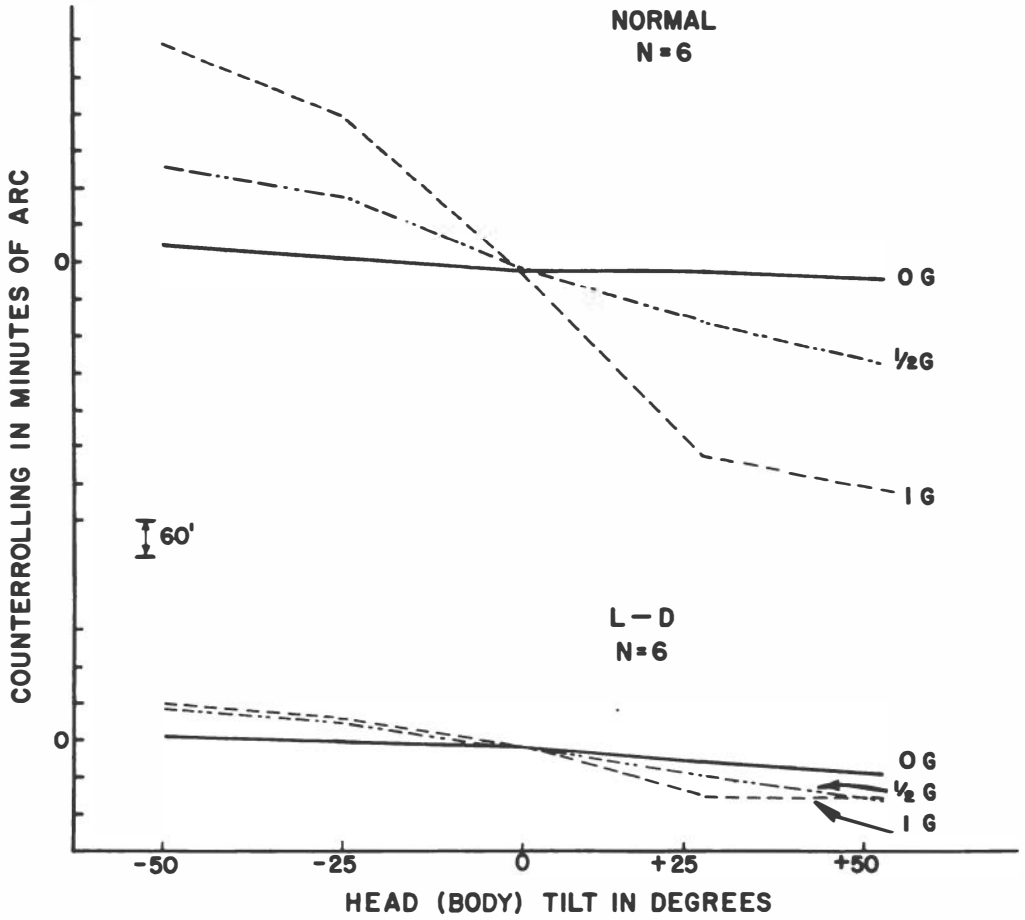

Fig. 3. Counterrolling as function of magnitude of gravitational force (zero G, 1/2 G, 1 G) and head (body) position with respect to direction of force in normal and labyrinthine defective (L-D) subjects.

by counterrolling response decreased in a regular fashion as the force was reduced. In the weightless condition tilting the normal individual would appear to have little effect upon the output of the otolith organs under the conditions of the test. The L-D subjects manifested a greatly reduced but similar pattern to the normals. This could be accounted for either as a residuum of otolith function in certain of the L-D subjects, or as an effect of stimulation to extra-labyrinthine source(s) of tonic innervation to the extraocular muscles. The former explanation seems more reasonable based on the results of the oculogravic illusion test and the care exercised to eliminate cervical, fixational, or binocular sources of cyclorotational eye movement. Even if these factors were involved, their importance is not great, as evidenced by the small maximum amount of counterrolling in the L-D group; thus, it seems more reasonable to assume that otolith function has been revealed. It is interesting to note

that, in the normal group of subjects, the 1/2 G curve falls somewhat short of the midway points between zero G and 1 G as might be predicted. The significance of this finding is not known.

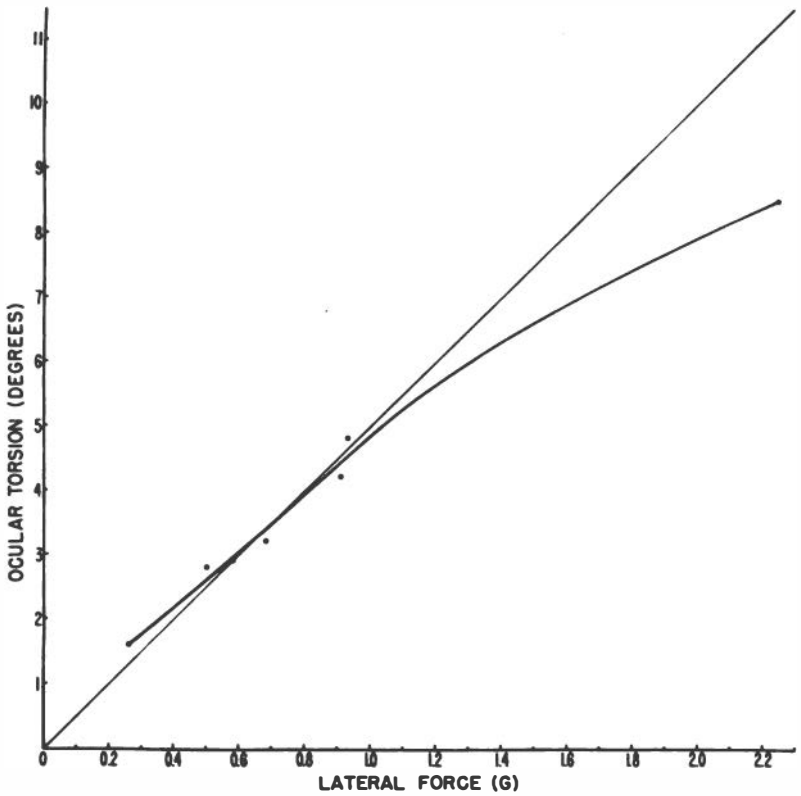

Fig. 4. Degree of counterroll as function of magnitude of force acting laterally on body (head).

Information concerning the effect upon otolith activity (counterrolling) of increased gravitational-inertial force is provided by another study (Woellner & Graybiel, 1959). As shown in Fig. 4, the counterroll varies as a function of the magnitude of the lateral force, even beyond the standard level of 1 G. This demonstrates the important fact that the counterrolling response is normally stimulus bound and its limit is not reached even with a lateral force of 2.25 G. The function at this higher level, however, is no longer linear.

Egocentric Visual Localization

Aubert's phenomenon and its variants. Man's absolute localization of objects in space is made with respect to his egocentric frame of reference. This frame of reference in turn is influenced by the action and interaction of certain body mechanisms providing visual, vestibular,

tactual, proprioceptive, and other cues. When adequate visual cues are visible, they normally dominate all others so that judgments of the principal axes of space are quite precise, stable, and easily rendered (Miller & Graybiel, 1963a). Removal of empirical visual cues, on the other hand, reveals considerable errors in perception, plus loss of stability and ease in localization, especially when the direction of the gravitational (inertial) force deviates appreciably from the longitudinal axis of the head (body). In the upright position, judgment of horizontality in normal individuals is not appreciably affected by the removal of visual cues. When individuals are placed in a recumbent position, however, and background cues are removed, suddenly they observe, after a brief lag period, a gradual spontaneous rotation of the phenomenal horizontal up to a maximum displacement typical for a given individual. Superimposed upon these changes is the fluctuant movement of the apparent horizontal—rotary autokinesis (Miller &Graybiel, 1963a). The time course of these illusions in four subjects is presented in Fig. 5.

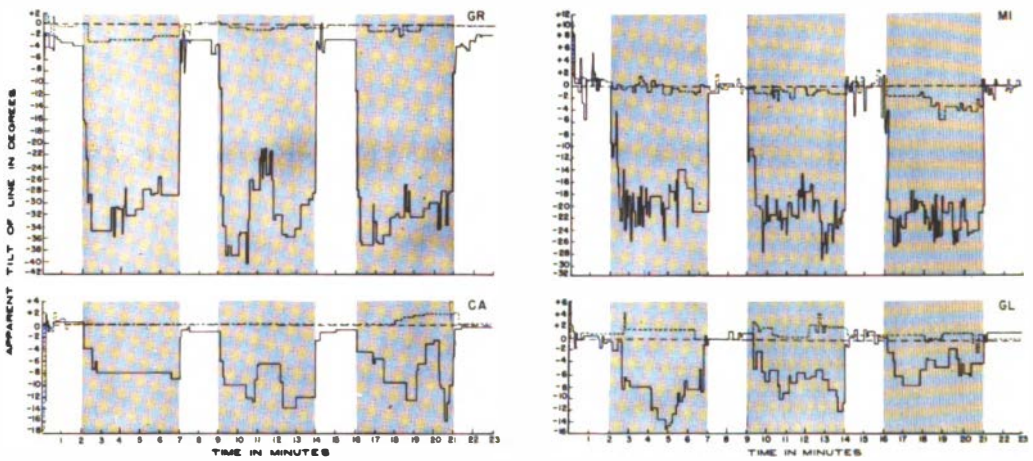

Fig. 5. Time course of perception of horizontality for each of four subjects in upright (broken line) or recumbent (continuous line) posture with (unshaded strips) and without (shaded strips) visual reference cues.

In addition to these relatively small fluctuations about the considerable average deviation, the average level of deviation itself was found to vary from test period to test period as illustrated in Fig. 6 (heavy lines represent average of the several daily curves [thin lines]). The variance in magnitude of deviation, however, does not appear to occur in a random manner but shows a regular dependence on the position of the head (body). It is, therefore, possible to describe a characteristic qualitative pattern of response, even though there are quantitative intertrial differences. In the three subjects tested at 10° intervals throughout the range of head tilts within ±90° from upright, the apparent visual horizontal tended to rotate in the same direction (E-phenomenon) as head (body) tilt in

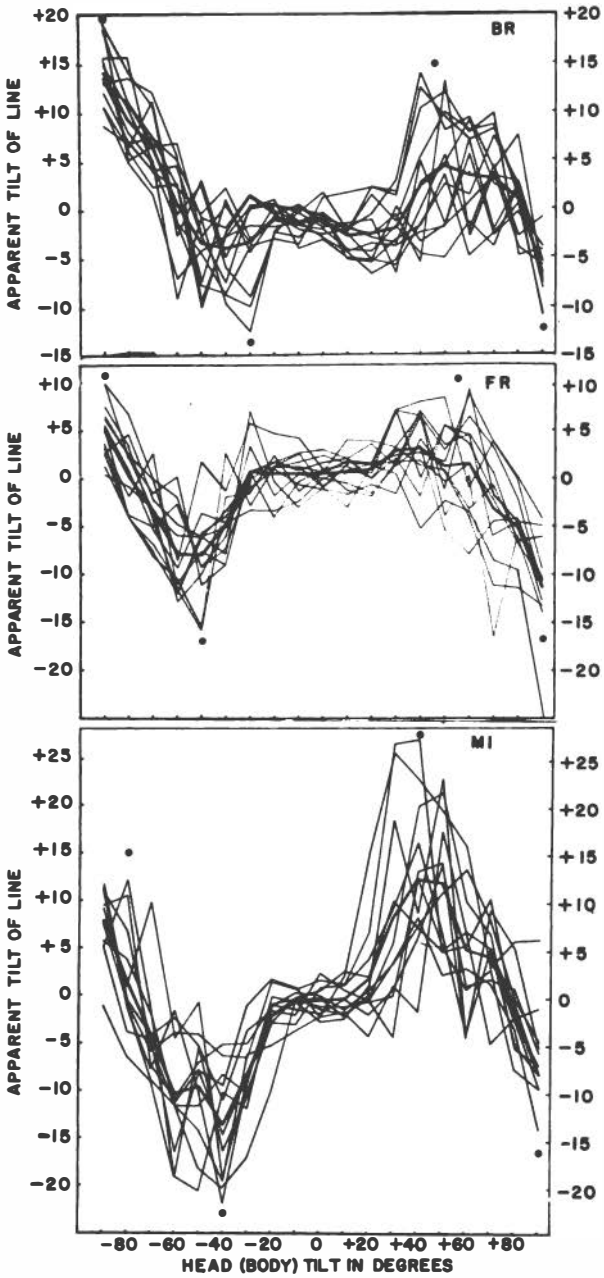

Fig. 6. Apparent position of visual horizontal as function of head (body) tilt in degrees as tested in three subjects during each of several sessions. (Heavy lines represent average of individual session curves [thin lines].)

moderate amounts from upright, reaching a peak bilaterally at approximately 40° to 50°. Then it reversed direction, causing the magnitude of deviation to decrease until the subjective was coincident with the objective horizontal. Tilting of the head beyond this point resulted in further displacement in the direction counter to head inclination (A-phenomenon). In all cases the deviation in the Aubert direction continued to increase on the average in proportion to head inclination beyond the "neutral" point, so that the greatest deviation occurred at the maximum positions of tilt (±90°) used in this study.

Considerable information about these curious illusions has appeared in the literature since Aubert's original work, but quantitative data are scarce, especially in larger angles of head tilt. The underlying mechanisms are still not completely known. Counterrolling, a plausible explanation of the E-phenomenon involving the visual system only, has been cited by certain authors. If this be the sole or primary cause of this phenomenon, L-D subjects without this compensatory eye movement would be expected to manifest little or no E-phenomenon. A recent study (unpublished) provides quantitative proof that this theory is untenable. A group of L-D subjects compared to a similar group of normals revealed significantly more deviation in the E direction in certain moderate angles of tilt.

An experiment (Miller & Graybiel, 1963b) was also conducted in which a group of subjects with known bilateral labyrinthine defects was compared with a group of normal persons with respect to ability to judge horizontality as a function of upright, recumbent, and inverted posture. The fact that the Aubert illusion and its variants have been reportedly observed by certain deaf subjects by no means proves that the labyrinths do not influence this perception. On the contrary, although similar qualitative responses were found among all subjects, there were significant quantitative intergroup differences. When upright, the normals were able on the average to maintain their accuracy, while the L-D subjects deviated significantly in their settings to the apparent visual horizontal when empirical visual cues were removed. Both groups of subjects in the recumbent position perceived the Aubert illusion, but the magnitude of the illusion was considerably less in the normal group. When inverted, both groups were less accurate in their estimates in the dark, but no significant intergroup difference was found. In spite of the fact that there was some overlap in the group distributions of settings obtained in the upright and recumbent positions, indicating extra-labyrinthine factors were involved, the intergroup perceptual differences are best explained as an effect of the loss of vestibular funotion in the L-D subjects. It was concluded that the otolith organs in man act to increase his accuracy in egocentric visual localization, at least in the upright and recumbent positions. This conclusion is in alignment with an earlier finding (Miller & Graybiel, 1962b) in which a group of L-D subjects as compared to a group of normals perceived significantly greater amounts of autokinesis, another indicator of egocentric visual localization.

Oculogravic illusion—normal subjects. Man seated upright can in effect be tilted by generating, as in the human centrifuge, a centrifugal force which is vectorially added to the standard gravitational force; as a result, upright is perceived in the direction of the resultant gravitational-inertial force. Tilting the subject with respect to gravity differs in one important aspect from tilting the gravitational-inertial resultant force with respect to the subject. The magnitude of the resultant force is always larger in the latter situation and bears a fixed but nonlinear relation to the angle phi.

It has long been known that normal persons perceive the oculogravic illusion, and some of its characteristics have been systematically investigated (Graybiel, 1952). Recent evidence (Clark & Graybiel, 1962) would indicate that the oculogravic illusion, as was found for the Aubert illusion, is a function of a number of complex factors other than input from the otolith organs. For example, this illusion increases with a reduction in visual framework exposed prior to the rendering of a judgment of horizontality. In making this judgment, however, using the frame of reference there was no evidence of adaptation in subjects exposed to constant centripetal force for four hours.

Normal subjects have been found to judge the visual horizontal in a similar manner which is more or less in accord with the resultant force environment (Graybiel, 1952). The curve (Fig. 7) depicting the mean

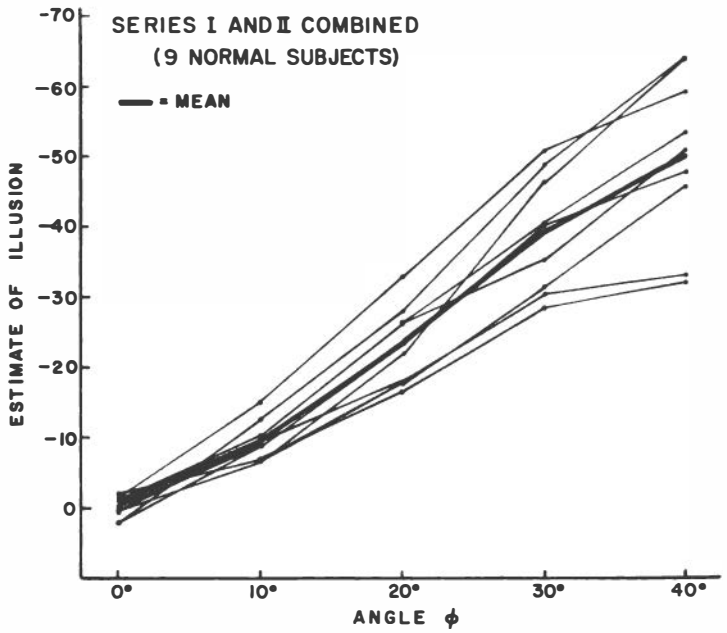

Fig. 7. Estimates of oculogravic illusion (OGI) by normal subjects. Single settings of luminous line.

values obtained by discrete settings to the apparent horizontal is typical of normal subjects. When continuous adjustments of the visual horizontal are made, a long delay is regularly observed between the time of peak acceleration and the time of the subject's peak response. This is perhaps due in part to a response lag of the peripheral sense organ, but is thought to be primarily due to delay in central nervous system mechanisms. A delay of similar character was seen in the static tilt studies.

Oculogravic illusion—labyrinthine defective subjects. Failure to perceive the oculogravic illusion has been ascribed to loss of function of the otolith apparatus, but few studies have been carried out on L-D subjects, and few quantitative data are available to validate this claim. A study (Graybiel & Clark, 1962) was, therefore, conducted to determine the validity of the oculogravic illusion as a specific indicator of otolith function. A group of deaf subjects having complete functional loss of their semicircular canals but with unknown functional loss of the otolith organ was compared with a group of normal subjects in regard to the oculogravic illusion. In selecting naturally occurring experimental subjects with labyrinthine defects, the usual procedure is to screen a group of deaf persons, selecting those who also have lost the function of the semicircular canals. In doing this, it was not assumed that loss of all canal function was a valid indication of the complete loss of otolith function. Indeed, evidence from counterrolling and the study just cited indicates that this assumption may be erroneous in some cases. The mean discrete settings to the apparent horizontal of the L-D subjects, in contrast to the normal group, were not characteristic for all members of the group (Fig. 8). Indeed, the variability was so great that consideration of the results of individual subjects in this group was necessary. Differences among subjects in the L-D group are explicable on the assumption that in certain members there was a specific level of residual function of the otoliths, and in others it was lost completely. Unilateral labyrinthine loss does not abolish the illusion (Graybiel & Niven, 1953).

Semicircular Canals and Vision

Nystagmus, induced by thermal stimulation or in response to angular or Coriolis acceleration, serves as an indicator of semicircular canal function, but its use in this regard is complicated by factors which may alter or abolish it. For example, it can be increased by mental activity. On the other hand, it can be reduced by introducing a visual fixation field, or by requiring a subject to repeat a particular pattern of vestibular stimulation. The reduction in nystagmic response through stimulus repetition may stem from a loss of arousal or drowsiness, but there is also evidence to show that nystagmus may be actively suppressed. Restriction of head movements to certain patterns diminished nystagmus during a 64-hour exposure to rotation at 5.4 RPM within a 15-foot diameter rotating room (Guedry & Graybiel, 1962). Efforts to maintain alertness by instructions did not restore nystagmus. Moreover, the nystagmus measured following the rotational period was opposite in direction to the

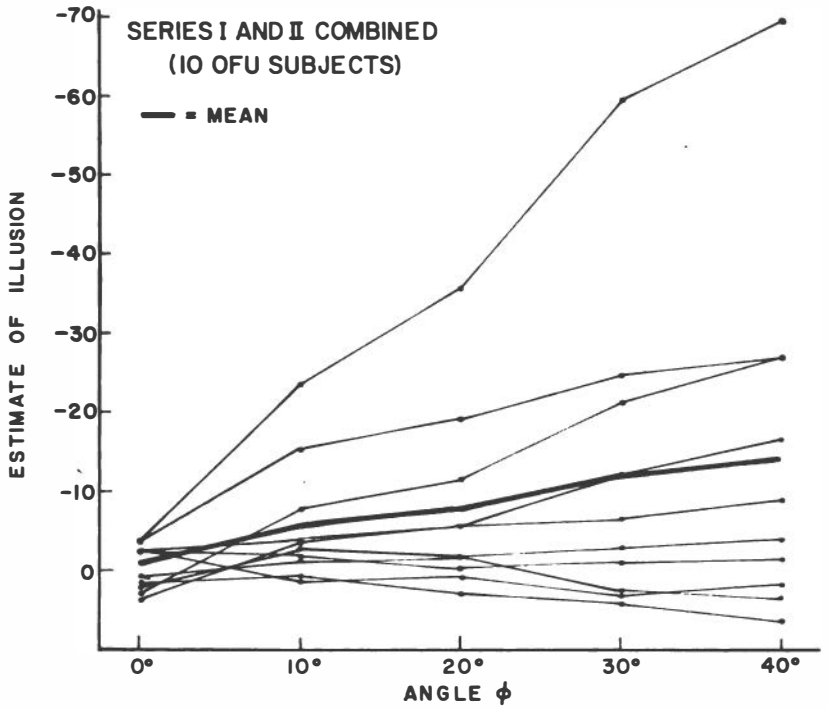

Fig. 8. Estimates of oculogravic illusion (OGI) by labyrinthine-defective subjects. Single settings of luminous line.

response produced by the same head movement during rotation, indicating that it was a conditioned response inasmuch as the stimulus was no longer Coriolis acceleration. Similar evidence of habituation was obtained from the subjective reports of the apparent motion (oculogyral illusion) of a target light in an otherwise dark room. For conditioning purposes, head movement was confined to one quadrant of the frontal plane. Subsequent tests were then made in this quadrant (practiced) and the opposite quadrant (unpracticed). Dramatic reductions in response occurred in the practiced quadrant, but habituation was not transferred to the unpracticed quadrant (Fig. 9).

Vestibular Organ Interaction and Vision

It is obvious that, in many areas, research concerning the interaction between vision and the vestibular organs has only begun. Differentiating the function of the otolith and cupula organs has occupied the interest of many investigators in the past, but the complete understanding of vestibular function seems dependent also on experimental programs which are directed at the physiological connections between the two types of vestibular organs and their combined influence upon vision.

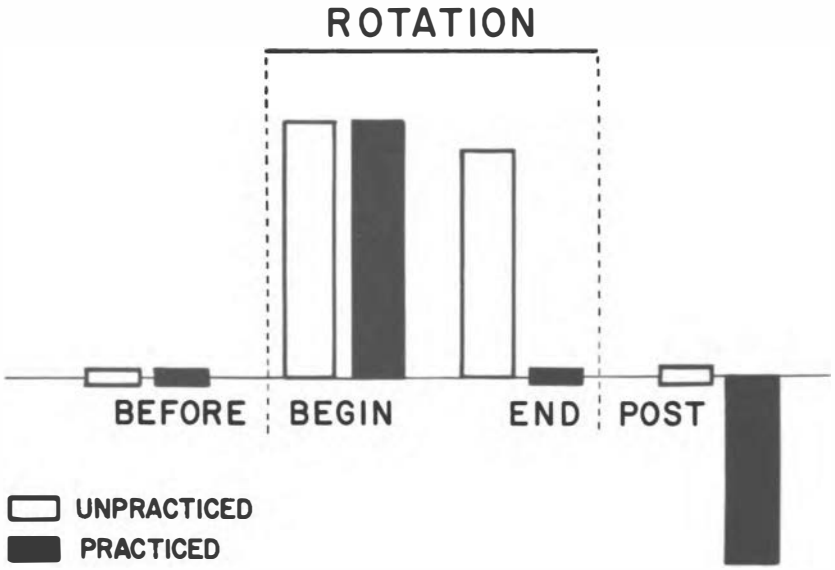

Fig. 9. Comparative magnitude and direction of Coriolis illusion associated with single head movements before, during, and after prolonged rotation at 5.4 RPM. Tests carried out at 7.5 RPM.

Based on overwhelming evidence, there can be little doubt that the so-called vestibular nystagmus is released by the action of the semicircular canals and, as in the examples cited above, is modified by the central nervous system. A basic question that now needs to be answered is whether under special circumstances the otolith organ may also either release it independently or contribute an essential element for its release by the canals. The fact that nystagmus can be elicited in certain individuals by simply changing the position of the head is strong evidence that the otolith organ is involved in this ocular response.

References

Clark, B., & Graybiel, A. Visual perception of the horizontal during prolonged exposure to radial acceleration on a centrifuge. J. exp. Psychol., 1962, 63, 294-301.

Graybiel, A. Oculogravic illusion. Arch. Ophthal., 1952, 48, 605-615.

Graybiel, A., & Clark, B. Validity of the oculogravic illusion as a specific indicator of otolith function. Pensacola: USN Sch. av. Med. (BuMed) Rep., 1962, No. 67; & NASA Order No. R-37. (Proj. MR005.13-6001, Subtask 1)

Graybiel, A., & Niven, J. I. The absence of residual effects attributable to the otolith organs following unilateral labyrinthectomy in man. The laryngoscope, 1953, 63, 18-30.

Guedry, F., & Graybiel, A. Compensatory nystagmus conditioned during adaptation to living in a rotating room. J. appl. Physiol., 1962, 17, 398-404.

Miller, II., E. F. Counterrolling of the human eyes produced by head tilt with respect to gravity. Acta Otolaryng. Stockholm, 1962, 54, 479-501.

Miller, II., E. F., & Graybiel, A. A comparison of ocular counterrolling movements between normal persons and deaf subjects with bilateral labyrinthine defects. Pensacola: USN Sch. av. Med. (BuMed) Rep., 1962, No. 68; & NASA Order No. R-47. (Proj. MR005.13-6001, Subtask 1) (a)

Miller, II., E. F., & Graybiel, A. Comparison of autokinetic movement perceived by normal persons and deaf subjects with bilateral labyrinthine defects. Aerospace Med., 1962, 33, 1077-1080. (b)

Miller, II., E. F., & Graybiel, A. Rotary autokinesis and displacement of the visual horizontal associated with head (body) position. Aerospace Med., 1963, 34, 915-919.

Miller, II., E. F., & Graybiel, A. Role of the otolith organs in the perception of horizontality. Pensacola: USN Sch. av. Med. (BuMed) Rep., 1963, No. 80; & NASA Order No. R-47. (Proj. MR005.13-6001, Subtask 1) (b)

Woellner, R. C., & Graybiel, A. Counterrolling of the eyes and its dependence on the magnitude of gravitational or inertial force acting laterally on the body. J. appl. Physiol., 1959, 14, 632-634.

SOME RECENT ADVANCES IN INSTRUMENTATION AND PROCEDURES IN VISION RESEARCH

Robert Boynton, Chairman

INTRODUCTORY REMARKS BY THE CHAIRMAN

Robert M. Boynton
Department of Psychology
University of Rochester

Progress in science depends to an important extent on the development of new experimental techniques. In the interdisciplinary subject of visual science, such developments sometimes come from the work of those directly concerned with vision, and sometimes from those whose interests are quite different. This fact is reflected in the four papers presented in this section. Two of the authors, Drs. Krauskopf and Cornsweet, are recognized as outstanding vision researchers whose many contributions are well known. The other two authors, Drs. Blough and Stark, are not primarily vision-oriented, but have worked intensively on visual problems since such problems were amenable to attack by their methods.

The oldest of the techniques reported here, that of stabilized images, is only about ten years old. Since the first, nearly simultaneous, and independent reports of Riggs, Ratliff, Cornsweet, and Cornsweet and Ditchburn, in the early 1950's, many experiments have been devoted to this subject, whose importance seems to have been recognized instantly. The fact that the visual percept fades out completely under some conditions of retinal image stabilization serves to emphasize that the visual receptors tend to respond to change in illumination level, rather than to steady levels as such. Such effects are most easily observed with low contrast objects (or very small test objects) in peripheral vision, where the fading may be observed with careful fixation, even without the use of stabilizing optics (the so-called Troxler phenomenon). But with large, high-contrast, centrally-viewed stimuli, it is sometimes observed that fading does not occur, even with stabilizing optics, or that it is transitory, with vision returning unpredictably from time to time. Dr. Cornsweet believes such results are artifacts, usually associated with slippage between the eye and the contact lens which supports a mirror that is part of the stabilizing optics used in many experiments. He reviews some of the various methods and comments particularly upon the problem of artifact, which is very important for any theoretical interpretation of the results.

The other full-time vision expert, Dr. Krauskopf, reports on methods which had their start with the work of Campbell, Rushton,

Brindley, and Hagins in Cambridge, England, and Flamant in Paris in the middle 1950's. Images upon the fundus of the eye have, of course, been observed ophthalmoscopically for more than one hundred years but, until recently, these could not be easily measured due to the lack of sufficiently sensitive non-visual sensors. Photomultipliers have provided the needed detectors The modern methods have been applied principally to two problems: (a) the bleaching of retinal photopigments, and (b) measurements of the quality of the retinal image. Dr. Krauskopf, from his expert knowledge, explains the difficult technical problems involved in making such important measurements.

The use of animal subjects in sensory experiments is necessary because many physiological experiments can be performed on animals which are not possible on human subjects. Psychologists for many years have used animals in a variety of experiments in which visual discriminations were involved The methods used have been generally very different from those one would use with human subjects, because of a feeling that it would be impossible to instruct animals to make the kinds of discriminations that human subjects make (and then only highly-trained ones) in the experiments of classical visual psychophysics. The development of animal psychophysics, which began with the work of Blough and Ratliff at Harvard in the middle 1950's, is predicated on the assumption that it is possible to do classical psychophysical experiments with animals, provided that one is clever enough to succeed in "telling" the animal what he is to do. The procedures that are proving effective are those of operant conditioning introduced originally by Professor B. F. Skinner. An important aspect of these procedures is that they are automated: it takes a very long time to train an animal for some psychophysical problems and the patience of the experimenter is much less strained if he can put the animal in the box, turn on the automatic controls, and read a book, or even leave the laboratory. It should be mentioned that there is art as well as science involved in these training procedures. Dr. Blough, in addition to being a first-rate scientist, is one of the real artists in this field.

A few years ago it would have seemed ridiculous to predict that electrical engineers would some day come to have an intense interest in human sensory processes. Now this is a commonly accepted fact, and in a double sense. It is obvious that one's conceptualization of the visual system may be improved by applying progressively more sophisticated models borrowed from other areas, provided that the models really seem to fit, since much, if not most, theorizing about complex systems involves the use of models. It is perhaps less obvious that the study of biological systems may help to provide engineers with better solutions to their non-biological problems, but there is now a field of inquiry (bionics) dedicated to that proposition.

To get work started in a new field often requires an unusual human being whose background and talents spread beyond the usual boundaries

set up by the various academic and applied disciplines. Dr. Stark is such a man—a physician turned electrical engineer who has been able to bring the biological and engineering approaches together. Although classical physiologists recognized long ago that there are many servo-systems and feedback loops in the nervous system, they did not use such terminology and they knew little about man-made servo devices, many of which are very recent. Meanwhile, the electrical control engineers have been developing some very sophisticated concepts, devices, and mathematical techniques for the analysis of servomechanisms. Dr. Stark describes how such methods may be applied to the study of such biological servosystems as the pupillary control mechanism, and the system which controls eye movements.

It is to be expected that for many readers one or more of the four areas of methodology described here will be encountered for the first time, and it is to be hoped that this encounter will lead to further reading and to the development of new experiments and applications that might not otherwise have been forthcoming. For others, who may already have some knowledge about all four areas, up-to-date reviews by experts who are working with the methods should be useful.

VISUAL PSYCHOPHYSICS WITH ANIMALS

Donald S. Blough
Department of Psychology
Brown University

The past few years have seen renewed interest in animal psychophysics. The impetus has come largely from the desire to obtain physiological and psychophysical data from the same or comparable species, rather than relying on lower animals for the one and human observers for the other. New behavioral techniques are making this convergence increasingly practicable.

In many respects, the new methods are similar to classical techniques in which the animal chooses one of two stimuli by running or jumping to it, and is rewarded for "correct" responses. The new methods, however, are more efficient, and, in some cases, more sensitive. The animal stays in one place and responds rapidly to keys or levers; it remains unhandled for long periods and makes a high number of discriminative responses per minute.

Four illustrative techniques are cited here. All of them use pigeons as subjects, but, though the pigeon is a highly visual animal, there is reason to believe that the methods are applicable generally. Variations with monkeys, rats, and other species have been used successfully in visual and auditory work. Each procedure does two things: (a) it presents stimuli and records responses to these stimuli, and (b) it sets up and maintains the discriminative behavior through reinforcement techniques. To do these things some rather complex manipulations are necessary and they can be only roughly sketched here. (See references for more complete descriptions of some of the methods.)

The first method is a tracking technique for determining the absolute detection threshold through time. The subject stays in a dark enclosure, and it responds to visual stimuli by operating two keys. The essentials of the situation as used with the pigeon are shown in Fig. 1. The bird is first trained to peck either key for food reward. Next, it is trained to peck Key A when the stimulus is visible, and Key B when the stimulus is off. If it performs this task correctly it will "track" its absolute threshold, for pecks on Key A automatically reduce the intensity of the stimulus, while pecks on Key B increase the intensity. The method is similar to, and derives from, Bekesy's technique (1947) for determining the human auditory threshold.

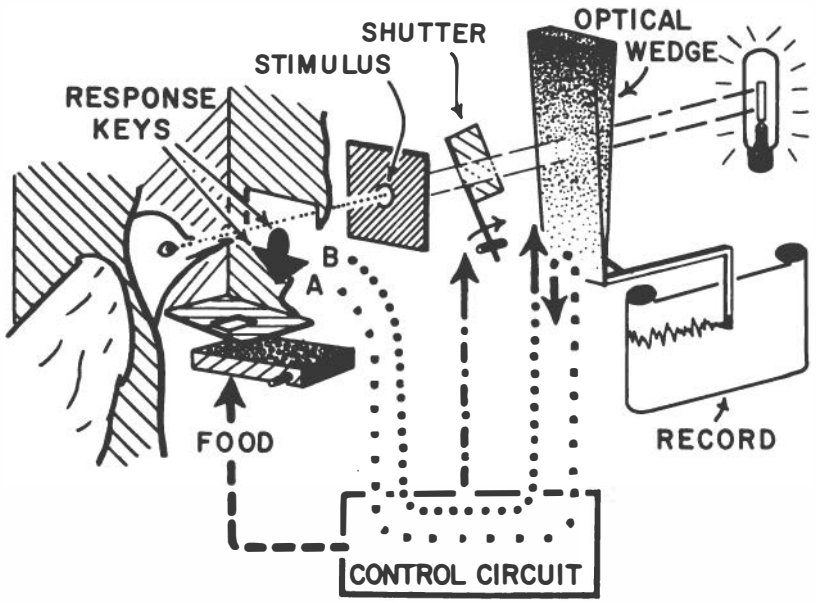

Fig. 1

Central to the method is the procedure used to reward correct behavior. One cannot consistently reward with food all pecks on Key A given when the stimulus is visible and all pecks on B when the stimulus is not visible, since the threshold of visibility is not known in advance. Hence, a "chain" is set up. Pecks on Key A, instead of producing food reward, occasionally cause a shutter to close. (See Fig. 1.) Pecks on Key B are rewarded only when the shutter has been closed in this way. Thus, the pigeon works on Key A "to turn off the stimulus"; it works on Key B, when the stimulus is off, "to get food." These reward contingencies are intermittent; much of the time, the pigeon's responses only vary stimulus intensity, and during these intervals the threshold tracking data is collected. A complete description of this method may be found in Blough, 1958.

Thresholds determined by this tracking method have yielded information on dark adaptation (Blough, 1956), spectral sensitivity (Blough, 1957a; Blough & Schrier, 1963), and drug effects (Blough, 1957b). The method has been applied to the determination of critical flicker frequency (CFF) in monkeys (Symmes, 1962), and in a number of auditory studies.

A related technique has been applied to the determination of wave length difference thresholds. The pigeon subjects view a circular split field projected upon one of two response keys. The field is divided horizontally into half-circles of the same or slightly different wave lengths. If the fields are of the same wave length, the bird is rewarded for pecking a dark key next to the spot. The number of successive pecks required

for reward can be varied independently for each key, allowing the experimenter to counteract position preferences. A correct choice of the dark key, when the wave lengths differ, causes the difference to increase 5 millimicrons (mμ) on the next trial. The difference level to which the bird adjusts the stimulus provides an index of its difference limen.

After considerable pretraining, birds were run with several basic wave lengths each day. Extensive data on one bird suggest that the shape of the wave length difference function over the range from 490 mμ to 620 mμ is similar to the human function. The absolute level of the difference limen—somewhat higher than the values usually cited for human subjects—has little meaning because it depends on experimental parameters.

An adjustment method has also been used to study brightness perception and contrast in the pigeon. Here the bird is "asked" to "report" which of two spots looks brighter. The spots appear on two keys side by side, and the bird is intermittently rewarded for pecking at the more intense spot. Pecking a given spot, however, causes the apparatus to dim that spot slightly and increase the intensity of the other. The trained bird switches from key to key, pecking at each spot in turn as it becomes the more intense. A strip-chart continuously records the bird's adjustments of the spots. Contrast effects were recorded in one study by putting a bright surround around one of the spots. In almost all cases, the birds pecked in such a manner as to increase the intensity of the spot on this bright field. This is, of course, the reaction of the human subject when asked to produce a brightness match in such a contrast situation.

Carr and Guttman, at Duke University, have produced impressive data on CFF (unpublished), using a new variant of the two-choice procedure. The pigeon faces two response keys. These keys are always identically illuminated at any given time. This stimulus illumination may vary from time to time with respect to intensity and flicker rate. If the stimulus (both keys) is flickering, the bird is rewarded for pecking the left key; if it is steady, the bird is rewarded for pecking the right key. Figure 2 shows the percentage of left-key responses typical of one bird, as a function of flicker rate. Carr and Guttman find a linear relation between CFFs determined in this manner and intensity. They hope to use this relation to determine equal brightness functions for the pigeon, choosing a constant CFF as the criterion.

A final new development is represented by the work of Herrnstein and van Sommers (1962). Using as their measure the response rate of an animal responding freely, they have obtained data suggestive of "intensity scaling" data from human experiments. The pigeon subjects were rewarded for pecking at different rates to each of several selected stimuli; their rates to other intensities, not specifically associated with reward, were recorded also. The results suggest a power law relation between pecking rate and stimulus intensity.

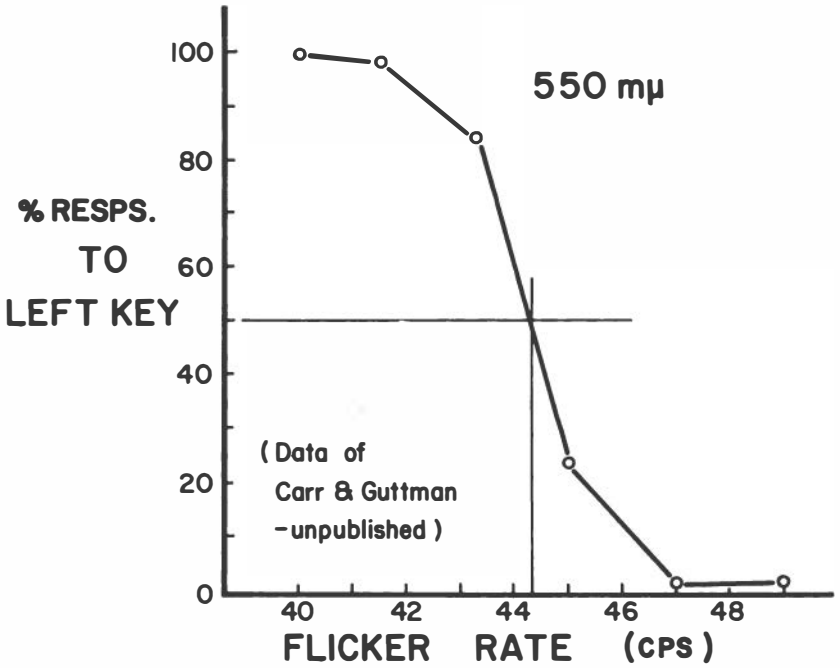

Fig. 2

The above summary indicates how new behavioral techniques may be used to attack with animal subjects some classical problems in vision. They show that the behavior of animal subjects can be closely controlled by stimuli—in some cases with a precision rivaling that achieved in experiments with human subjects. The new methods raise the efficiency of animal work by the use of intermittent reward, free responding with the opportunity for many "critical responses" per minute, and "feed-back" in the form of stimulus adjustment dependent on responding. The fundamental training problem is the same as ever: to "tell" the animal what to discriminate. The solution to the training problem is to maximize reward for the desired discriminative behavior, and to minimize reward for unwanted behavior.

References

Bekesy, G. v. A new audiometer. Acta Oto-laryn., 1947, 35, 411; 422.

Blough, D. S. Dark adaptation in the pigeon. J. comp. physiol. Psychol., 1956, 6, 49, 425-430.

Blough, D. S. Spectral sensitivity in the pigeon. J. opt. Soc. Amer., 1957, 47, 827-833. (a)

Blough, D. S. Effect of lysergic acid diethylamide on absolute visual threshold of the pigeon. Science, 1957, 126, 304-305. (b)

Blough, D. S. A method of obtaining psychophysical thresholds from the pigeon. J. exp. anal. Behav., 1958, 1, 31-43.

Blough, D. S., & Schrier, A. M. Scotopic spectral sensitivity in the rhesus monkey. Science, 1963, 139, 493-494.

Herrnstein, R. J., & van Sommers, P. Method for sensory scaling with animals. Science, 1962, 135, 40-41.

Symmes, D. Self-determination of critical flicker frequencies in monkeys. Science, 1962, 136, 714-715.

MEASUREMENTS OF LIGHT REFLECTED FROM THE RETINA

John Krauskopf
University of Maryland
and
Walter Reed Army Institute of Research

When one looks into the eye using an ophthalmoscopic arrangement, reflections from the sclera, iris, cornea, lens surfaces, and retina may be observed. All of these reflections have been used to measure characteristics of the eye. This paper is concerned with three recent uses of light reflected from the retina: experiments on the spectral reflectivity of the retina; studies of photopigments in vivo; and measurements of retinal image formation.

Retinal Reflectivity

The first of these experiments may be considered as analogous to the test tube study of the absorption spectrum of pigments, but is greatly complicated by the fact that the experiments are performed on the living eye. In the test tube case, monochromatic beams, weak enough not to bleach the pigments, are passed through test solutions and solvent controls and allowed to fall on a phototube. Comparison of the phototube output for test and control samples at various wave lengths throughout the spectrum yields the absorption or density spectrum for the pigment. The spectrum thus measured is not necessarily related to visual function. Impurities may yield spurious absorption and the photopigment itself may absorb light in certain spectral regions with thermal but not photochemical effect and, therefore, has no visual effect.

Alpern and Campbell (1962) were not directly interested in photochemistry. Rather, they were concerned with retinal reflection in the interpretation of the spectral sensitivities of the pupillary response. To this end, they compared the amount of light entering the eye at various wave lengths with that emerging after reflection through the pupil. These measurements were translated into retinal spectral reflectivities by correction from the transmission properties of the ocular media. Both absolute and relative reflectivity data have been published. Interpretation of these experiments is difficult. It seems quite likely that the relative reflectivity of the retina may be measured with accuracy, but data to be presented later make it clear that it is quite difficult to measure the absolute reflectivity to a useful precision.

Measurement of Photopigments

If there is interest in photopigments, it is obvious that retinal reflectivity per se will not produce the information required. A variety of impurities is present with an inhomogeneous mixture of photopigments. In the study of photopigments, which in the main has been conducted in England by Rushton and Weale and their collaborators, primary interest has centered on the difference spectrum.

In the test tube case, the difference spectrum is measured by comparing the phototube output at various wave lengths before and after bleaching. If the solution contained but one photopigment, and the photoproducts did not significantly absorb in the region of interest, the result might be simply interpreted as giving the effective absorption spectrum of the photopigment, but this is not usually the case Even in those cases where purified extracts are measured, an increase in absorption in certain parts of the spectrum is found following bleaching. This means that the photoproducts do significantly absorb visible light, and the difference spectrum must be interpreted as yielding the absorption spectrum of the photopigment minus the absorption spectrum of the photoproducts. In the case of rhodopsin, the difference spectrum does agree rather well with the psychophysically measured scotopic spectral sensitivity curves over most of the spectrum, except in the short wave lengths where the photoproduct absorbs.

In extending the measurement of photopigments to the living eye, Rushton and Weale have followed somewhat different approaches. Weale (1959) has concentrated on getting data rapidly throughout the spectrum. Rushton's method, while a good deal slower in producing data, more closely fits the ideal of null measurement. This review is primarily concerned with Rushton's experiments, as they are more extensive and typify what can be achieved.

A recent version of the apparatus used by Rushton (1958a) is shown in Fig. 1. The main beam of the apparatus is a double monochromator. Slits in the spectrum plane Q...Q allow the selection of different monochromatic test bands. On the assumption that little bleaching takes place in the far red end of the spectrum, a long wave length reference light is selected by use of the uppermost slit which is covered by a polaroid P_1 oriented in one direction. Test lights may be selected by uncovering one of the other slits which are covered by a second polaroid P_2 oriented at right angles to P_1. Polaroid P_o is rotated so that light alternately is passed by P_1 and P_2. W is a neutral wedge which is used to adjust the output of the photocell P.C. to a steady level when the two lights alternately reflected from the retina are equal. S_1 and S_2 are bleaching sources which may be introduced into the main beam. Suitable stops are present to eliminate stray light from the iris, sclera, and non-focal parts of the retina. The corneal reflex is eliminated in this arrangement by being deflected to one side, since the input beam enters one side of

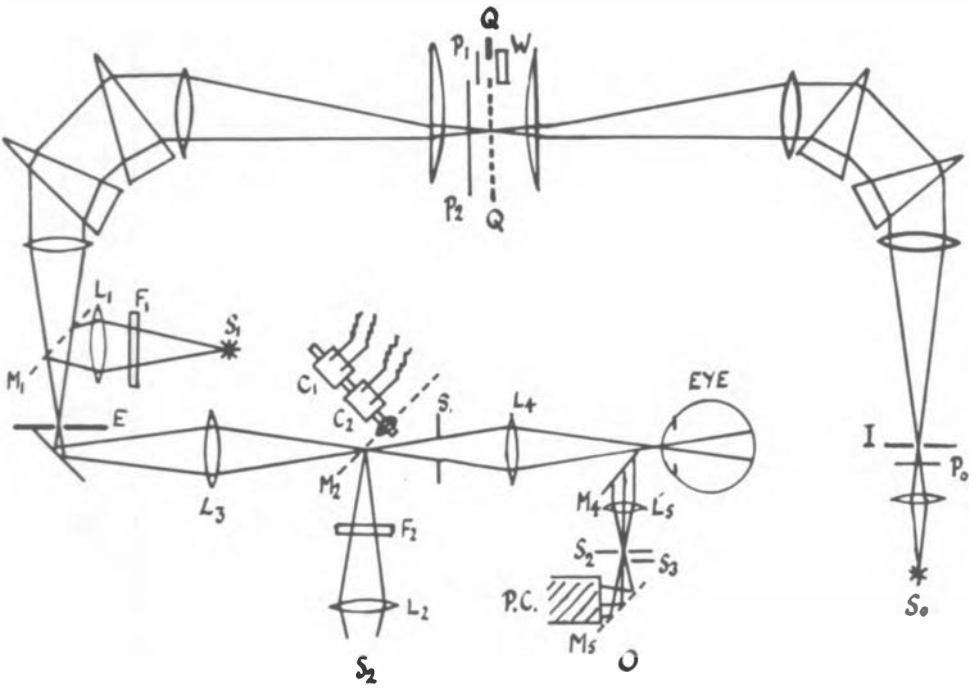

Fig. 1. Rushton's reflection densitometer.

the pupil and the recorded beam is taken out of the other side of the pupil. A suitable stop insures that the deflected beam does not enter the photomultiplier.

An example of measurements of bleaching and regeneration of rhodopsin by Campbell and Rushton (1955) is given in Fig. 2. The ordinate is in centimeters (cm) of wedge displacement, which may be converted to pigment density if the wedge calibration is known. The three limbs of the bleaching curve (open circles) represent the effects of lights of different intensities in the ratios indicated. The time course of bleaching and regeneration (solid circles) are in accord with expectations from psychophysics. A good deal of other supporting evidence justifies the conclusion that a visual pigment was being measured. These results were obtained by recording with the light reflected from the peripheral retina.

When attacking the cone pigments, a much more difficult situation is encountered. In order to escape contamination by rhodopsin, measurements must be made in the small, rod free, area of the fovea. Since efforts to extract cone pigments have been very disappointing, it is reasonable to assume that little cone pigment is present. Furthermore, even in the testtube, the situation becomes much more difficult if more than one photopigment is present in the solution. Rushton (1958a) therefore, began the study of cone pigments with color blind (protanopic and

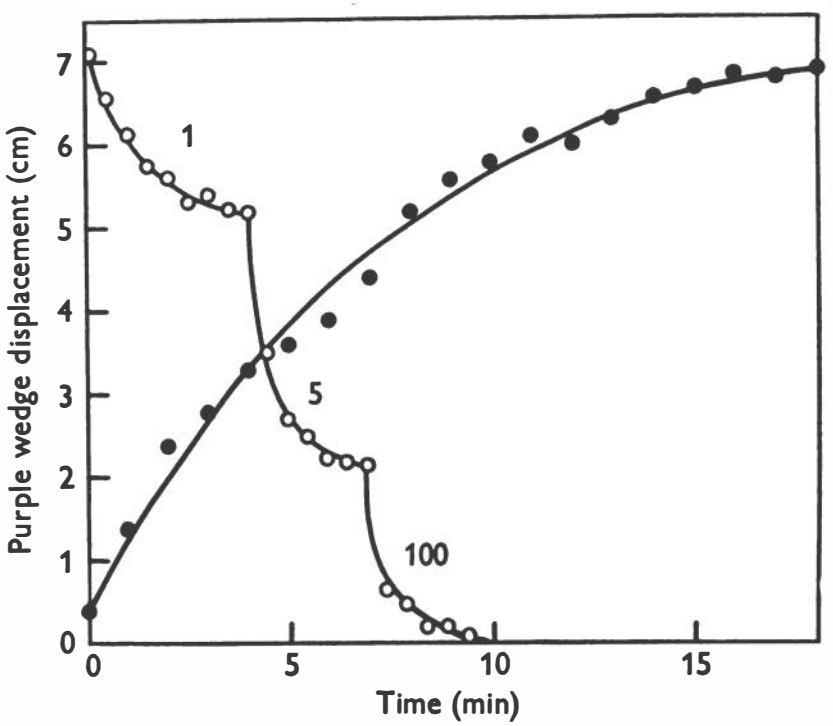

Fig. 2. Bleaching and regeneration curves for human peripheral retina.

deuteranopic) subjects. The protanope is of particular interest, since it is generally agreed that he has but one pigment operating in the middle to long wave length portion of the spectrum.

Figure 3 shows a regeneration curve for a protanopic subject (Rushton, 1958a). In general form it is like the rhodopsin curve, but, as expected, the time course is speeded up. Difference spectra recorded with two protanopic subjects are illustrated in Fig. 4. The line and circles are luminosity data. Considering the difficulties of the experiments, the difference spectra data (the boxes) show remarkably good agreement with the luminosity data. A puzzling feature of these data is the absence of any evidence of a blue receptor. Three possible explanations of this lack have been offered. One involves the notion of foveal blue blindness. Perhaps there are no blue receptors in the fovea. Secondly, the yellow macular pigment may absorb the blue light so strongly that too little remains to reveal the blue pigment. Finally, in agreement with the low contribution to luminosity of short wave length light, there may be little blue pigment present. In any case, to date no evidence of a blue pigment has been obtained.

The deuteranope is a less satisfactory subject since more doubt exists with regard to the number and nature of the pigments in his eye.

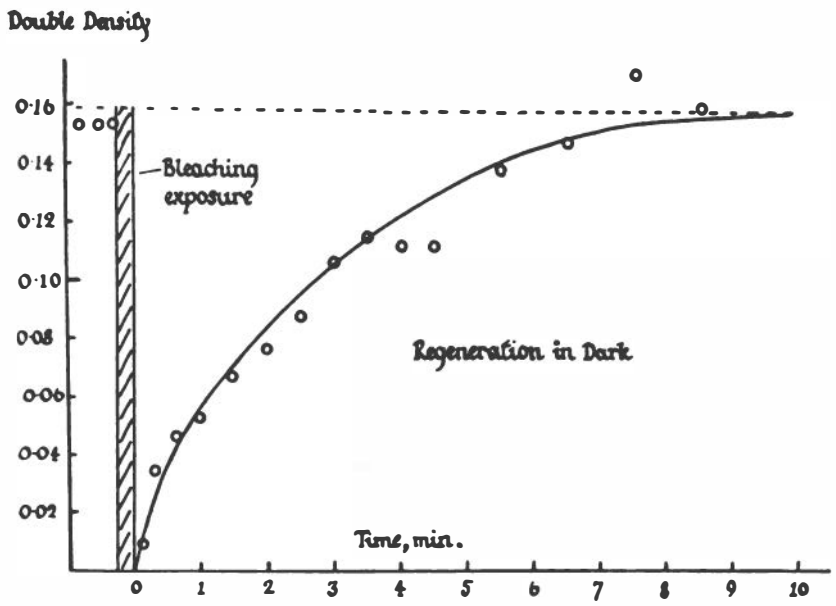

Fig. 3. Bleaching and regeneration in protanopic fovea.

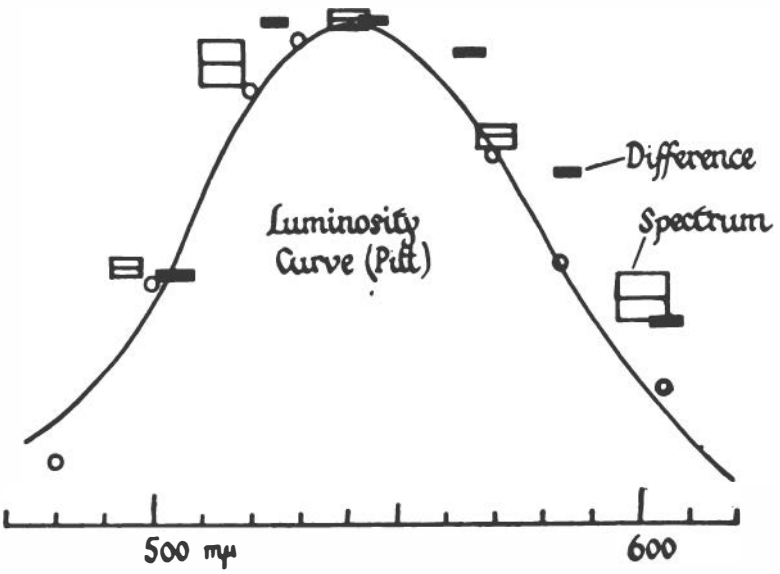

Fig. 4. Difference spectra for protanopic subjects.

Willmer (1955) presents data suggesting that two classes of deuteranopes may exist: one missing a green receptor, and the other a fusion type in accordance with the Fick-Leber hypothesis. Rushton reported some data on one deuteranope which indicated two pigments, but recent psychophysical data suggest that this is true for few if any deuteranopes (Speelman & Krauskopf, 1963).

The normal subject definitely presents the problem of measuring a mixed sample of photopigments. In test tube work, one can test a solution for homogeneity by bleaching with lights of different spectral composition. If but one photopigment is present the difference spectrum will be invariant under different bleaching lights. If it is not it may be possible to reduce to insignificant concentrations all but one class of photopigments, and to demonstrate this by further homogeneity tests, which at the same time will yield the difference spectrum of the residual component (Dartnell, 1957).

Results obtained by the method of partial bleaching on the normal subject are shown in Fig. 5. First, the retina was bleached with a long wave length light which had been shown to have no effect on the protanope. This produced the right hand difference spectrum. This was followed by further bleaching with white light which produced the second difference spectrum.

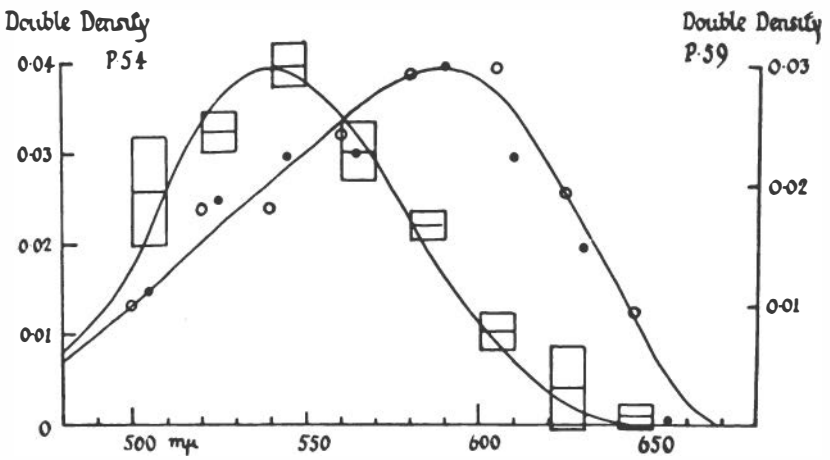

Fig. 5. Difference spectra for deuteranope by method of partial bleaching.

Almost all psychophysical spectral sensitivity curves are based on an equal response criterion. Thus, it is advantageous to use the same approach in collecting data which are to be compared with psychophysical data. For example, it is now common practice in electroretinogram work to find the stimulus required to evoke a criterion electrical output rather than to measure the output for equal energy stimuli. The photochemical equivalent is the action spectrum. In this case, a suitable measuring light is chosen, one for which the difference in density before and after bleaching is large. The bleaching effectiveness of various spectral lights is then assessed by finding that level of illumination required to produce some criterion change in density for the test light. In the test tube case, colored impurities will distort these measurements; where the impurities absorb strongly they rob light from the photopigments and make it appear that more light is required to bleach. Again,

the case in which two or more photopigments are present greatly complicates matters. The partial bleaching technique can be used, but artifacts may be introduced if the photoproducts absorb significantly in the specral region of interest, since they would act in the same manner as other impurities.

Action spectra were measured by Rushton (1958b) by determining the bleaching effect of lights which were judged equal in brightness by his subjects. The test light was always the same, while the spectral composition of the bleaching lights was varied. The expectation that lights which look equal in brightness should be the same in bleaching effect was substantially confirmed in the case of rhodopsin and the cone pigment of the protanope. Fairly good agreement was also obtained between the difference spectra and action spectra. A more complex analysis was involved in the determination of action spectra in the case of two pigments of the normal observer.

In addition to the measurement of spectra, results have been produced which are designed to provide evidence on the amount of pigments present, their photosensitivity, density, and apparent density, and the kinetics of light and dark reactions.

In this interpretation of the data, Rushton has assumed that the measuring light passes through the photopigments twice, and that the density changes recorded are, therefore, double the changes in the photopigment density. For this to be correct it would be necessary for all the light to pass through the pigments. But it does not seem likely that such a perfect arrangement exists. Lewis (1956) has presented data on the rat retina which suggests that some of the light passes between the receptors. Another requirement for Rushton's interpretation is perfect elimination of stray light from other ocular surfaces. In all probability, the quantitative interpretation of bleaching and regeneration will need revision as more is learned about the nature of reflection by the retina.

In this review of the experiments no attempt has been made to go into the precise shape of the spectra obtained. There is still a good deal of uncertainty in these matters. Nor have the differences between the findings of Weale and Rushton been discussed. There exists fairly good agreement in regard to the general spectral character of the pigments, but the two groups do disagree on details. Considering the complexities of the measurement problem and the low levels of light this is hardly surprising. Important work remains to be done on these problems. Refining the measurements of the two cone pigments already identified and seeking the evasive blue pigment are two of the more important outstanding problems.

Retinal Image Formation

The light reflected from the retina may also be analyzed to provide information about the quality of the optical system. Although this is not a new idea, there has been a recent outbreak of work on this problem. The pioneer work was done by Flamant (1956) nearly ten years ago. She used a difficult but elegant technique which involved the photographing of the retina with an ophthalmoscopic arrangement while the subject viewed a vertical bar target. In more recent work, the sensitivity of the measurements has been greatly increased by the use of photomultiplier tubes allowing more detailed quantification. This report, therefore, will concentrate on the later work.

Work in this area has been stimulated by the recent burst of activity in optics in the application of sine-wave-response theory. An important event in this context was the appearance of Duffieux's book (1947) on the application of Fourier analysis to optical systems, but, as is often the case, this was preceded by important work of some of the luminaries of the 19th century, notably Michelson and Rayleigh.

In using an ophthalmoscopic system to measure the light distribution on the retina, one is faced with the problem that the retinal image cannot be examined directly. In animal eyes, as in DeMott's experiments (1959), it is possible to remove the back of the eye and measure the light distribution after a single passage through the optics of the eye. Figure 6 illustrates an apparatus which has been used to make the ophthalmoscopic type of measurements (Krauskopf, 1962). The subject views a bright vertical bar target, T, forming an image, T′. The light, diffusely reflected from the retina, passes out of the optics of the eye and is imaged by them back in the target plane, but part of the light is reflected by a beam splitter M1 so that an image, T″, of the retinal image, is formed in the plane of L4. This is the image that is to be measured, but in order to make provisions for controlling effective pupil size, a relay system L4 and L5 (which contributes negligible degradation) is included so that a last image T‴ is formed. Another vertical slit, located in this plane, provides a window for a photomultiplier. When the photomultiplier is moved horizontally, its output traces the light distribution in the image of the target slit, doubly degraded by the eye optics.

A second set of images may be traced through the system, starting with the source filament and proceeding through D1, the eye pupil plane, and D2. Since the eye is dilated by instillation of cyclogel, the effective pupillary aperature for the incoming beam is determined by the size of D1 and that for the outgoing beam by D2.

Westheimer and Campbell (1962) used a similar but simpler and apparently more efficient system in which the pupil size was controlled by a conventional artificial pupil located near the eye. Yet another comparable arrangement has been used by Röhler (1962). Happily, this

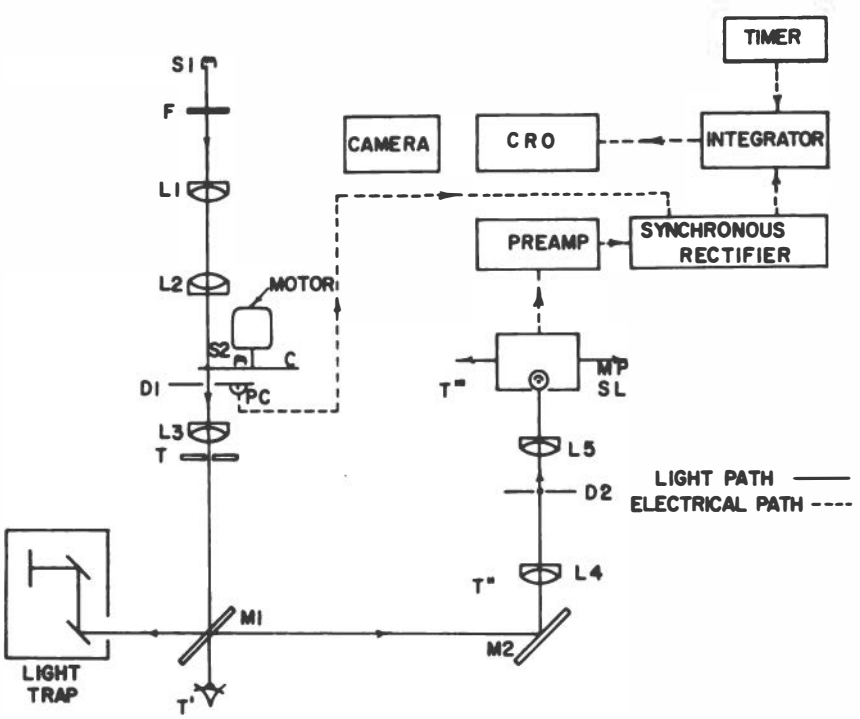

Fig. 6. Photoelectric ophthalmoscope.

is one of those situations in which the results of all investigators are in accord in all but the most minor details.

Once the light distribution of the doubly degraded target has been measured, the problem is to deduce the quality of the image on the retina. One way to look at the problem is to consider the optics as consisting of two optical systems of identical character in tandem. On the hypothesis that rays travelling in opposite directions along the same path behave in the same way, this is a reasonable model. In this model, the image of the first system serves as the object of the second system. One can make this assumption since the light is diffused by the retina. A schematic representation of the light distributions produced on the retina and in the plane of the scanning slit is given in Fig. 7. The target, the uppermost graph, is assumed to be an infinitesimally narrow bright bar. On passing through the optical system once, the distribution becomes a roughly bell-shaped curve. This distribution is known as the "line spread function" of the system. If a point instead of a line target had been used, one would get a similar radial distribution known as the "point spread function." On re-imaging the light diffusely reflected from the retina, the retinal image can be considered as composed of an infinite number of infinitesimally narrow lines which vary in intensity in accordance with the line spread function. Each of these elements produces its own light distribution in the second image plane. All these distributions have the shape of the line spread function, but their heights vary according to

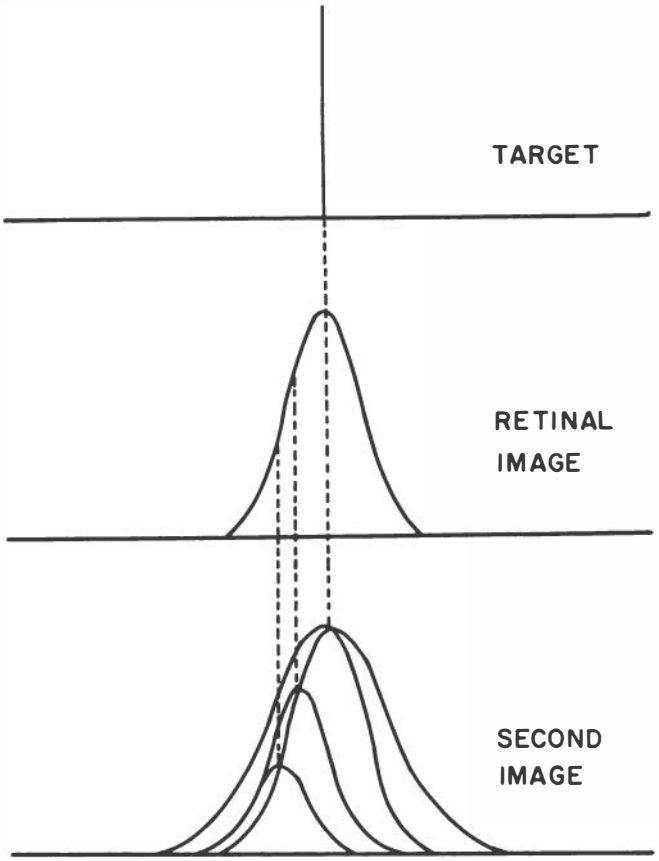

Fig. 7. Schematic representation of imaging of narrow bright line target in ophthalmoscope.

their location in the first image. In all of this, it is assumed that the light is incoherent, and, thus, the contributions of the elementary distributions can be summed to compute the shape of the resultant distribution of light in the second image plane.

The problem in the ophthalmoscopic case is that the initial and final distributions are known and one seeks to deduce the intervening, retinal light distribution. This might be done in a variety of ways, but it turns out to be most convenient to apply the techniques of Fourier analysis. This procedure is not only simple but pays dividends in that it yields a sine-wave response curve, characteristic of the optics, which allows one to deduce the light distribution of the retinal image for any target. The use of Fourier methods does not necessarily imply any special properties of the optics other than superposition as discussed in the preceding paragraph, but, in fact, the eye, like many other optical systems, may be considered as a low pass filter of spatial sinusoids. The use of filter theory in the case of electrical circuits is more familiar,

so it may be helpful to think in terms of electrical analogs. In the analog, the target may be replaced by a temporal voltage pulse, the eye in the ophthalmoscopic arrangement by two, equal, low pass filters in cascade. The retinal image is considered as analogous to the temporal voltage variation observed at the output of the first filter, and the second image as analogous to the voltage variation observed at the output of the second filter.[1] The input pulse can be decomposed into a series of sine waves of varying frequency and amplitude, and the same can be done with the two later wave forms. For the cascaded filter case, one finds that if the first filter reduces the amplitude of a particular component sinusoid, such that the output equals R times the input amplitude, then the output of two filters in cascade is equal to R^2 times the input amplitude. In other words, the response function of the cascaded system is equal to the square of the response curves for the individual filters. Thus, if a Fourier analysis of the output of the second filter is performed and it is divided by a Fourier analysis of the input, the squared response curve of the component filters is obtained, and by taking the square root the component response curves are attained. The intermediate wave shape can be deduced by determining how the input pulse is transformed by a filter of this sort. With this method the bonus of learning the response function is obtained. This function, which is mathematically equivalent to the line spread function, may be used to derive the shape of the outputs at either terminal for any input.

In this form of analysis, fine lines and points may be considered as high-frequency disturbances, broad areas are rich in low frequency. In order to resolve small objects good high-frequency response is needed. An illustrative application of this approach to optics is to be found in automatic star trackers. The problem of detecting a star may be translated to finding a high-frequency disturbance against a low-frequency background of noise (clouds and a light sky). By use of appropriate chopping reticles and electronic filters it has been possible to develop high-performance star trackers that "see" stars in the daylight sky.

Figures 8-11 illustrate the application of this approach to the eye. Figure 8 shows the recorded output of the photomultiplier obtained with the apparatus described above. The abscissa is the horizontal scanning dimension, the height to the tops of each line gives the light level at that point. The target in this case is a bright vertical bar. By performing the analysis discussed previously, the response function shown in Fig. 9 is obtained. In this case, the abscissa is in terms of lines/minute (min) of visual angle and is logarithmic, while the ordinate is linear. The curves have been normalized by equating the D. C. levels of input and

[1] In the electrical analog voltages varying in time are measured; in the optical case light distributions varying in space are of interest. Thus, an electrical pulse is the analog of a narrow bright bar, a series of square waves the analog of a grid target.

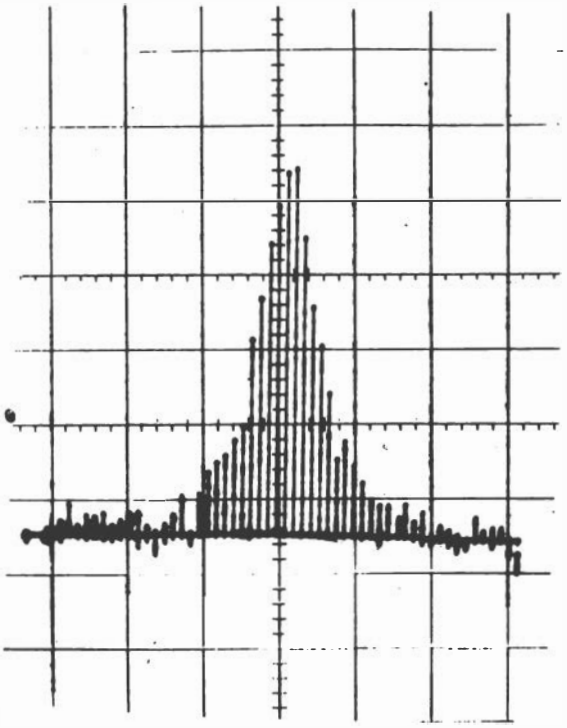

Fig. 8. Sample record from photoelectric ophthalmoscope.

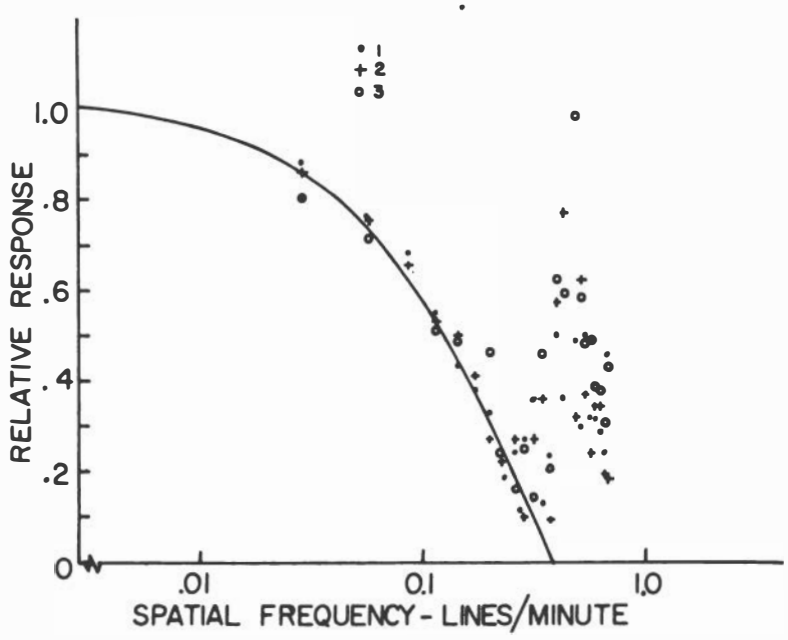

Fig. 9. Response of eye to various spatial frequencies. Three experiments. Pupil diameter—5 mm.

output. The results of three experiments using a 5 millimeter (mm) pupil are shown. The scattered points in the right-hand side of the figure may be disregarded as artifacts, due principally to the fact that the high frequencies are not well represented in the target. Figure 10 shows response functions for various pupils from 3 to 8 mm in diameter.

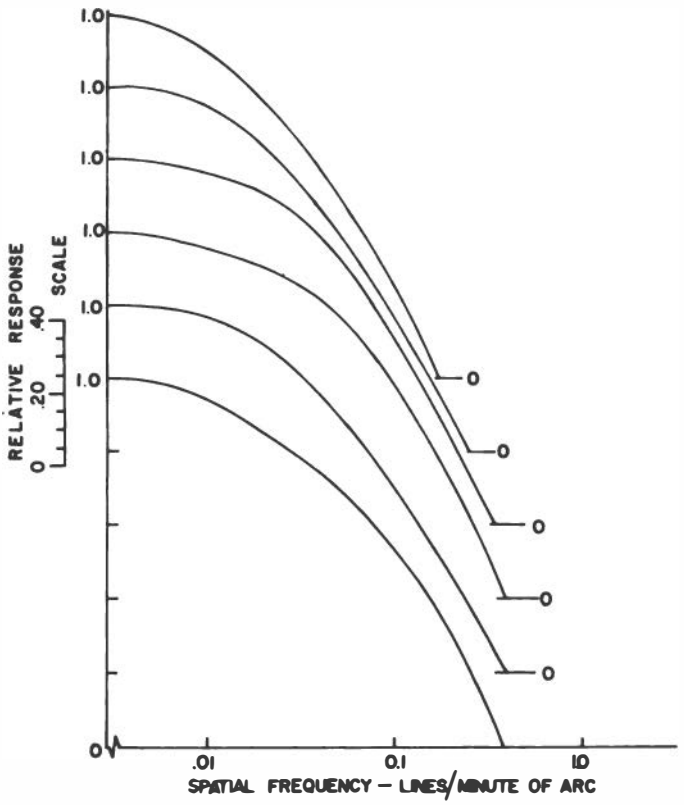

Fig. 10 Spatial frequency response curves for various pupil diameters. Pupil diameters—3, 4, 5, 6, 7, and 8 mm from bottom to top. Ordinates displaced.

They were determined and plotted in the same way as the previous one. For clarity the data points are eliminated and the ordinates displaced. Pupil size varies in steps of 1 mm downward from 8 mm to 3 mm. These curves reveal the variation of performance of the eye with aperature, showing that imagery is best with moderate sized pupils (4-5 mm) and deteriorates considerably with larger pupils. Figure 11 shows the light distributions on the retina. Again, the 8 mm pupil is at the top, the 3 mm pupil at the bottom. The relative deterioration with large pupils can be seen here also.

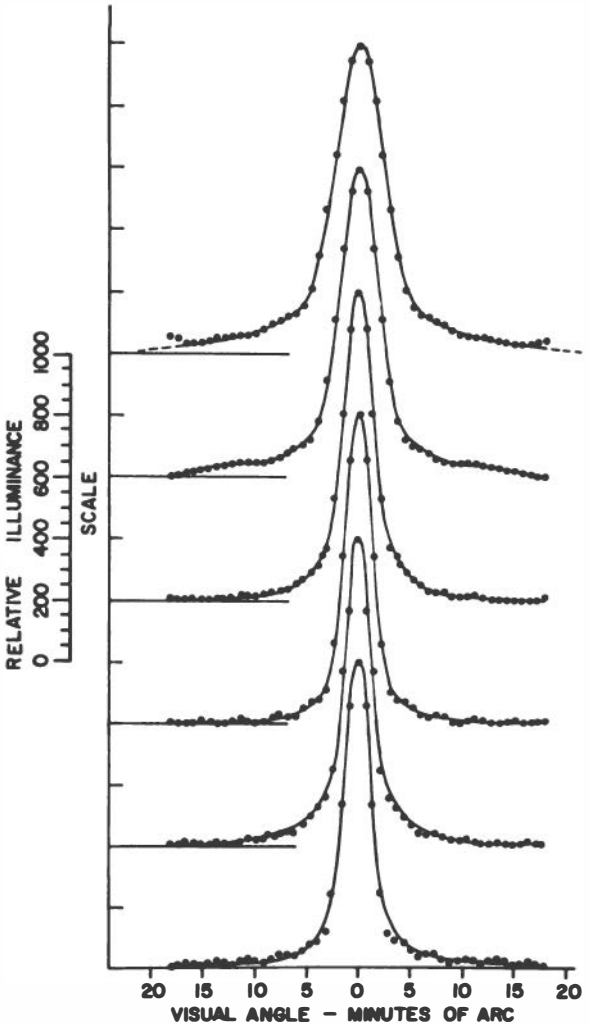

Fig. 11. Reconstructed retinal images of 1.6′ bright vertical-line target. Pupil diameters 3, 4, 5, 6, 7, and 8 mm from bottom to top. Ordinates displaced.

If it is assumed that the optics of the eye are radially symmetrical these results could be used to compute the image of any object. (If the assumption proves invalid, the calculations could still be made if the point spread function were known.) The process of determining the image distribution is known as convoluting the object function by the spread function. The application of this procedure is illustrated in Fig. 12 taken

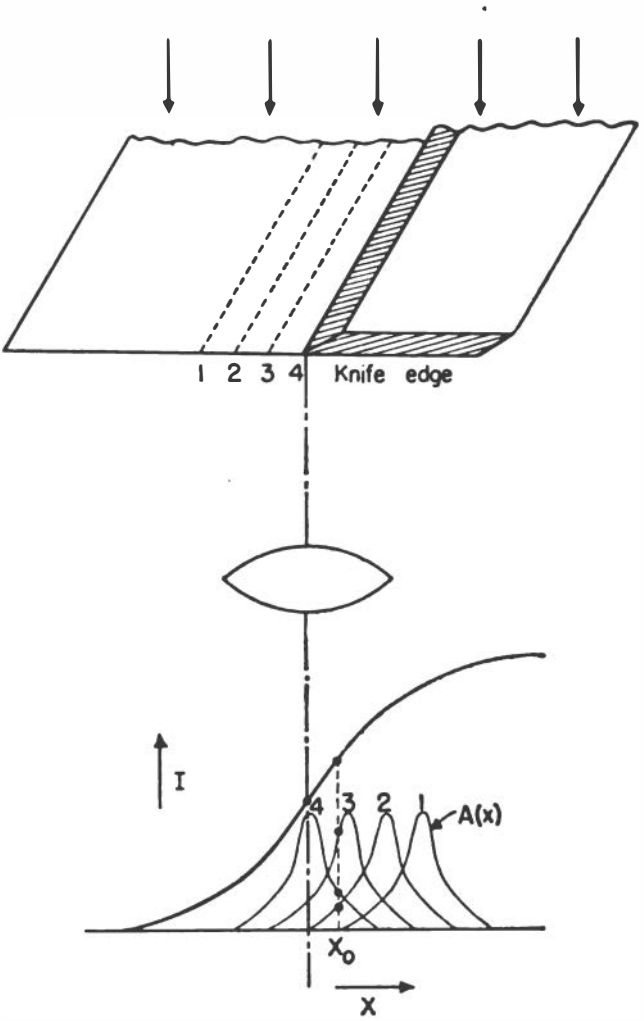

Fig. 12. Example of convolution. Target is knife edge. Bell-shaped curves indicate line spread function of optical system. Smooth curve is resultant light distribution in image obtained by summing of weighted spread function for each linear element of target.

from Perrin (1960). Although the mathematical calculations are carried out in terms of the summation of sinusoids, the process, as illustrated here, is precisely equivalent to summing the spread functions appropriately weighted by the light distribution in the object, in this case a knife edge. Comparison of this figure with Fig. 7 may be useful.

The performance of the eye may be compared with theoretical expectation. A good model to use is the diffraction-limited lens, which is

assumed to be free of chromatic and spherical abberration and other defects. This is a condition which is often closely approached in good optics. Figure 13, taken from an Eastman Kodak publication (1962), shows the general response function for such a lens. The ordinate is the

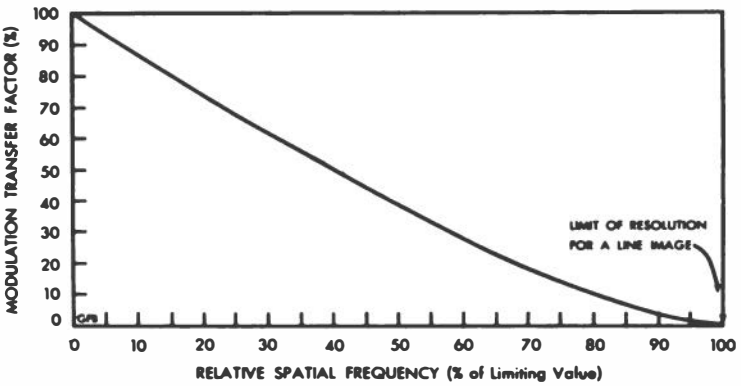

Fig. 13. Theoretical response functions for aberration-free, diffraction-limited lenses. Limit of resolution for particular lens is determined by its aperature and wave length of light employed.

normalized response. The abscissa is in terms of line frequency. It is also normalized in terms of the cut-off frequency. The curves are modern representations of diffraction theory and, with a little mathematical manipulation, can be related to cases which are generally more familiar, such as the Airy diffraction pattern. The cut-off frequency is determined by the wave length of the light used and the lens aperature. In angular terms, it is given by kd/λ, where d is the diameter of the aperature, λ is the wave length, and k is a constant to adjust for the units used. Some typical computed values for the eye are about 1 line/min with a 2 mm pupil, 2 lines/min with a 4 mm pupil, and 4 lines/min with an 8 mm pupil, when λ = 550 millimicron. These limits are never closely approached experimentally.

Of the probable causes for the failure to achieve maximal performance the principal ones appear to be chromatic and spherical aberration. Experiments have been recently performed using monochromatic light. The results at each wave length are essentially identical to those obtained with white light. This does not mean that there is no chromatic aberration. In fact, the existence of chromatic aberration was verified in the experiments by the variation of the power of the auxiliary spectacle lenses which had to be placed before the subjects' drugged eye to achieve best imagery. The results, however, agree with the data which show that acuity is little effected by the spectral composition of the light when luminance is controlled. In the case of acuity, the spectral sensitivity

of the eye determines that the light derived from the center of the visual spectrum predominates. In the ophthalmoscopic studies, the spectral variation in the light source, eye media, retinal reflectivity, and photomultiplier response combine to produce similar selectivity. Thus, the white light measurements are not truly white, but, rather, give a good approximation of the effective performance of the eye in white light.

If the eye exhibited simple spherical aberration it might be possible to take corrective measures and achieve better than normal acuity. The older measurements of Ivanoff (1953) together with new detailed measurements by van den Brink (1962) and Smirnov (1961), demonstrate that the aberration is not simply spherical. While there is an overall radial variation, there is little radial symmetry. Nevertheless, experiments with zonal or annular pupils were attempted. The decision to do this was abetted by the suggestion in the literature that better resolution of certain classes of targets, specifically points and grids, might be achieved through the use of such pupils (O'Neill, 1956). This idea has a considerable history in the literature of optics. Apparently, the first to use it was the great English astronomer Herschel, who placed a central occluder in the plane of the objective of his telescope (Rayleigh, n.d.). The development of the modern sine-wave treatment of optics has allowed the detailed solution of such problems and a number of papers have appeared in the last ten years or so. In Fig. 4, taken from O'Neill, are plotted a family of normalized response curves for aberration-free lenses with varying degrees of central occlusion. It can be seen that with a perfect lens a relative improvement in high-frequency performance is predicted with central occlusion. It is also apparent that a lens exhibiting simple spherical aberration ought to be improved in performance by using

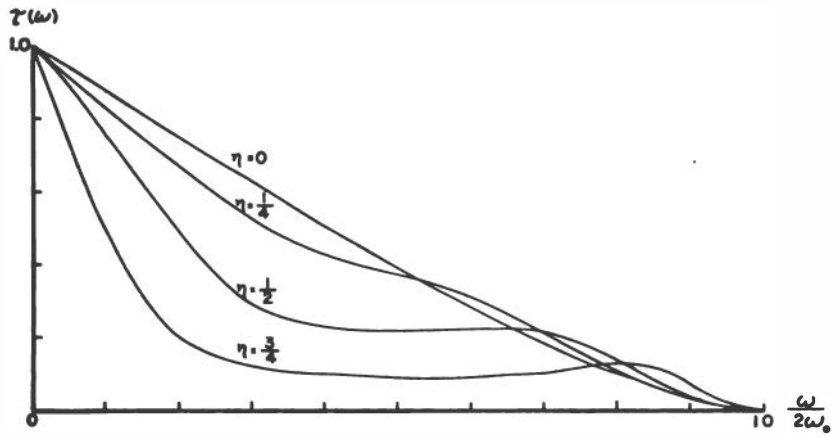

Fig. 14. Theoretical response functions for aberration-free lenses with various degrees of central occlusion. Parameter is relative diameter of occluded region.

annular pupils. Thus, double benefits might well be expected. There is no need to dwell on this for the experiments failed to support any of the expectations. A variety of annular pupils were tried with uniform results: performance is always poorer than that achieved with circular pupils of the same outer diameter. Herschel's observations are the only data in which improvement with the eye is reported. There is little information available about the precise conditions involved. Perhaps the improvement he obtained involved the optics outside rather than inside the eye.

Something of interest did show up in these experiments. In the course of performing the Fourier analysis of the output light distribution, one gets, as a matter of course, a measure of the total light in the image. It was observed that the amount of light in the images produced with annular pupils was less, in comparison with a circular pupil of equal outer diameter, than would be expected on considerations of area. That is, there seems to be an effect similar to the Stiles-Crawford effect to the utilization of light from different parts of the pupil (Stiles & Crawford, 1933). To investigate this further, the optics were rearranged so that the photomultiplier, supplied now with a small circular aperature, could be used to scan through an image of the pupil. Referring to Fig. 6, aperature D1 was opened up to fill the dilated pupil completely, the slit T was removed providing a circular target about 2-1/2 degrees in diameter, and the photomultiplier was moved to the plane of D2. Figure 15 shows the results of a horizontal pass through the pupil image. The horizontal axis is position, the vertical, light reflected from the eye pupil. It can be seen that the corneal reflex makes it impossible to measure throughout the whole of the diameter. This can be reduced, however. Figure 16 shows the effect of using crossed polaroids, one in the path before the eye, and the other in the return path. Comparison of these figures makes it clear that this procedure effectively removes the specular reflection from the cornea without altering the shape of the distribution of the light due to the pupil. In Fig. 16, one can identify the reflection due to the iris and discern the margin of the pupil. The ordinate is linear. Comparing the height at the margin of the pupil to the maximum, the ratio is about 1/3 to 1/2. It should be pointed out that this is considerably less than the ratio obtained by Stiles and Crawford. This record was obtained from the subject's right eye. The temporal margin is to the left. A similarly skewed distribution was obtained for the right eye of another subject.

The similarity of these results with the psychophysical Stiles-Crawford effect is suggestive, and experiments comparing these results with psychophysical data on the same subjects are planned. In seeking an explanation of the finding, the idea of a light-trapping effect is attractive. This might be reinforced by studies of subjects with "tilted" retinas. Experiments have been attempted with monochromatic light, but to date they are not sufficiently good to justify strong conclusions. It is reasonably sure, however, that there are no large variations in the shapes of the distributions with wave length.

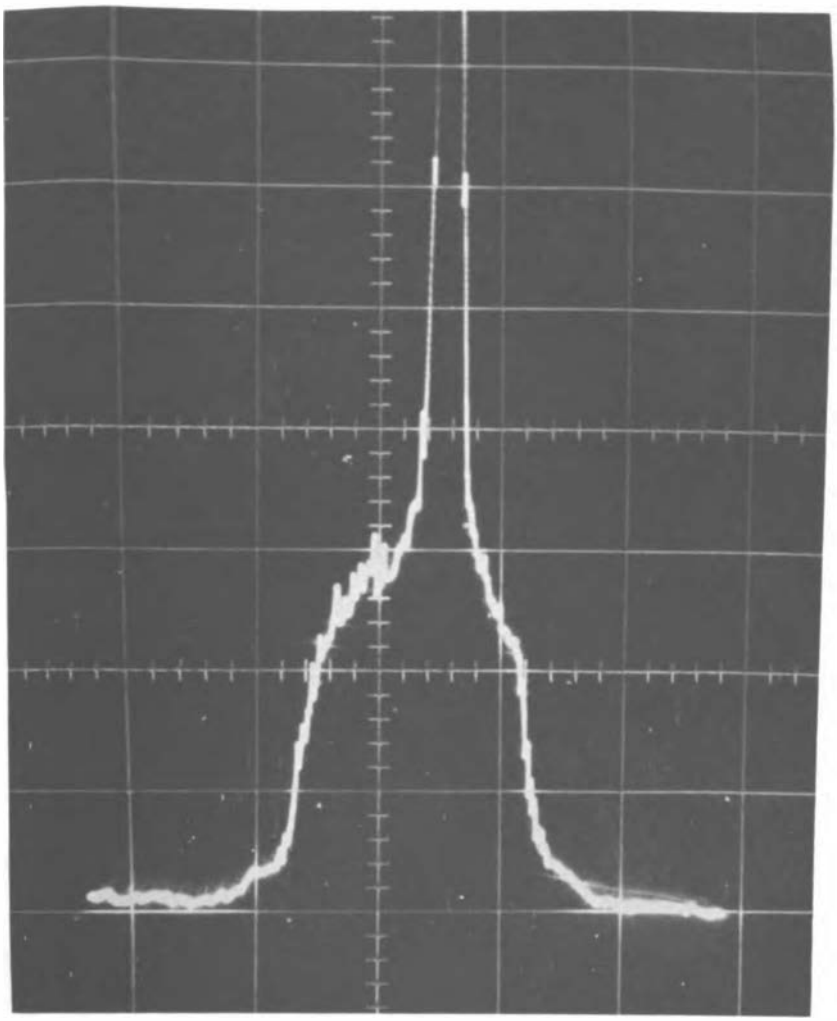

Fig. 15. Oscilloscope tracing of distribution in plane of pupil of light reflected by retina. No polaroids in beam.

The doubts expressed earlier about the quantitative interpretation of the Alpern and Campbell experiments should now be clearer. The light reflected from the retina is directional; that which is scattered as stray light is relatively less than would appear by examining the light which gets out of the pupil. Furthermore, the obviously complicated situation makes correct quantitative interpretation of the photopigment seem difficult.

It may prove useful to employ Fourier analysis to the processing of spatial patterns by the nervous system. An example of this approach

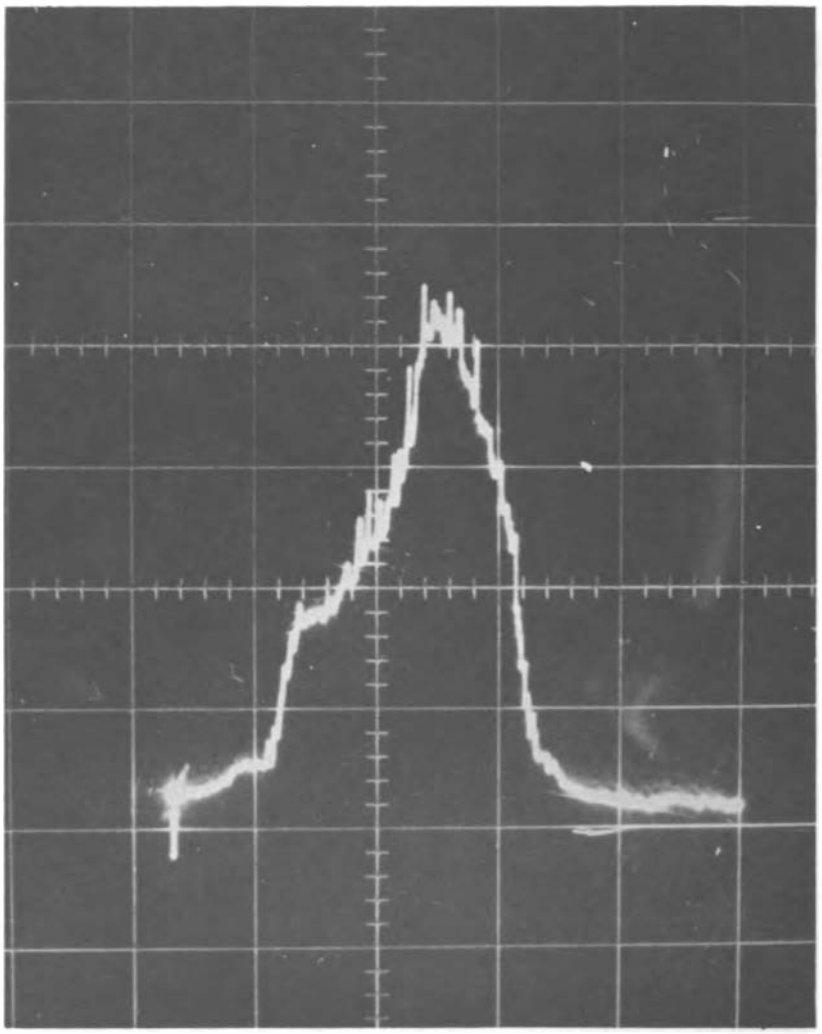

Fig. 16. Oscilloscope tracing of distribution in plane of pupil of light reflected from retina. Crossed polaroids in input and output beams.

is the interpretation by Lowry & De Palma (1961) of their photometric studies of Mach bands. Applying this approach to the nervous system raises tricky problems of psychophysics and mathematics, particularly because of the non-linearities involved. Nevertheless, interesting things may be learned, particularly with regard to the problems of summation and inhibition.

References

Alpern, M., & Campbell, F. W. The spectral sensitivity of the consensual light reflex. J. Physiol., 1962, 164, 478-507.

van den Brink, G. Measurements of the geometrical aberrations of the eye. Vis. Res., 1962, 2, 233-244.

Campbell, F. W., & Rushton, W. A. H. Measurement of scotopic pigments in the living human eye. J. Physiol., 1955, 130, 131-147.

Dartnall, H. J. A. The visual pigments. London: Methuen, 1957.

DeMott, D. W. Direct measures of the retinal image. J. opt. Soc. Amer., 1959, 49, 571-579.

Duffieux, P.M. L'Integrale de Fourier et ses application a l'optique. Rennes: Sociéte Anonyme des Imprimerie Oberthur, 1947.

Eastman Kodak Co. Modulation transfer data for Kodak films. Rochester (N.Y.): Kodak Pamph., 1962, No. P-49.

Flamant, Francoise. Etude de la repartition de luminère dans l'image rétinienne. Probs. contemp. Opt. (Istituto Nazionale di Ottica, Arcetri-Firenze) 1956, 561-569.

Ivanoff, A. Les aberrations de l'oeil. Rev. d'optique theoretique et instrumentale (Paris), 1953.

Krauskopf, J. Light distribution in human retinal images. J. opt. Soc. Amer., 1962, 52, 1046-1050.

Lewis, D. M. Rat retinal photo-pigments by reflected and transmitted light. J. Physiol., 1956, 133, 55-56.

Lowry, E. M., & DePalma, J. J. Sine-wave response of the visual system. I. the Mach phenomenon. J. opt. Soc. Amer., 1961, 51, 740-746.

O'Neill, E. L. Transfer function for an annular aperature. J. opt. Soc. Amer., 1956, 46, 285-288.

Perrin, F. H. Methods of appraising photographic systems. J. Soc. Motion Picture & Television Engrs, 1960, 69, 151-156; 239-249.

Rayleigh, J. W. S. Scientific papers. Cambridge: University Press, n.d. Vol III, p. 87.

Röhler, R. Die Abbildungseigenschafter des Augenmedien. Vis. Res., 1962, 2, 391-429.

Rushton, W. A. H. Human cone pigments. In Visual problems in colour. London: H.M.S.O. 1958, Pp. 71-105. (b)

Rushton, W. A. H. Kinetics of cone pigments measured objectively in the living human fovea. Ann. N.Y. Acad. Sci., 1958, 74, 291-304. (a)

Smirnov, M. S. Measurement of wave aberration in the human eye. Biophysics, 1961, 6, 52-65.

Speelman, R. G., & Krauskopf, J. Effects of chromatic adaptation on normal and dichromatic red-green brightness matches. J. opt. Soc. Amer., 1963, 53, 1103-1107.

Stiles, W. S., & Crawford, B. H. The luminous efficiency of rays entering the eye pupil at different points. Proc. roy. Soc., 1933, B112, 428-450.

Weale, R. A. Photosensitive reactions in the fovaea of normal and cone-monochromatic observers. Optica Acta, 1959, 6, 158-174.

Westheimer, G., & Campbell, F. W. Light distribution in the image formed by the living human eye. J. opt. Soc. Amer., 1962, 52, 1040-1045.

Willmer, E. N. A physiological basis for human colour vision in the central fovea. Doc. Ophthalmol., 1955, 9, 235-313.

STABILIZED IMAGE TECHNIQUES

Tom N. Cornsweet
Department of Psychology
University of California

There is a large amount of evidence, both physiological and psychophysical, to suggest that the human retina transmits information about changes in retinal illumination very well, but transmits steady-state information poorly, if at all. But so far there is almost no understanding of the processes by which steady-state information is lost, and this lack of understanding is due in part to the technical difficulties involved in producing a true steady state of illumination on the retinal elements. Fixate the dot numbered 1 in Fig. 1 as steadily as possible, occluding one eye. The blurred disk rapidly disappears but the sharp one remains

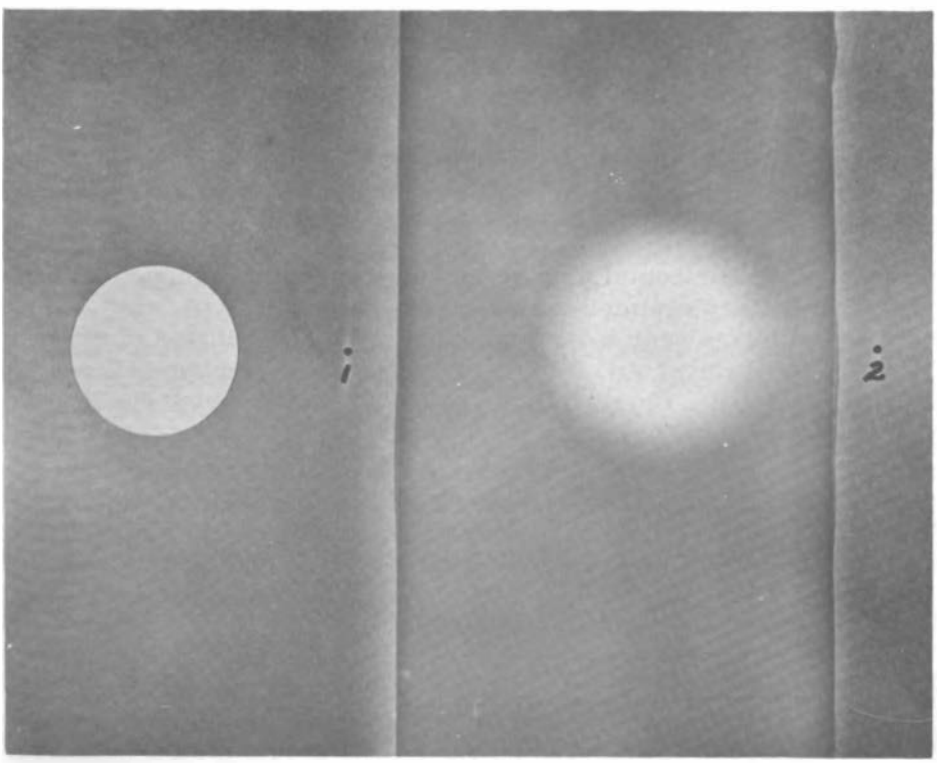

Fig. 1. Demonstration of disappearance of steadily fixated object.

visible. If, after the blurred disk has disappeared, fixation is shifted to point 2 the disk will reappear and subsequently disappear again.

The solid line in Fig. 2 is a plot of the retinal illuminance at the edge of the retinal image of the sharp disk in Fig. 1. The vertical

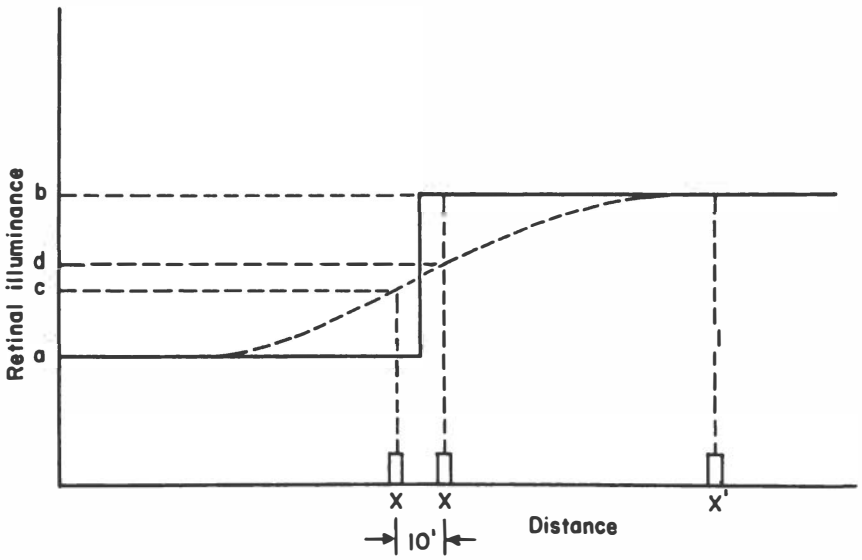

Fig. 2. Distributions of retinal illuminance at edges of retinal images of disks in Fig. 1. Solid line represents sharp disk, and dashed curve blurred disk. Rectangles on horizontal axis represent positions of receptor.

rectangles on the horizontal axis represent a receptor. During "steady" fixation, involuntary eye movements cause the receptor to "shift" in relation to the image over a distance labeled 10' (10 minutes of arc). The actual displacement will depend on the exposure duration (Riggs, Armington, & Ratliff, 1954). Such "shifts" of the receptor cause the illuminance on it to change from level "a" to "b" and back repeatedly during fixation. The dashed curve in Fig. 2 represents the retinal illuminance for the image of the edge of the blurred disk. Note that the same involuntary eye movements produce much smaller changes in retinal illuminance on receptors near the edge of the blurred disk (from "c" to "d"), and the disk disappears. When fixation is shifted to the second fixation point, the receptors under the image of the blurred disk undergo relatively large changes in illumination (the new fixation point is represented in Fig. 2 by "X'"), and it reappears. Change in the illumination on receptors seems to be a necessary condition for seeing patterns. Visibility depends on the size of the shifts of the retinal image relative to the steepnesses of the gradients of retinal illuminance.

Retinal Blood Vessel Patterns

Light arriving at the receptors in the human retina passes first through a layer of tissue containing blood vessels, and the vessels cast shadows upon the receptors. If the eye is dark-adapted, and then a white field is suddenly turned on, a trained observer can see this pattern of shadows for a brief time, but the pattern rapidly disappears and the field looks homogeneous. The shadows cannot move with respect to the retina, and there are thus no corresponding changes in retinal illuminance after the first change when the field is turned on. However, if the shadows are made to move with respect to the retina they appear again, but disappear as soon as they stop moving. Movement of the shadows may be produced by changing the direction of the light incident upon the retina. For example, Campbell and Robson (1961) describe a device in which the spot on the face of an oscilloscope is imaged in the plane of the observer's pupil, so that he sees a uniform field in Maxwellian view. When the spot is moved, the blood vessel shadows move proportionately.

The blood vessel shadows can be experimentally manipulated to some extent. They can be moved as described above. Their contrast can be changed by changing the wave length composition of the incident light. The shadows are darkest relative to their background when the light is monochromatic at 415 millimicrons (mμ), where there is a very strong absorption band for blood (Glasser, 1950). Different mixtures of light at 415 mμ and light at another wave length poorly absorbed by blood yield different amounts of contrast. Similarly, it should be possible to provide a visual field in which the only thing that is changing is the stimulation of receptors behind blood vessels. This may be accomplished by showing the observer a field that is alternately lighted with 415 mμ and then with a mixture of two other wave lengths each of which is absorbed less strongly by blood, but so chosen that their mixture will match the 415 mμ light in regions not lying behind vessels.

A retinal image that does not move with respect to the retina can also be provided by a device that might be called an auto-ophthalmoscope (Cornsweet, 1962). This optical device forms an image of the observer's peripheral retina on the fovea of the same eye with a magnification of xl and so arranged that it does not move with respect to the retina regardless of movements of the eye. The observer looking into the device sees at first a sharp view of his own peripheral retina (with its blood vessels, optic disk, etc.), but the detail rapidly fades out and soon the field looks homogeneous, the detail reappearing only if the image is deliberately moved across the retina, for example, by jarring the apparatus.

The salient aspect of the perception of each of the patterns discussed thus far is that detail rapidly fades out and disappears, the observer being left viewing a field that is apparently homogeneous with respect to the patterns that have been made motionless. Any superimposed patterns that do move across the retina, such as a fixation point or dust in the

optics, remain visible. The detail never reappears unless it is deliberately moved across the retina or its contrast is deliberately changed. In other words, only changes in illumination result in seeing.

Other Stabilized Images

Several procedures have been developed which allow the eye to move normally and provide a retinal image that moves along with the eye, so that the image remains relatively stationary with respect to the receptors. Changes in illuminance are thus reduced. These procedures may be divided into two types. In the first, a mirror is attached to the eye and the image to be viewed is reflected from the mirror in such a way that the retinal image moves with the eye (Riggs, Ratliff, Cornsweet, & Cornsweet, 1953; Ditchburn & Ginsborg, 1952; Yarbus, 1956; Clowes & Ditchburn, 1959). In the second type, the object to be viewed is itself attached to the eye so that its image moves with the eye (Yarbus, 1957; Pritchard, Heron, & Hebb, 1960). The attachment to the eye can be either by a tightly fitting contact lens or by a small cylindrical chamber attached by suction (Yarbus, 1957; Barlow, 1963). Retinal images rendered motionless with respect to the retina in this way are called stopped or stabilized images.

Every report of images thus stabilized states that the stabilized aspects of the images disappear, and, in this way, these images are apparently identical with the blood vessel shadows and blurred images discussed above. However, when images are stabilized using attachments to the eye, it is also almost always reported that the images reappear from time to time. Whether this reappearance is the result of some artifactual movement of the retinal image, or is actually produced by an autonomous process in the visual nervous system, is a subject of some debate, and perhaps even of consequence (Hebb, 1963).

It is obvious that the extent of stabilization of an image depends on the extent to which the attachments to the eye follow eye movements. Any slippage of a contact lens, or any change in the shape of the eyeball which results in motion of the retina with respect to the lens, will produce some displacement of the image with respect to the retina. It is equally obvious that any attachment to the eye must slip a little. The important question is whether or not the slippage that does occur is big enough to account for reappearance.

Barlow (1963) has recently reported his measurements of the slippage of two types of attachments to the eye, using a very sensitive measuring procedure. According to that report, what he calls a tightly fitting contact lens, fitted with a very strong lens and a stalk holding a target at a position where the lens and the optics of the eye image the target on the retina, slips about 3 1/2 minutes (min) of arc between the beginning and the end of a 5 to 10 second (sec) period of time. This is the kind of lens used by Hebb et al (1963). Barlow also measured slippage for the

cylindrical attachment held on by suction, such as first described by Yarbus (1956). According to Barlow, this device slipped only 40 sec of arc between the beginning and end of a 5 to 10 sec period. Barlow did not test the type of lens used by Riggs and many of his co-workers. Their lenses fit extremely tightly, and have only a very small mirror attached to them. Riggs, using a procedure similar to Barlow's, reports that his lenses slip about 15 to 30 sec of arc during 60 sec viewing periods and as a result of voluntary saccadic movements of a few degrees.[1]

Consequences of Slippage

The solid curve in Fig. 3a is the distribution of retinal illuminance produced when a human with emmetropic vision views a bar 10 min of arc wide through a 6 millimeter (mm) pupil. The dashed curve in Fig. 3a is the distribution for the same bar shifted sideways through 1 min of arc.

The solid curve in Fig. 3b is a plot of the difference between the solid and dashed curves in 3a. In other words, it is a plot of the change in illuminance produced when a bar 10 min of arc wide is shifted 1 min of arc. The dashed line in 3b is a plot of the distribution of illuminance produced by a bar 1 min of arc wide and having the same luminance as the bar in Fig. 3a. Shifting a bar 10 min of arc wide 1 min of arc sideways produces an increase in illuminance that is almost identical with the increase produced by presenting a bar 1 min of arc wide of the same luminance. A bar 10 min of arc wide also produces a decrease in illuminance, so that the total change in illuminance is greater than that produced by the introduction of a bar 1 min of arc wide.

Shifting a bar 10 min of arc wide 10 sec of arc sideways produces an increase in illuminance almost identical to the increase produced by its initial presentation. In general, a small displacement of a wide bar causes an increase in illuminance that is very nearly the same as that produced by presenting a bar whose luminance equals that of the wide bar and whose width equals the extent of displacement. This is true for dark bars on a light ground as well as light bars on a dark one, except that the word "decrease" must be substituted for "increase."

The threshold for resolution of a dark line is about 1/2 sec of arc under optimal conditions (Hall & Mintz, 1939). A bright or a dark line 10 sec of arc wide is easily seen unless it has very low contrast. Ten sec of arc is just 3 per cent of the median size of involuntary saccadic eye movements, and only one-half of 1 per cent of the 30 min of arc saccadic movements that occur occasionally during fixation. Further, if the eyeball changed its shape (because of muscular pulls or pulse pressure, for example) in such a way that the fovea was displaced 750 mμ with respect to the optic axis, the target would shift 10 sec of arc. Therefore, it is quite likely that reappearance will occur during viewing

[1]Riggs, L. A., & Shick, A. Personal communication.

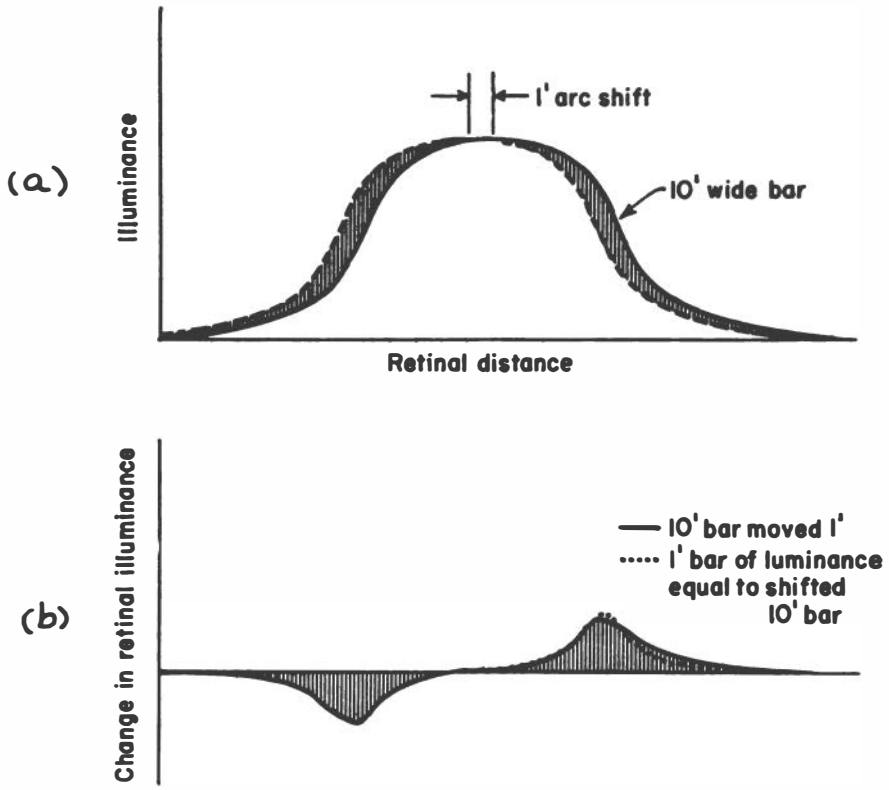

Fig. 3. (a) Distribution of retinal illuminance for bar 10 min of arc wide seen through 6 mm pupil. Dashed curve is distribution when bar has been shifted 1 min of arc with respect to solid curve. Shaded area is change in illuminance produced by shift.

(b) Solid curve represents change in illuminance shown as shaded in (a). Dotted curve is distribution of retinal illuminance produced by stationary bar 1 min of arc wide and having same luminance as 10 min wide bar.

of an image stabilized with an attachment to the eye. (The appearance of the restored image may not be identical with that of the original image, e.g., if the field is a set of lines in haphazard directions, any slip would maximize the likelihood of the reappearance of lines perpendicular to the plane of slippage, the resulting perceptions being "simpler" than the original ones.)

Figure 4 shows distributions of retinal illuminance for bars of different sizes. As the width of the bar decreases, the maximum slope of the illuminance distribution decreases, and this trend continues for bars smaller than those in the figure. As the slope of the distribution

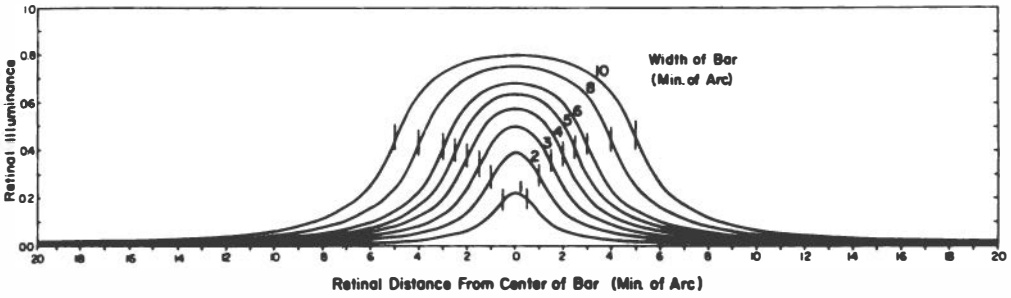

Fig. 4. Light distribution in retinal image of long bars for human eye, best focus, 6 mm pupil.

decreases, the distance that the entire distribution must be shifted to achieve some fixed amount of change in illuminance increases. Therefore, it is to be expected that, using a stabilization system that is short of perfect, very fine lines might never reappear while wider ones (or ones with greater contrast) would reappear from time to time as a consequence of slippage, and such findings are reported in the literature (Riggs et al., 1953; Ditchburn & Ginsborg, 1952). In general, the proportion of time during which a bar is visible during fixation would increase as the width of the bar increases, even if artifactual retinal image movement were the only cause of reappearance.

To summarize, "spontaneous" reappearance of stabilized patterns has been reported only when the stabilization was produced by a system using an attachment to the eye. It is never reported for patterns of retinal illuminance which are known to be perfectly fixed to the retina. Slippage does occur in contact lenses and in devices attached to the eye by suction. While this slippage can be made very small, it is not negligible in relation to the reappearance of many visual targets.

A Device for Perfect Stabilization

To study the processes that cause an image to disappear, and the other side of the coin—processes that render an image visible, it would be highly desirable to have a device which produced patterns of retinal illuminance which are perfectly stabilized and are manipulatable. The only perfectly stabilized patterns currently available, the retinal blood vessel shadows and related entoptic phenomena (Maxwell's spot, Haidinger's brushes, etc.), can be manipulated only within very restricted limits. But it is theoretically possible to produce perfect stabilization of any desired image.

When an observer looks at a target, an image of his own retina is formed on the target. If it were possible to know, at each instant, the exact position of some landmark or set of landmarks in the image of the retina with respect to the plane of the target, and if the target itself were

then moved so as to be in a fixed position relative to the image of the retina, then the image of the target would be perfectly stabilized on the retina (Cornsweet, 1958). In other words, if a star were moved continuously so that it was always located in the exact center of the image of the observer's fovea, the retinal image of the star would always be exactly at the center of the observer's fovea, and would thus be stabilized. So long as the relationship between the star and the image of the retina were fixed, the image would remain stabilized regardless of movements of the eye or the head, and regardless of distortions of the shape of the eyeball or changes in the position of the retina with respect to the optic axis.

A first, and hardest, stage in building such a device is to construct a system which will give an electrical output which signals the instantaneous position of the image of the retina, that is, a system to track the image of the retina. The output of such a tracker could then control the position of a visual target, for example a pattern displayed on the face of a cathode-ray tube.

In order to track the retina, light must be sent into the eye, and the light reflected back out must be processed to extract the information it contains about the position of the retina. Since light is quantal in nature, it is necessarily true that perfect tracking cannot be achieved at all times. For example, there are times when no quanta arrive at the sensing system. Such a small proportion of the light incident on the retina is actually reflected out of a human eye that quantal considerations become important. That is, a very large amount of light must be put into the eye in order that enough quanta come back out to yield precise information about the location of the retina. For example, suppose that a point source were imaged on the edge of a blood vessel in the human retina. If the light were restricted to a wave length of 415 ± 2 1/2 mμ (for optimal contrast between blood vessel and background), the source must deliver approximately 90 x 10^{12} quanta per sec per mm^2 to the pupil of the eye in order that the light reflected back out of the eye contain enough information to locate the horizontal position of the blood vessel within 1 sec of arc every 10 milliseconds (ms). That is roughly the intensity of a 500 watt high pressure mercury arc lamp. The intensity required is directly proportional to the precision in time, e.g., ten times as many quanta are required for a precision of 1 sec of arc every millisecond, and proportional to the square of the spatial precision, e.g., 10^{-2} times as many quanta are required for a precision of 10 sec of arc. The derivation of the function relating incident intensity to precision of tracking is included as an appendix to this report.[2] In other words, if the light sensing and tracking machinery itself were perfect, that is, if the apparatus lost no information, tracking of this kind could be made just about precise enough to provide good image stabilization. This solution is marginal. With real apparatus, it is possible that the intensities required would damage the retina.

[2]The writer is indebted to Mr. Michael Davidson, Department of Psychology, University of California, for the derivation.

The figures discussed above are calculated for an apparatus that images a single point source on the retina. If two sources were imaged and the sensing system acted upon both of them, the intensity of each could be reduced by one-half. Thus, it seems that the most promising approach to tracking of the human retina involves gathering light from a large region of the retina rather than from the image of a single point. If a section of the retina, say, for instance, the entire optic disk, were scanned at a very high rate, the intensity at each point could be reduced to easily achieved values, while excellent tracking could still be accomplished.

Appendix

Michael Davidson
Department of Psychology
University of California

Calculation of number of quanta required per unit time for eye-movement tracker.

1. Incident light, nominal

Let the line-spread function for the optical system be a Gaussian function with variance σ^2, and let a point source be such that Q_s quanta per second (sec) are imaged onto the retina. Then the density distribution of incident light is

$$q_n(x, y) = [Q_s/2\pi\sigma^2] \cdot \exp[-(x^2 + y^2)/2\sigma^2] \quad (1)$$

the units being those of Q_s/σ^2, e.g., quanta $\cdot$ sec^{-1} $\cdot$ (minutes of arc)$^{-2}$. Note that the peak density is given by

$$q_{max} = Q_s/2\pi\sigma^2. \quad (2)$$

2. Incident light, stochastic

Assumption: every photon which traverses a particular path from the source of the eye strikes the retina at precisely the same point. Then the probability distribution of the density of incident light at the point (x, y) on the retina is given by a Poisson distribution whose mean is the nominal intensity at the point, viz.

$$P\{q(x, y) = u\} = [q_n(x, y)]^u \cdot [u!]^{-1} \cdot \exp[-q_n(x, y)], \quad (3)$$

where $q_n(x, y)$ is the nominal intensity, given by equation (1). (Note: strictly speaking, one should use no. of quanta within a small time δt, and a small area $\delta x \delta y$, but this would lead to the same result.) Since the

emission from the source at a particular angle is independent of that at other angles, the distribution at each point is independent of that at each other point, under the assumption stated.

3. Reflected light, local

As long as the number of quanta reflected during the time interval of interest remains large, the probability distribution of reflected light is also Poisson, with mean given by

$$r_n(x,y) = R(x,y) \cdot q_n(x,y), \tag{4}$$

$R(x,y)$ being the reflectance of point (x,y). Now, assume that the retina is divided into two regions:

$$R(x,y) = \begin{cases} R_1, & x \leq c, \\ R_2, & x > c. \end{cases} \tag{5}$$

Then the density of reflected light, $r(x,y)$, is given by

$$\begin{aligned} P\{r(x,y) = \nu\} &= [R_1 q_n(x,y)]^{\nu} [\nu!]^{-1} \cdot \exp[-R_1 q_n(x,y)], \\ &\qquad \text{if } x \leq c, \\ &= [R_2 q_n(x,y)]^{\nu} [\nu!]^{-1} \cdot \exp[-R_2 q_n(x,y)], \\ &\qquad \text{if } x > c. \end{aligned} \tag{6}$$

4. Reflected light, total

Since the sum of two independent Poisson-distributed random variables is also Poisson-distributed, with mean equal to the sum of the separate means, the light reaching the detection device has a Poisson distribution with a mean given by the integral of the mean reflected density over the spot. Denoting the total number of quanta per sec by T, and the mean value of the distribution of T by T_n, one obtains

$$\begin{aligned} T_n(c) &= \int_{-\infty}^{c} \int_{-\infty}^{\infty} [Q_s R_1 / 2\pi\sigma^2] \cdot \exp[-(x^2 + y^2)/2\sigma^2] \, dxdy \\ &\quad + \int_{c}^{\infty} \int_{-\infty}^{\infty} [Q_s R_2 / 2\pi\sigma^2] \cdot \exp[-(x^2 + y^2)/2\sigma^2] \, dxdy \\ &= Q_s [R_1 \Phi(c/\sigma) + R_2 (1 - \Phi(c/\sigma))], \end{aligned} \tag{7}$$

where the error integral $\Phi(x)$ is given by the usual relation

$$\Phi(x) = \int_{-\infty}^{x} [2\pi]^{-1/2} \exp[-t^2/2] \, dt. \tag{8}$$

Then, since T is Poisson,

$$P\{T(c) = k\} = [T_n(c)]^k \cdot [k!]^{-1} \exp[-T_n(c)]. \tag{9}$$

5. Case of line close to center; normal approximation

Letting $C = \sigma\delta$, where $|\delta| \ll 1$; then the Taylor approximation may be used

$$\Phi(c/\sigma) \approx \tfrac{1}{2} + [\delta\sigma/\sigma] \cdot \Phi'(c/\sigma)\big|_{c=0} = \tfrac{1}{2} + \delta/\sqrt{2\pi} \tag{10}$$

Further, if it is assumed that Q_s will be quite large, the Poisson distribution may be approximated with the appropriate normal distribution:

$$P\{T(c) = k\} \approx [2\pi T_n(c)]^{-1/2} \exp[-(k-T_n(c))^2/2 \cdot T_n(c)]. \tag{11}$$

Substituting (10) into (7) gives

$$T_n(\sigma\delta) = Q_s[(R_1 + R_2)/2 + (R_1 - R_2) \cdot \delta/\sqrt{2\pi}] \tag{12}$$

as the common value of the mean and variance of the distribution (11), for the case where the edge is displaced by an amount $\delta\sigma$ from the incident distribution. One further approximation is made: since $\delta \ll 1$, the variance of the family of distributions under consideration may be approximated well by

$$\text{Var} = Q_s[(R_1 + R_2)/2],$$

whence, from (11),

$$P\{T(c) = k\} = [\pi Q_s(R_1 + R_2)]^{-1/2} \exp[-(k-T_n(c))^2/Q_s(R_1 + R_2)]. \tag{13}$$

6. The estimation problem

Assume that the task is to follow the eye movements with a tracking machine so that the line is within a specified distance ϵ of the center of the distribution a fraction $(1-\alpha)$ of the time. Let the machine be constructed so that it works as follows.

a. The time scale is broken into small intervals of τ sec.

b. During each period of τ sec, the machine counts the quanta incident upon it. Let the number be q_o.

c. The machine finds the value of δ corresponding to q_o, by solving the equation:

$$q_o = \tau Q_s \left[(R_1 + R_2)/2 + (R_1 - R_2) \cdot \delta/\sqrt{2\pi} \right],$$

i.e.,

$$\delta = (2\pi)^{1/2} (R_1 - R_2)^{-1} \left[q_o/\tau Q_s - (R_1 + R_2)/2 \right]. \qquad (14)$$

d. The machine moves the spot by an amount $\delta\sigma$ (to the right or to the left according as δ is positive or negative).

Thus, this machine will move, at the end of a time interval, to the estimated average location of the line during that interval.

This movement will be correct $(1-\alpha)$ of the time, to within error $\pm\epsilon$, provided that the estimated value of $\delta\sigma$ is correct within a confidence interval of radius ϵ, confidence level $(1-\alpha)$. This means that q_o is the center of a confidence interval for the number of incoming quanta during the period τ, the center and radius of which, from (14), are found as follows:

$$\min q_o = \tau Q_s \cdot \{ (R_1 + R_2)/2 + (R_1 - R_2) \left[(\delta\sigma - \epsilon)/\sigma \right]/\sqrt{2\pi} \};$$

$$q_o \pm \Delta q = \tau Q_s \cdot \left[(R_1 + R_2)/2 + (R_1 - R_2) \cdot \delta/\sqrt{2\pi} \right] \pm \tau Q_s \epsilon (R_1 - R_2)/\sigma\sqrt{2\pi}. \qquad (15)$$

But now this radius is also given by the distribution (13) to be:

$$(1-\alpha)/2 = \int_o^{\Delta q} \text{Normal} \left[o, \tau Q_s (R_1 + R_2)/2 \right] dx, \qquad (16)$$

i.e., that value of x for which a normal distribution with variance $\tau Q_s (R_1 + R_2)/2$ has $(1-\alpha)$ of the area between -x and x.

7. Calculation rule

a. Choose confidence level $(1-\alpha)$, allowable spatial error ϵ, time sampling interval τ.

b. Find value of Z_α such that a normal distribution with mean 0 and variance 1 has area $(1-\alpha)$ between $(-Z_\alpha)$ and Z_α.

c. Find: (a) standard deviation σ of the line-spread function,

(b) reflectance R_1 of lighter surface (this = probability that a quantum incident on the retina will enter the measuring instrument),

(c) reflectance R_2 of darker surface (similar).

d. Then the number of quanta incident in the entire spot per unit time is given by the solution of

$$\tau Q_s (R_1 - R_2)\, \epsilon / \sigma\sqrt{2\pi} = Z_\alpha [\tau Q_s (R_1 + R_2)/2]^{1/2}$$

which is

$$Q_s = \frac{\pi \sigma^2 Z_\alpha^2 (R_1 + R_2)}{\tau \epsilon^2 (R_1 - R_2)^2} \qquad (17)$$

References

Barlow, H. Slippage of contact lenses and other artifacts in relation to fading and regeneration of supposedly stable retinal images. Quart. J. exp. Psychol., 1963, XV, 36-52.

Campbell, F. W., & Robson, J. G. A fresh approach to stabilized retinal images. J. Physiol., 1961, 158, 11P.

Clowes, M. B., & Ditchburn, R. W. An improved apparatus for producing a stabilized retinal image. Opt. Acta, 1959, 6, 252-265.

Cornsweet, T. N. New techniques for the measurement of small eye movements. J. opt. Soc. Amer., 1958, 48, 808-811.

Cornsweet, T. N. A stabilized image requiring no attachments to the eye. Amer. J. Psychol., 1952, 75, 653-656.

Ditchburn, R. W., & Ginsborg, B. L. Vision with a stabilized retinal image. Nature, 1952, 170, 36-37.

Glasser, O.(Ed.) Medical physics (Vol. II). Chicago: Yearbook Publishers, Inc., 1950. Pp. 1071-1072.

Hebb, D. O. The semiautonomous process: its nature and nurture. Amer. Psychol., 1963, 18, 16-28.

Hecht, S., & Mintz, E. U. The visibility of single lines at various illuminations and the retinal basis of visual resolution. J. gen. Physiol., 1939, 22, 593-612.

Pritchard, R. M., Heron, W., & Hebb, D. O. Visual perception approached by the method of stabilized images. Canad. J. Psychol., 1960, 14, 67-77.

Riggs, L. A., Armington, J. C., & Ratliff, F. Motions of the retinal image during fixation. J. opt. Soc. Amer., 1954, 44, 315-321.

Riggs, L. A., Ratliff, F., Cornsweet, J. C., & Cornsweet, T. N. The disappearance of steadily fixated test objects. J. opt. Soc. Amer., 1953, 43, 495-501.

Yarbus, A. L. Perception of an immobile retinal image. Biofizika, 1956, 1, 435-437.

Yarbus, A. L. A new method of studying the activity of various parts of the retina. Biofizika, 1957, 2, 165-167.

PRINCIPLES OF NEUROLOGICAL FEEDBACK CONTROL SYSTEMS FOR EYE MUSCLES

Lawrence Stark
Neurology Section
Electronic Systems Laboratory and Biology Department
Massachusetts Institute of Technology

A review of recent work on neurological control systems indicates that certain system-design properties seem to be relatively widespread, although individual systems may employ only one or two examples of such mechanisms. Stability of system performance may be provided by either adequate gain margin, or adequate phase margin, or both. However, in some cases, oscillations occur which may have a relationship to function. Non-linear properties such as scale compression or other types of saturation may permit the system simultaneously to maintain stability in one domain and oscillatory behavior in another. (Noise with various bandwidths and amplitude ranges may be present with or without a functional role.)

Often, systems are composed of a symmetrical component whose interaction probably improves system performance at minimum cost. Even error signals are sometimes employed. Discontinuous control computations result in sample data properties with attendant characteristic features. These are often accompanied by prediction operators to enable closer following of repetitive signals. Interaction between different systems and time-varying characteristics, such as adaptation, extend the repertoire of design principles found in these biological feedback control mechanisms.

In order to study and analyze biological servomechanisms graphic displays such as Bode, Nyquist, and Phase plane diagrams are supplemented by analytic descriptions such as linear transfer functions, nonlinear describing functions, and higher order functional analysis.

Simulation by analog models, special digital computer programs which simulate analog computers, and most recently, hybrid models have been employed. The hybrid models use analog elements for dynamics and time delays. Nonlinearities are obtained from the digital computer. An online digital computer is now being used to contain models and adjust parameters in real time during the course of an experiment as identification and matching becomes possible.

A number of different approaches have enabled dissection into the black box defined by the above input-output experimental analytic technique. These approaches include the use of dissected invertebrate preparations; stereotactic, electrophysiological experiments on cats; and the use of pharmacological agents on normal subjects. Neurological patient material has been extremely valuable in providing subjects with altered control systems. Utilization of classical physiological literature has sometimes proven to be of great value for modelling, and conversely, the black-box analyses have often suggested crucial physiological experiments to be done. Chronic experiments in conditioned animals with implanted electrodes are now being planned since it is deemed most important to identify the physical behavior of the physiological elements which together comprise any control system.

The linear and nonlinear properties of the pupil servomechanism were reviewed in 1959 (Stark). Since then material on the pulse response of the pupil (Stark, Van der Tweel, & Redhead, 1962), rapid dark adaptation measured by means of a null pupil-response technique (Stark, 1962a), and environmental clamping of the pupil (Stack, 1962b) has been published. Current work on pupillary noise, nonlinear modeling with analog-digital hybrid computers, stereotactic electrode studies, higher order kernel approximation, and drug experiments has as yet appeared only in progress report form.

The human accommodation system is a most interesting example of a complex biological control system. A nonlinear servoanalytic treatment of experimental steady state data (Stark, Takahashi, & Zames, in press) and a special examination of the evidence for the absence of an odd error signal mechanism (Stark & Takahashi, in press) have been reported recently.

The eye target tracking system has been studied using electronic means to measure horizontal eye movements. It is important to eliminate the effect of the "prediction operator" by using unpredictable signals (Stark, Young, & Vossius, 1962; Stark & Young, in press—a). Then the discrete or sampled-data nature of the position (saccadic) and velocity (pursuit) dual control system operating together (Stark & Young, 1962; Stark & Young, in press—b) becomes apparent. A model formulated in engineering terms shows remarkable agreement with the real behavior of the system under variable feedback experimental operating conditions.

Studying interactions between various loops of a single control system and between different control systems operating upon the same final effector is being continued. The classification of many previously unexplained phenomena, and the prediction of novel phenomena as, for example, a high-gain oscillation, strongly justifies the effort required to apply the essentially mathematical concepts of servoanalysis to the motor control systems of the intra-ocular and extra-ocular muscles.

References

Stark, L. Stability, oscillations and noise in the human pupil servomechanism. Proc. Inst. Radio Engrs, 1959, 47, 1925-39.

Stark, L. Biological rhythms, noise and asymmetry in the pupil-retinal control system. Ann. N. Y. Acad. Sci., 1962, 98, 1096-1108. (a)

Stark, L. Environmental clamping of biological systems. The pupil servomechanism. J. opt. Soc. Amer., 1962, 52, 925-30. (b)

Stark, L., & Takahashi, Y. Absence of an odd error signal mechanism in human accommodation. J. opt. Soc. Amer., in press.

Stark, L., Takahashi, Y., & Zames, G. Nonlinear servoanalysis of human lens accommodation. J. opt. Soc. Amer., in press.

Stark, L., Van der Tweel, H., & Redhead, J. Pulse response of the pupil. Acta Phys. Pharm. Neerlandica, 1962, 11, 235-239.

Stark, L., & Young, L. Dependence of accuracy of eye movements on prediction. J. opt. Soc. Amer., in press. (a)

Stark, L., & Young, L. A discrete model for eye tracking movements. Reglungitechnik, 1962 (Jan.). (Also: Bionics Conf., March, 1963, Dayton; Inst. Elec. & Electronic Engrs, Trans. Prof. Tech. Group on Military Electronics, in press.)

Stark, L., & Young, L. R. Variable feedback experiments supporting a discrete model for eye tracking movements. Inst. Radio Engrs, (Trans.) Human factors—spec. manual control issue, in press. (b)

Stark, L., Young, L., & Vossius, G. Predictive eye movement control. Inst. Radio Engrs, (Trans.) Human factors in electronics, 1962, No. HFE-3, 52-57.

THE EFFECTS OF DRUGS ON VISION

INTRODUCTORY REMARKS BY THE CHAIRMAN

Arthur Jampolsky
Eye Research Institute
Presbyterian Medical Center

It is the purpose of this symposium to review the direction and results of some previous investigations, and to point out the probable directions for best future potential in solving some of the practical problems, and acquiring more fundamental knowledge in this field.

There is a large body of literature pertaining to drug effects on visual perception, behavior, and performance. There is a paucity of information on the specific sites and modes of action of drugs on the visual apparatus. It seems appropriate to examine the tools available to the psychophysicist, the electrophysiologist, and the biochemist to see what information may be derived from different approaches.

The format has been organized to bring out the sites and modes of drug action on the visual apparatus; to assess the sensory input in electrophysiological terms; to discuss the drug effects on the extraocular muscles and on the accommodative-convergence mechanism; to relate these findings to psychophysical parameters, and to the more general topics of performance and behavior; and to point out the potentials, limitations, and blind spots requiring future examination.

In the sixteen years since lysergic acid diethylamide (LSD) entered the scene, there have been thousands of descriptive reports vividly depicting such visual experiences as the pristine beauty of the pearl-covered mountains described by a variety of laymen and scientists. An attempt will now be made to examine the pearls more critically, and to determine from the point of view of visual scientists how on earth they reached this unlikely perch.

OCULAR PHARMACODYNAMICS

Albert M. Potts
Department of Ophthalmology
University of Chicago

Although the desirability of obtaining drugs that influence the visual process favorably is perfectly evident, most of the actual effects here reported deal with deleterious influences of drugs. Investigation in this area is, however, by no means an exclusively rear-guard action, for the knowledge that is gained of the functioning of the visual system under the influence of deleterious drugs leads to a knowledge of normal function and how to modify it in both directions.

The action of drugs on the eye is specifically conditioned by a number of factors which are unique to the eye. One of these has to do with the way ocular anatomy and physiology determine the access of drugs to the intraocular structures where their actions are exerted. The ionizability of a drug, the pH and tonicity of the solution carrying it determine how much will penetrate the multiple-layered cornea and reach the interior of the eye. To get beyond the anterior chamber, the drug must resist the sluggish but real current of aqueous humor which tends to wash it out once more. Furthermore, the location of the end-organ, whether in the anterior chamber as with the iris, or in the posterior chamber as with the ciliary body, will determine what effective concentration of locally applied drug will reach its destination.

Systemically administered medications have different but equally stringent conditions laid upon them. They must either diffuse into the eye from the vessels of choroid, iris, and ciliary body, or they must be actively secreted with the aqueous humor, or they must diffuse from the limbal vessels into the avascular cornea. Which of these occurs will largely be determined by the chemical nature of the substance in question, and one may find selective secretion into the eye of substances like ascorbic acid, or selective exclusion from the eye as in the case of urea, or even extrusion from the eye as in the case of certain iodinated contrast media. The breathtakingly rapid advances in biochemistry have been reflected in changing concepts of mechanisms of drug action. Now, when the actual three-dimensional structure of protein molecules, as in the case of myoglobin, can actually be diagrammed, the concept of molecular site of drug action can rapidly pass the stage of theorizing. The work of Wilson on the nature of the site for anticholinesterase activity, and the

work of Belleau on the nature of the adrenergic receptor site deal with the bonding of functional groups of the sort that occur in known protein structures, and the day in which stoichiometric pharmacology reaches its ascendency may be very near, indeed. With pharmacology at the molecular level in this way, the unique advantage that the iris offered as a test object behind a transparent window is no longer as all-absorbing as it once was. However, the new work in molecular pharmacology will contribute to the knowledge of how ocular autonomic structures operate, but a number of problems in the area still remain to be solved. This is particularly true in the area of the control of intraocular pressure. Despite the possibility of dual control of rate of aqueous formation and rate of aqueous outflow, it is not completely understandable why a parasympathetic stimulator such as pilocarpine can lower the intraocular pressure, and a sympathetic stimulator such as epinephrine can accomplish the same effect. This is all the more curious when certain adrenergic inhibitors, given locally, can once again cause decrease of intraocular pressure.

With the increasingly rapid rate of appearance of new drugs on the scene, the advent of some with unique actions on the eye is apparently increasing in frequency. Explaining these unique actions is a fascinating occupation. Witness one of the studies in progress in the author's own laboratory. Some years ago it was found that certain phenothiazine tranquilizers cause a pigmented choroidopathy in humans. Subsequent investigations revealed the curious phenomenon that phenothiazines and other polycyclic compounds store in the pigment of the uveal tract in higher concentration than anywhere else in the body. This storage, which also occurs with synthetic melanin, may well be attributable to the charge transfer reaction which is only now being studied intensively by biologists. It has been recently shown in the laboratories of the National Institutes of Health that the antimalarial drugs which exhibit a different type of ocular toxicity are also stored in the uveal tract. This is cited simply as an unsuspected and new aspect of the ocular toxicity of chemical compounds, and how knowledge of dynamics in this case may lead to prevention of damage from future similar compounds, and may also prove an effective way of directing desirable substances into the eye.

Thus, preoccupation with the pharmacodynamics of harmful compounds is largely a measure of relative ignorance. As this ignorance is dispelled by increasing knowledge in the area, toxicity can be avoided and beneficial effects can be controlled.

THE SENSORY EFFECTS OF DRUGS: ELECTROPHYSIOLOGICAL INVESTIGATIONS OF THE MECHANISM OF THE ACTION OF DRUGS ON THE EYE

Geoffrey B. Arden
Department of Physiology
University of California Medical Center[1]
San Francisco

Since only about six of the many thousands of references in each volume of ophthalmic literature deal with the electrophysiological investigation of the action of drugs, this review is in one sense easy to write. However, the fact that so little work is being done makes it impossible to cover the pharmacology of the retina in any comprehensive fashion. Therefore, this report discusses the methods available to the electrophysiologist, and how they may be used to investigate the mechanism of drug action. Illustrations mainly from the author's own work are used since several of the most prominent workers in this field have recently given their own reviews of their experiments (Noell, 1958; Potts, 1962).

The great advantage of electrophysiological techniques is that one can use them to determine the precise level in the retina that is affected by a particular drug. Perhaps the most interesting observations concern the steady potential of the eye, which is produced not in the retina proper, but in the pigment eipthelium which lies behind it. Since the rods and cones have no blood supply, their metabolic requirements must be met by the pigment epithelium cells. In particular, it has been shown that the pigment epithelium is concerned in the synthesis of visual purple. Vitamin A, liberated by the photolysis of rhodopsin, actually travels out of the rods into pigment epithelium cells. There it is modified before being transported back into the receptors (Dowling & Gibbons, 1960).

These observations form the background of work undertaken (Arden & Fojas, 1962a) to elucidate the mode of action of diaminophenoxyalkanes. These compounds have a schistosomiacidal action, and were at first thought to be non-toxic. Indeed, it was only when the research chemists concerned took the drugs themselves, that a retinotoxic activity was disconvered. Subsequently, it was found that cats and frogs too could develop a diaminophenoxyalkane retinopathy, and histological studies in cats showed that the

---

[1] Current address: Institute of Ophthalmology, Judd Street, London W.C.1, England.

outer part of the retina is affected (Ashton, 1957). With this in mind, a method for the assay of the retinotoxicity was developed, based on the decrease in the concentration of visual purple in the frog retina after administration of the drug (Goodwin, 1957). Of course, any chemical which kills retinal receptors will stop the accumulation of visual purple, but it seemed likely that the assay method was doing more than causing the death of rods: perhaps the diaminophenoxyalkane was affecting the visual purple cycle, possibly via the pigment epithelium.

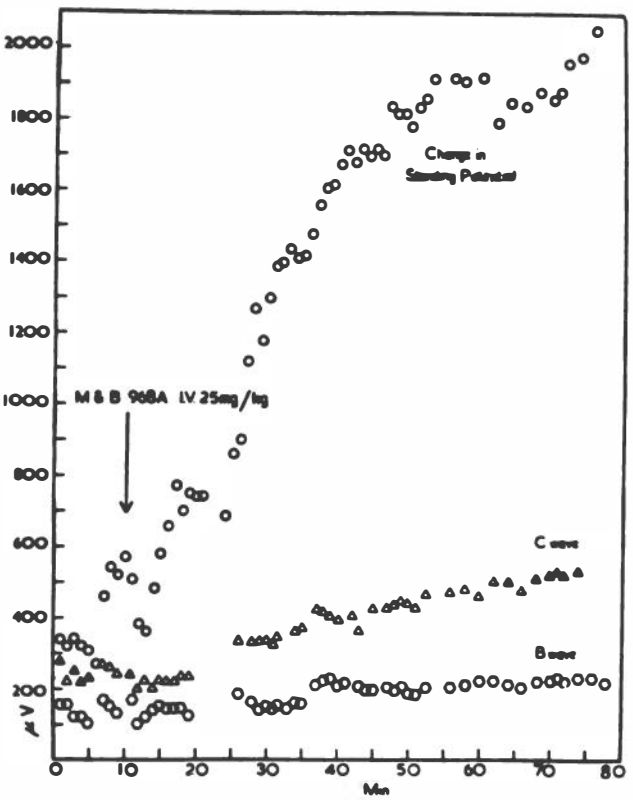

Fig. 1. Action of phenoxyalkane derivative on rabbit eye. Note increase of D. C. eye potential, and c-wave, while b-wave unaffected. (Arden & Fojas, 1962a)

Figure 1 shows the effect of an intravenous dose of a modified phenoxyalkane in a rabbit. The steady potential of the eye increases very greatly, and at the same time, the c-wave amplitude also increases. This action is exactly the same as that caused by small doses of sodium azide, another drug which selectively damages the pigment epithelium (Noell, 1953). It will be noted, however, that the b-wave of the electroretinogram (ERG) is unaffected by the injection. This is not surprising because the rabbit does not suffer from a retinopathy after injection of phenoxyalkanes

(there is a marked species specificity), and the amount of the injection is smaller than would cause a retinopathy, even in a susceptible cat. It seems, therefore, that this class of drugs interferes with the pigment epithelium in smaller doses than are required to produce a retinopathy. This deduction has recently been confirmed. It has been shown that the P 32 uptake of pigment epithelium is abolished by diaminophenoxyalkane, but the uptake of retina is not affected (Glocklin & Potts, 1962).

Of course, there was considerable interest in discovering what functional disturbance, if any, resulted from sub-toxic doses of diaminophenoxyalkane. The author and his associates found it possible to give cats a small dose of a phenoxyalkane derivative which produced no ophthalmoscopic or long-term electrophysiological abnormality. However, the drug had an effect on the retina, as was discovered when the ERG dark adaptation curve was measured. This is shown in Fig. 2.

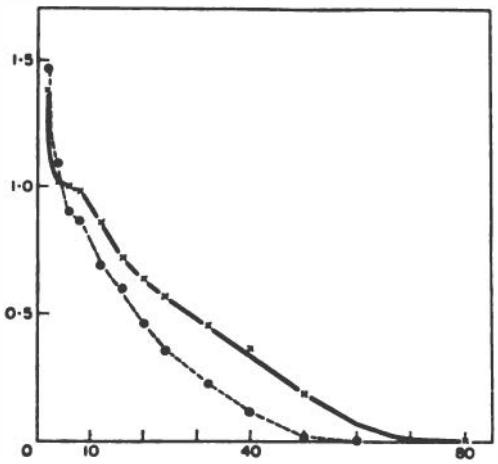

Fig. 2. ERG dark adaptation curves before (•) and after (x) administration of phenoxyalkane derivative. Drug did not affect waveform or sensitivity of dark-adapted ERG. (Arden & Fojas, 1962a)

Each point represents the intensity of light required to elicit a b-wave of constant amplitude at various times after the end of moderate light adaptation. After administration of the drug, the cat's eye dark-adapts more slowly than normal. The final dark-adapted threshold of the retina is unaffected by the drug. Also, the early part of dark adaptation is not really altered. This early part is predominantly "neural," while the later part of dark adaptation may, in part, reflect the accumulation of rhodopsin.

Interpretation of this result was, therefore, that the drug had affected the rate of synthesis of visual purple, but the retinal neurones were unaffected, and it was speculated that the diaminophenoxyalkanes might be specific poisons for some part of the rhodopsin cycle.

That suggestion will remain a speculation until the photochemists and biochemists attack the problem, but it is reasonable. It is interesting that many compounds which are relatively inactive in other sites in the body specifically affect the pigment epithelium. For example, the phenothiazines are specifically concentrated in the uveal tract, and although this has not been proven to be the mechanism of the retinotoxic effect, it seems likely. If one is looking for a difference between pigment epithelium metabolism and the metabolism of other structures in the body, the visual purple cycle, with its unique use of vitamin A, springs instantly to mind. Of all the ill effects produced by phenothiazine retinopathy, the impairment of dark adaptation is most striking (Burian & Fletcher, 1958).

The clinical effects of the drugs mentioned to date are negligible. However, one occasionally retinotoxic compound, chloroquin, is in common use, and clinical accounts of chloroquin retinopathy are becoming more and more common. So far, the disease has not been reproduced in any animal, and experimental pathology is not available. In man, the symptoms and signs of the retinopathy are variable. It is striking that the onset of the condition is quite sudden and occurs after many years of drug administration, during which there have been no obvious ill effects. Even though the drug is then withdrawn, the retinopathy may progress, so that though there may be some slight recovery from the acute phase, progressive deterioration of visual function follows. This is paralleled by a slow appearance of pigment in the fundus.

It is possible to investigate pigment epithelium function in man. The steady potential of the eye cannot be measured directly, but, since it gives rise to the eye movement potential, a method based on the electrooculogram can be devised to test the functional capability of the pigment epithelium (Arden, Barrada, & Kelsey, 1962). The technique is explained in Fig. 3. Owing to the geometry of the globe, the potential difference recorded between electrodes placed near the medial and lateral canthi varies with eye position, and a sudden standard eye movement can be recorded as an artifact-free voltage change. The magnitude of the voltage varies from person to person, and depends on the shape of the orbit and the position of the electrodes. However, if the eye movement potential alters in the same person from minute to minute, this reflects a change in the magnitude of the generator of the potential. It has been found that alteration of retinal illumination affects the steady potential in a characteristic way. It falls to a minimum in dark adaptation and rises to a peak in subsequent light adaptation. The percentage change in potential is relatively constant in normal eyes, and is decreased in disease. These findings have been elaborated into a clinical test, the electrooculogram (EOG). Since analogous experiments have not been performed in animals, there

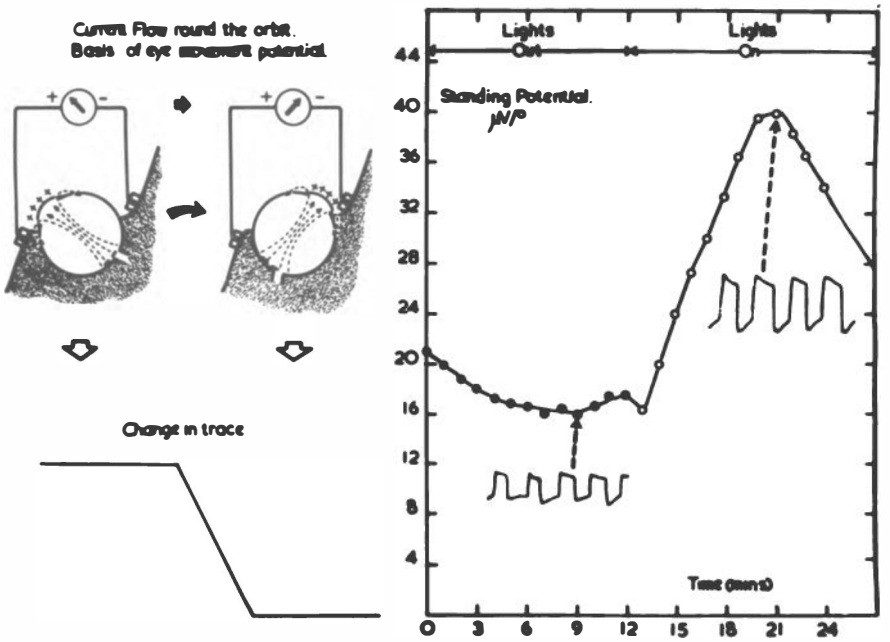

Fig. 3. Use of corneo-fundal potential as index of retinal function. Left—schematic cross section of eye with skin electrodes showing how rotation of eye alters p.d. between electrodes. If eye movements are standard, observed p.d. is constant fraction of corneo-fundal potential. Right—observed changes in corneo-fundal potential with change of retinal illumination. Sequence is that adopted in clinical testing, and more prolonged complex potential oscillations occur. (Arden, Friedman, & Kolb, 1962)

is no absolute proof that the EOG potential is generated in the pigment epithelium. However, it is easy to show in man that the EOG is affected in retinal detachments and in choroiditis where the neuroretina is still functioning. These observations are analogous to the animal experiments which established the site of origin of the steady potential in animals, so the evidence is fairly compelling. Again, it is not understood why the potential changes are related to retinal illumination. It is easy to show that they are linked to the rhodopsin cycle, but this merely means that light has no direct action on the pigment epithelium and has no further localizing value (Arden & Kelsey, 1962a; 1962b). The potential is certainly maintained by active metabolism—it is very sensitive to anoxia—and it is convenient to think of the EOG as testing the maximum working rate of some metabolic process within the pigment epithelium.

In chloroquin retinopathy, the EOG is abnormal (Fig. 4). The figure summarizes some of the results obtained in a severely affected patient.

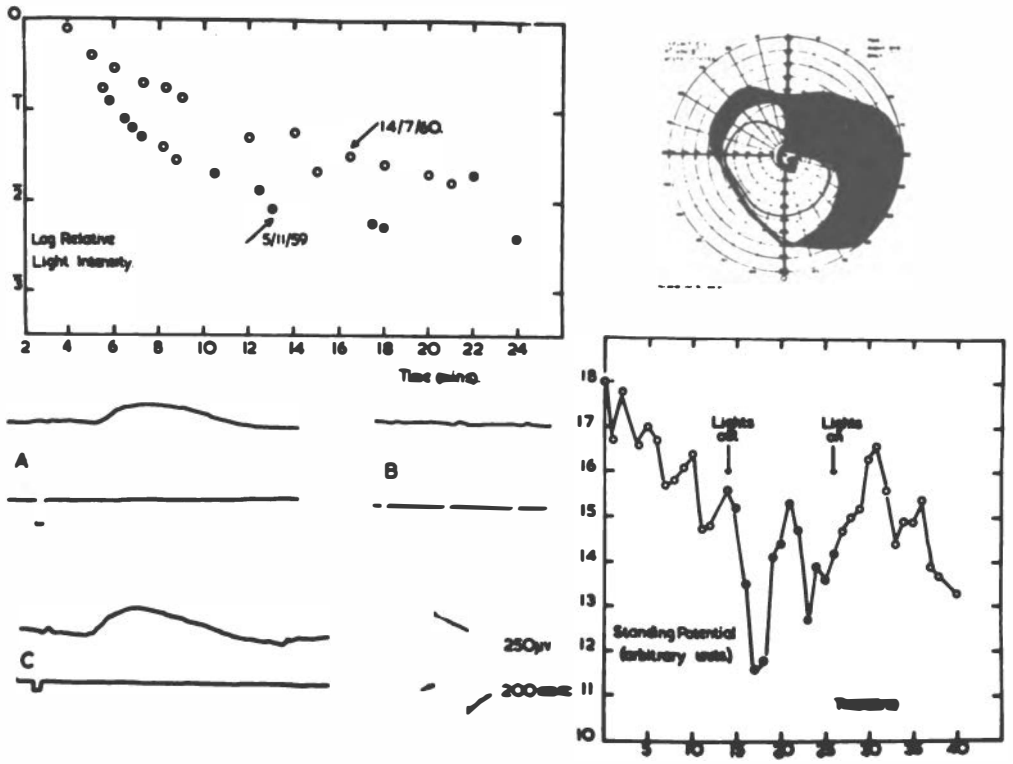

Fig. 4. Some electrophysiological and clinical abnormalities in chloroquin retinopathy. Upper R—visual field. Upper L—dark adaptation curves, showing progressive deterioration. Lower L—ERG A & B—moderately light-adapted; C, fully dark-adapted; lower R—EOG. (Arden & Fojas, 1962b)

There is great field loss, dark adaptation is incomplete, and the ERG is abnormal. The b-wave is tiny, and it is followed by an unusually large c-wave, which in this case is not a pupillary artifact. It recalls the large c-waves found in azide-poisoned rabbits. The EOG, lower right, is grossly abnormal and, though there are large "spontaneous" fluctuations in potential, the normal response to illumination is completely absent. In other cases of this condition that have been encountered by the author, even in mild ones where field loss was minimal and the ERG normal, there has always been a depression of the EOG. Even in patients taking chloroquin, in whom there are no signs of a retinopathy, and in whom the ERG and subjective tests are absolutely normal, the EOG may be depressed (Arden, Friedman, & Kolb, 1962).

Since it has proved possible to use ERG and EOG to distinguish between different sorts of drug action, it might be thought possible to use the various components of the ERG in the same way. This is especially true since the demonstration (Brown & Wiesel, 1961a, 1961b) that the

negative component of the mammalian ERG, PIII, is produced by the receptors, and the positive components are produced by cells in the inner nuclear layer. While this work will certainly be applied to understanding the mechanism of drug action, it is not easy to do so, particularly in man, and there are right and wrong ways of going about this task. For example, in the investigation of the diaminophenoxyalkanes, Fojas and the author naturally gave larger doses than those mentioned above. When this is done, the ERG waveform changes considerably (Fig. 5). Immediately after the administration the ERG gets bigger; and then it declines in amplitude until the b-wave has vanished and only

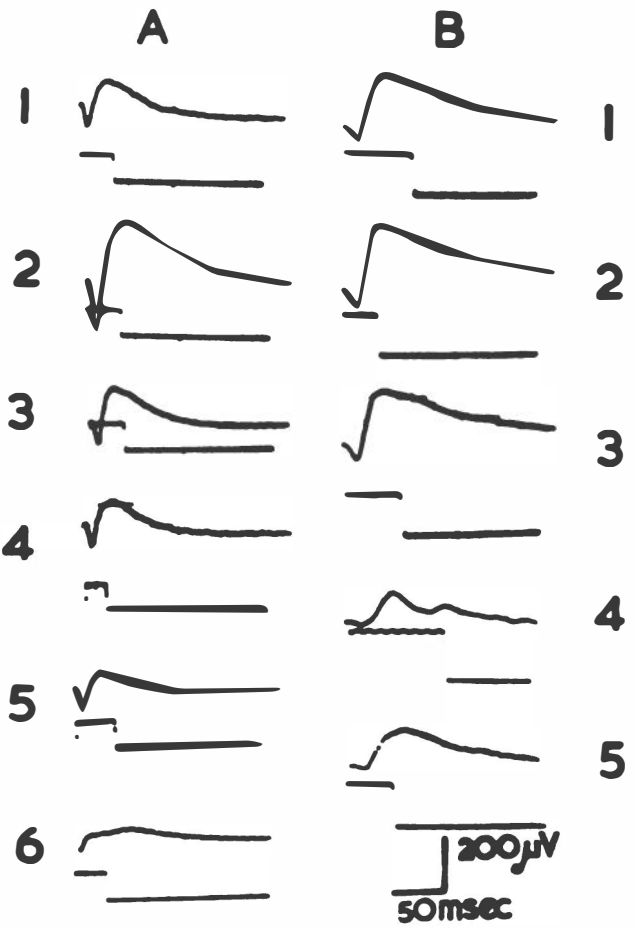

Fig. 5. Effect on cat ERG of toxic dose of modified phenoxyalkane. Left-hand column: 1. control record; 2. immediately subsequent to injection; 3. 2 min later; 4. 10 min; 5. 20 min; 6. 40 min. Right-hand column: effect of smaller dose: 1 and 2 as before; 3. 1 hr later; 4. 1 wk later; 5. 4 wks later. (Arden & Fojas, 1962a)

the a-wave is left. Such a sequence of events has often been observed, and equally often it has been assumed that the b-wave is selectively damaged by the drug. This assumption is quite unwarranted, as subsequent results showed. Any and every toxic agent, from nembutal to anoxia, can produce this series of changes, so it is entirely non-specific.

The trouble is that the ERG is the algebraic summation of two potentials of opposite sign (Granit & Riddel, 1934), and each in isolation is much bigger than the entire combined ERG. Therefore, a change like that shown in Fig. 5 could also be due to an increase in the size of the a-wave component. Another difficulty facing the interpretation of the ERG abnormalities is the fact that it is produced by the entire retina, mainly by light scattered in the fundus. A localized lesion will not affect the ERG and if in the presence of a large area of retinal damage the ERG is abnormal, it is not possible to decide, in any one case, what fraction of the recorded ERG is derived from the small area of normal retina, and how much represents the diminished response of the diseased tissue. Even if a microelectrode is thrust into the retina, as can be done in animals, it still records the ERG of the entire eye, unless special precautions are taken. In clinical practice it is hoped that the use of weak, localized retinal illumination, and computer techniques will enable the response of small areas of retina to be distinguished. The microelectrode experiments referred to are not entirely convincing: but if the computers succeed, this will be obvious. The true focal ERG has a waveform which is in many respects dissimilar to that seen with conventional recording. Another reason for mistrust of ERG analysis is that alterations in the ERG amplitude may be due to non-visual factors, e.g., an alteration in the distribution of the recording resistance. Finally, in clinical practice, the technique is very difficult, so that although many workers have published very handsome individual records, the incidence of unrepeatable results is high. For these reasons, it is necessary to be extremely circumspect in attempting to relate ERG and psychophysical data. One way in which this may be attempted is the analysis of dark adaptation, as shown in Fig. 2. However, even here caution is necessary. The dark adaptation curves in the figure extend over a small sensitivity range of only 3 log units. This implies that the light adaptation used was fairly weak, as was the case. It is possible to do better than this but then the ERG waveform changes considerably, and there seems to be no valid reason for relating the sensitivity of the eye to a constant voltage of ERG if, early in the experiment the response is a sharp spike, superimposed on a continuous negative drift, while later it is a gently rising positive wave.

A good example of the potentialities and the limits of the ERG is provided by a recent investigation by Dr. Ikeda, in the clinic in London (Institute of Ophthalmology) on the effect of alcohol on vision and the ERG. When the fully dark-adapted subject takes alcohol by mouth, the flicker-fusion frequency decreases and the visual threshold decreases slightly, i.e., the visual system becomes more sensitive as though dark-adaptation had progressed further than is normally possible (Fig. 6).

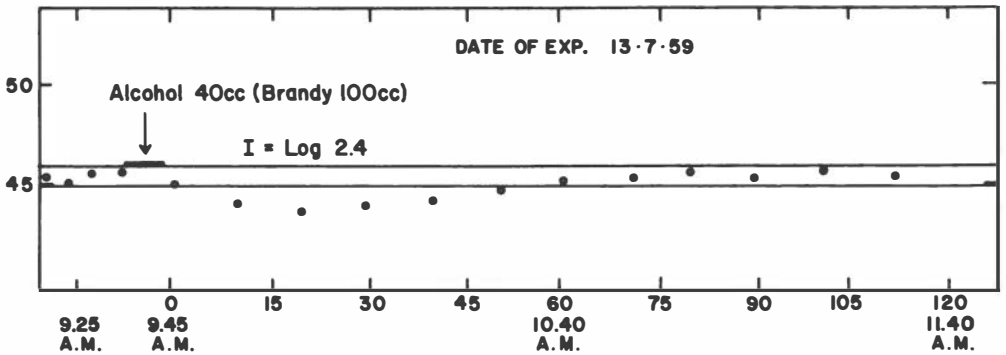

Fig. 6. Effect of alcohol on flicker fusion rate of human subject. Ordinate—flashes/sec. Abscissa—time. Note time course of effect. (Ikeda, 1963)

The effect on the intoxicated subject (in this case Dr. Ikeda herself) is small, and runs a peculiar time course. When lovely woman stoops to folly to the extent of 100 milliliters of brandy, the effect is not maximal after 15 minutes, nor is it over at about an hour. The ERG (Fig. 7) also increases and decreases in amplitude along the same time course, and the correspondence is so good that it is possible to state that alcohol has an effect on the receptors or on the inner nuclear layer. The change in amplitude in the ERG is rather striking, much more so than the actual change in sensitivity, but if one carries the analysis a little further, it can be seen that this is not really the case. In the fully dark-adapted eye, a large increase in b-wave amplitude results from a small change in light intensity. In addition (Fig. 8), the action of alcohol varies with the light

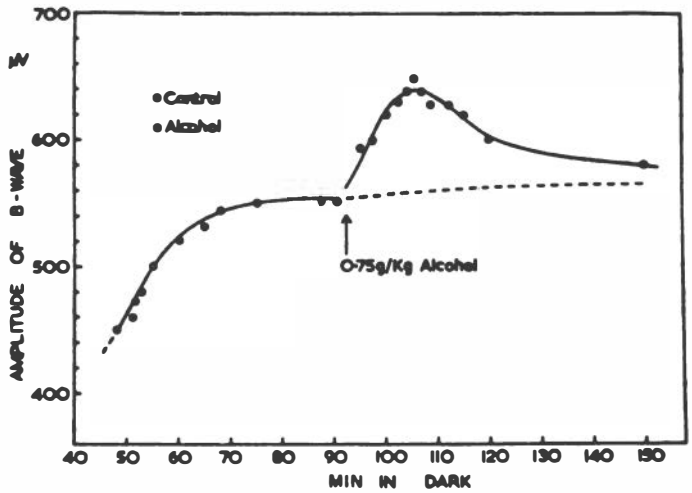

Fig. 7. Effect of alcohol on dark-adapted ERG. Note similarity in time course between ERG and psychophysical changes of Fig. 6. (Ikeda, 1963)

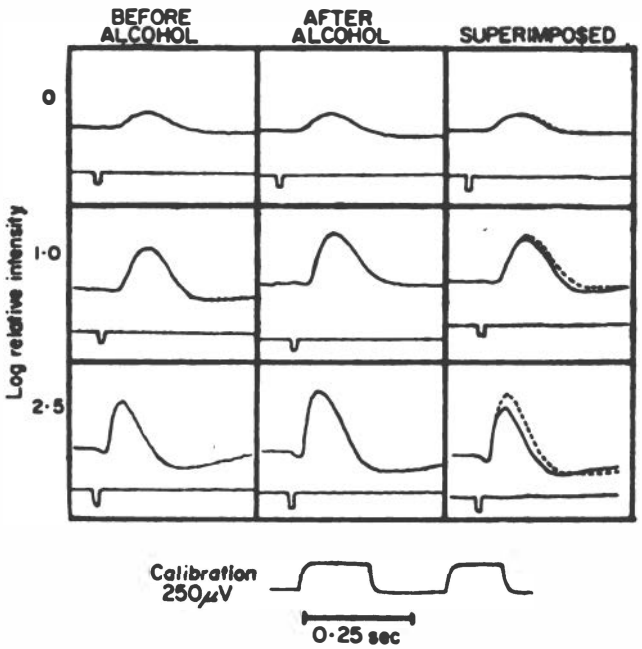

Fig. 8. Waveforms of ERG's before and after alcohol. Note later part of ERG is affected. On right, two traces are shown superimposed, with that taken after alcohol shown dotted. (Ikeda, 1963)

intensity used to evoke the ERG. When the b-wave is small the alcohol has little effect, while intense lights cause a proportionately greater increase. Since all the stimuli needed to evoke ERG's were much more intense than those used in the psychophysical experiments, it is impossible to relate the b-wave to the subjective threshold, and only the correspondence of the time courses enables one to be sure this is the same phenomenon.

Dr. Ikeda's ERGs are possibly the best ever recorded from a human subject. The contact lens electrode was individually fitted, and the subject selected. As a consequence, the ERGs are large and artifact-free. They were recorded on a distortion-free system, and Dr. Ikeda has been able to superimpose ERGs taken before and after the administration of alcohol. It can be seen that it is the latter part of the b-wave that has been affected. In view of the fact that the spikes in the cat's optic nerve have a shorter latency than the conventionally recorded ERG, it seems most unlikely that the observed alteration in b-wave amplitude can have any bearing whatsoever on what the cat actually sees, or that it is possible to extrapolate such results to human thresholds; yet this is commonly done by electrophysiologists. This is not to imply that electrophysiological

results cannot be used to infer anything about the mechanism of vision, but of course this must be done in terms relevant to electrophysiology. It is interesting to speculate a little on how one may interpret Dr. Ikeda's results.

First of all, how do these experiments compare with others in which the eye has been treated with alcohol? The increase in amplitude of the b-wave was first demonstrated by Bernhard and Skoglund (1941), but they also observed that as the b-wave increased in size, the a-wave disappeared. Their interpretation was that alcohol selectively reduced PIII, the negative component of the ERG. They were quite aware that the a-wave might merely be hidden in the enlarged b-wave, but other observations made them reject this idea. Now that it is known that the a-wave is the leading edge of a much larger receptor potential, it seems less likely that the interpretation of Bernhard and Skoglund was correct, and it seems possible to explain their results in another way. For the moment, however, it should be pointed out that in Dr. Ikeda's experiments, the a-wave is unaffected by alcohol so that reinterpretation is necessary. There is a discrepancy here, which may be due to the different concentration of alcohol, or to the different stimulus conditions in the two series of experiments. This naturally brings to mind the question of under just what conditions can the b-wave be shown to be increased after alcohol administration. In the human experiments, the dosage of alcohol is limited. A 120-pound woman can take 100 ml of brandy on an empty stomach, but not much more. Therefore, other stimulus parameters had to be altered. Chief of these was the intensity, and rate of repetition of the stimulus. When this was done it was found that the results after alcohol could be quite different. With a moderate repetition rate—say, 1 flash per second—the ERG was smaller, not bigger in amplitude. This is shown in Fig. 9. There is a curve relating ERG amplitude and stimulus-repetition rate, which to a first approximation is an exponential. What alcohol has done is to change the time constant of the exponential. This correlates with the fact that alcohol decreases the flicker fusion rate.

With this finding, the effect of alcohol on the ERG is more understandable, for it is exactly the same as the effect of anaesthetics, like nembutal, which also have the twin effects of making the single flash ERG bigger, but decreasing the amplitude of the responses to a series of flashes. This phenomenon has been analyzed in the cat (Arden, Granit, & Ponte, 1960); in man it appears quite similar. During retinal illumination, some process builds up in the retina with apparently the same time course as retinal excitation itself, and has the property of suppressing the response to a subsequent stimulus. For this reason, the process was called "suppression." It outlasts the stimulus, and decays exponentially after the end of the stimulus. The effect of alcohol and anaesthetic agents can be described by saying that they increase the amplitude of the b-wave, and increase the time constant of suppression.

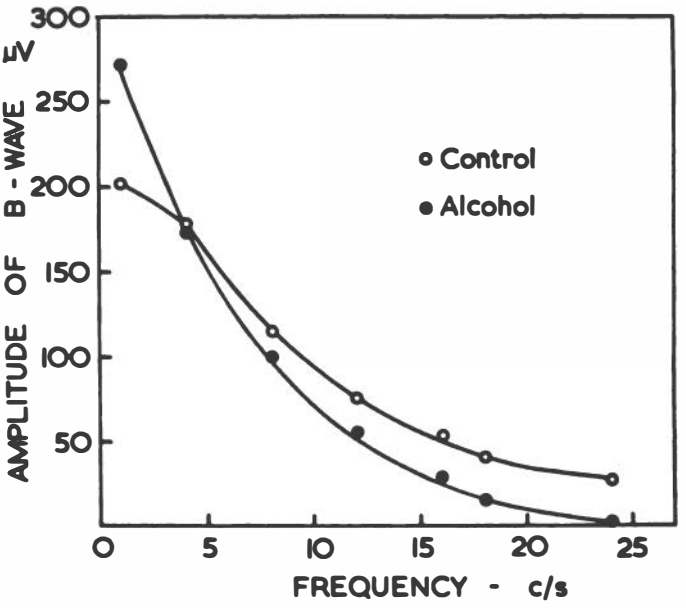

Fig. 9. Amplitude of b-wave as function of flicker frequency. Administration of alcohol increases size of b-wave only if stimulus repetition rate is low. (Ikeda, 1963)

The next step is to find some electrical expression of this process, and it is possible that this has been achieved. In some recent experiments, Dr. Brown, Dr. Murakami, and the author have been investigating the effect of nembutal on the isolated receptor potential of mammalian retina. When the stimulus begins, there is an abrupt change in potential, cornea negative, and the potential is maintained throughout the subsequent illumination. When the stimulus ends, the potential gradually returns to its previous resting level. The action of light seems to be merely to change the receptor potential to a new level, from which it recovers exponentially with a time course which approximates the ERG suppression; the action of nembutal is to increase greatly the size of the change in receptor potential produced by any light stimulus, as can be seen in the fast sweeps of Fig. 10. In addition, the recovery of the receptor potential is delayed. It is difficult to see this, for though it is easy to eliminate the b-wave (Brown & Watanabe, 1962), the receptor potential cannot be obtained without an interfering c-wave. However, by illuminating the retina, and temporarily interrupting the light—stimulating, as it were, by brief flashes of darkness—one can see the recovery process, and this is so slowed by nembutal that in some experiments no return of the receptor potential toward the base line level can be seen for as long as a second.

So, although none of these electrical phenomena can be seen in the intact eye, there is a plausible explanation for the effect of nembutal on the normal ERG, and, extrapolating boldly, for the effect of alcohol on

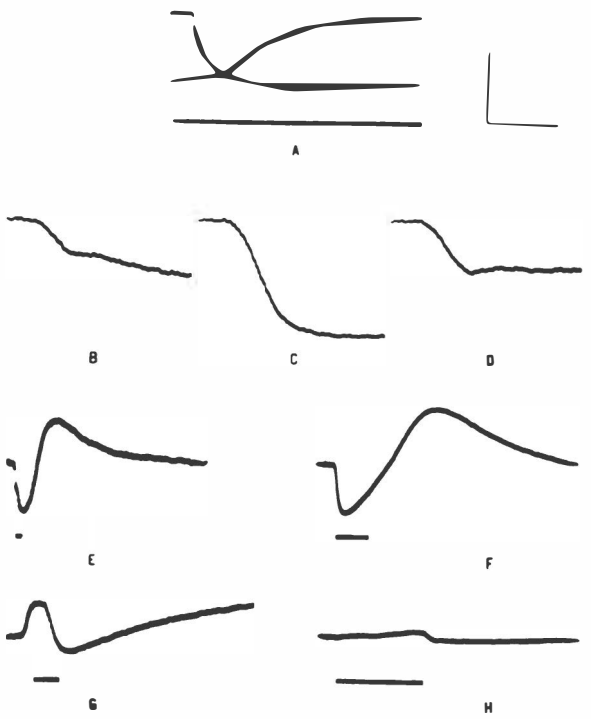

Fig. 10. "Receptor potentials" of mammalian retinas. Records obtained with electrodes in vitreous and on sclera, after selective blocking of retinal circulation.

A. Waveform obtained from night monkey in which c-wave is very small. Two sweeps superimposed. At beginning of stimulus (downward pip) cornea-negative potential develops, and is maintained through 5.2 sec illumination. When stimulus ends, potential slowly returns to base line (cal. 500 μV, 0.5 sec).

B, C, D. Effect of injecting 5 mg nembutal i.v. on cat receptor potential. Only initial development of potential shown on these fast sweeps (cal. 500 μV, 20 ms). B—control. C—following injection. D—recovery. Note great transient increase in effect of light.

E, F, G, H. Recovery of cat "receptor potential" in different stages of anaesthesia. E,G—lightly; F,H—deeply anaesthetised. Receptor potentials E & F are of equal amplitude, but recovery phase cannot be seen due to large positive C-wave. In G & H, retina constantly illuminated and signals show short periods (280 ms) of darkness. In this way, C-wave is eliminated and it can be seen that rate of recovery of receptor potential in G, lightly anaesthetised, is greater than in H. Calibrations, 500 μV and 500 ms for E and G; 200 ms for F and H.

vision. It seems likely that both these drugs affect the receptors, so that a given quantity of light causes a greater depolarization of their terminals, but the repolarization in the dark is slower. A second stimulus, following close on the first, will now depolarize the receptors to the active level, but because recovery has been delayed, the change in observed potentials as normally seen (the a- and b-wave, and subsequent discharge of nerve impulses) will be smaller than usual. In psychophysical terms, one would predict that the dark-adapted threshold would decrease, and that the flicker fusion frequency would also decrease. This is just what occurs. One is also in a position to explain Bernhard's interpretation of the effect of alcohol on the frog eye. Observing a diminishing a-wave and an enlarging b-wave, he suggested that alcohol depressed PIII—the negative component of the ERG. This interpretation was strongly supported by experiments in which the eye was reilluminated at the time of the "off response." In the frog, this leads to the production of a large a-wave and the appearance of pre-excitatory inhibition. After treatment with alcohol, the a-wave is not seen, and this suggests that PIII is suppressed. Bernhard was unable to obtain either PIII or PII in a pure form and, therefore, his results can be equally well explained by supposing that PIII was in fact increased, but its recovery delayed.

These observations, then, may not only explain an old and puzzling ERG phenomenon, but may aid in understanding the effects of drugs on vision. The most interesting point to notice is the progress made from the observation of an increased b-wave amplitude to an increased sensitivity and delayed recovery of a receptor potential. How far from the truth would have been merely an attempt to relate crude electrophysiological and psychophysical data.

References

Arden, G., Barrada, A., & Kelsey, J. New clinical test of retinal function based upon the standing potential of the eye. Brit. J. Ophthal., 1962, 46, 449-467.

Arden, G., & Fojas, M. The mode of action of diaminophenoxyalkanes and related compounds on the retina. Vision Res., 1962, 2, 163-173. (a)

Arden, G., & Fojas, M. Assessment of the value and the basis of electrophysiological abnormalities in pigmentary degenerations of the retina. AMA Arch. Ophthal., 1962, 68, 369-390. (b)

Arden, G., Friedman, A., & Kolb, H. Anticipation of chloroquine retinopathy. Nature (London) 1962.

Arden, G., Granit, R., & Ponte, F. Phase of suppression following each retinal b-wave in flicker. J. Neurophysiol., 1960, 23, 305-314.

Arden, G., & Kelsey, J. Changes produced by light in the standing potential of the human eye. J. Physiol., 1962, 161, 189-205. (a)

Arden, G., & Kelsey, J. Some observations on the relationship between the standing potential of the human eye and the bleaching and regeneration of visual purple. J. Physiol., 1962, 161, 205-224. (b)

Ashton, N. Degeneration of the retina due to 1.5 Di (p-aminophenoxy) pentane dihydrochloride. J. path. Bact., 1957, 74, 103-112.

Bernhard, C., & Skoglund, C. Selective suppression with ethyl alcohol of inhibition in the optic nerve and of the negative component PIII of the electroretinogram. Acta Physiol. Scand., 1941, 2, 10-21.

Brown, K., & Watanabe, K. Rod receptor potential from the retina of the night monkey. Nature (London), 1962, 196, 547 & 550.

Brown, K., & Wiesel, T. Analysis of the intraretinal electroretinogram in the intact cat eye. J. Physiol., 1961, 158, 229-256. (a)

Brown, K., & Wiesel, T. Localisation of origins of electroretinogram components by intraretinal recording in the intact cat eye. J. Physiol., 1961, 158, 257-280. (b)

Burian, H., & Fletcher, M. Visual functions in patients with retinal pigmentary degeneration following the use of NP-207. AMA Arch. Ophthal., 1958, 60, 612-629.

Dowling, J. E., & Gibbons, I. The effect of vitamin A deficiency on the fine structure of the retina. In G. K. Smeltzer (Ed.), The structure of the eye. N.Y.: Academic Press, 1960. Pp. 85-100.

Glocklin, V., & Potts, A. Metabolism of retinal pigment of cell epithelium. 1. The in vitro incorporation of P-32 and the effect of diaminodiphenoxyalkane. Invest. Ophthal., 1962, 1, 111-117.

Goodwin, L. G., Richards, W. H. G., & Udall, V. The toxicity of diaminodiphenoxyalkanes. Brit. J. Pharmacol., 1957, 12, 468-474.

Granit, R. & Riddel, L. The electrical responses of light- and dark-adapted frogs' eyes to rhythmic and continuous stimuli. J. Physiol., 1934, 81, 1-28.

Ikeda, Hisako. Effects of ethyl alcohol on the evoked potential of the human eye. Vision Res., 1963, 3, 155-169.

Noell, W. Studies on the electrophysiology and metabolism of vision. Brook AFB: USAF Sch. av. Med. Rep., 1953, No. 1. (Proj. No. 21-1202-0004)

Noell, W. Differentiation, metabolic organization and viability of the visual cell. AMA Arch. Ophthal., 1958, 60, 702-738.

Potts, A. Concentration of phenothiazines in the eye of experimental animals. Invest. Ophthal., 1962, 1, 522-530.

STUDIES IN THE PHARMACOLOGY OF EXTRAOCULAR MUSCLES[1]

G. M. Breinin and J. H. Perryman

The literature has suggested that extraocular muscle is a primitive type intermediate between striated muscle of mammals and lower forms, and that it demonstrates an affinity with smooth muscle. These unusual features have been linked to the peculiar nerve supply and highly specialized functions of extraocular muscle. The anatomical and histological distinction of extraocular muscle, its low innervation ratio, variety of nerve and nerve endings, and membrane-permeability characteristics have been adduced in explanation of certain aspects of ocular motility. Studies of the authors, however, tend to show that differences between eye muscles and limb muscles are quantitative rather than qualitative, and may be considered modifications related to the highly specialized nature of eye movements.

This paper summarizes a series of experimental observations on the pharmacology of extraocular muscles in cat and dog, primarily addressed to the question of whether the postulated uniqueness of extraocular muscle actually exists and, if so, to what extent. The failure of epinephrine to elicit muscle contraction was seen. Epinephrine in massive dosage injected directly into the carotid artery produced no measurable change in the rest tension of the inferior oblique, lateral, or medial rectus, while changes in the epinephrine-sensitive structures in the orbit (nictitating membrane and pupil) were readily observable. A gross comparison was made between the effect of acetylcholine in the extraocular muscle and that in the limb muscle. An injection of 80 micrograms (μg) of acetylcholine into the carotid regularly produced maximal contraction of extraocular muscles. The drug was administered with a hypodermic syringe through a polyethelene cannula tied into the stump of the lingual artery. Eighty μg of acetylcholine injected into the popliteal artery also produced a strong contraction of the anterior tibial muscle. With intracarotid injection, it required about 30 to 50 μg of acetylcholine to produce a significant ocular muscle contraction, while anterior tibial contraction could be produced with as little as 2 to 5 μg of acetylcholine. It is difficult to draw conclusions as to the relative sensitivity of ocular and limb muscles to acetylcholine since the responses are so largely affected by the technique employed. It is clear, however, that both types

[1] In M. B. Bender (Ed.). In the oculomotor system symposium, in press.

of muscle respond briskly to minute amounts of acetylcholine. Choline is said to produce a slow, tonic contraction of extraocular muscle and to be without effect on innervated skeletal muscle. Although large amounts are required to evoke a response, a definite contractile effect (with about 100 times concentration of acetylcholine) was seen in both extraocular muscle and anterior tibial muscle with close arterial injection. Nicotine was also tested. It was found that with close arterial injection as previously explained, strong contraction could be elicited from the extraocular muscle with the intracarotid injection of 1 cubic centimeter of nicotine in a 0.1 per cent solution of saline, and with one-half of this amount in the normal anterior tibial muscle. Topical application of atropine in vivo was ineffective, while close arterial injection would produce a short-term block in both sets of muscle. Intravenous or intracarotid injection of succinylcholine produced a strong, sustained extraocular muscle contraction. Close arterial injection of the anterior tibial muscle, however, produced a comparable result.

Differences in the route and technique of drug administration can produce marked differences in result. An intracarotid injection is in reality a close arterial injection of extraocular muscle. A comparison of effect in other muscles can be made only when they also receive a close arterial injection, especially when a drug is quickly inactivated in the blood as in the case of acetylcholine. The amount of drug, the rate of injection, and the volume of diluent are interrelated factors in making a comparison of drug effect in different muscles. The effector site is the motor endplate. The peripheral skeletal muscle has proportionally fewer effector sites than the extraocular muscle, and these are spread out because of larger mass. The flow velocity and percentage saturation of blood is higher in extraocular muscle and lower in peripheral skeletal muscle. Taking many of these factors into consideration, much of the so-called uniqueness based on intrinsic physical or chemical factors falls away, and many of the reactions attributed to the peculiar physiology of eye muscles become understandable in terms of ordinary skeletal muscle behavior. The distinctions that exist are quantitative rather than qualitative.

References

Adler, F. H. Physiology of the eye. (3rd ed.) St. Louis, Mo: C. V. Mosby Co., 1960.

Breinin, G. M. Electrophysiology of the extraocular muscles. Toronto: Univer. of Toronto Press, 1962.

Brown, G. L., & Harvey, A. M. Neuromuscular transmission in the extrinsic muscles of the eye. J. Physiol., 1941, 99, 379-399.

Cooper, S., & Fillenz, J. Afferent discharge in response to stretch from the extraocular muscles of cat and monkey and the innervation of these muscles. J. Physiol., 1955, 127, 400-413.

Duke-Elder, W.S. New observations on the physiology of the extraocular muscles. Trans. Ophth. Soc., (U.K.) 1930, 50, 181.

Lincoff, H. A., Ellis, C. H., DeVoe, A. G., DeBeer, E. J., Impastato, D. J., Berg, S., Orkin, L., & Magda, H. The effect of succinylcholine on intraocular pressure. Amer. J. Ophth., 1955, 40, 501-510.

McCouch, G. P., & Adler, F. H. Extraocular reflexes. Amer. J. Physiol., 1932, 100, 78-88.

Rowley, P. T., Wells, J. B., & Irwin, R. L. Tension response of mammalian muscle to intra-arterio acetylcholine. Amer. J. Physiol., 1960, 198, 507.

DISCUSSION

on

The Effects of Drugs on Vision

DRUGS AND EYE MOVEMENT RESPONSES IN MAN

Gerald Westheimer
School of Optometry
University of California

Barbiturate nystagmus, a well-known clinical phenomenon, was shown by Rashbass (1959) to be tied in with the observation that barbiturates selectively abolish the smooth pursuit eye movements while leaving saccadic movements unaffected. Barbiturates also interfere with disjunctive eye movements: vergence movements are appreciably reduced in speed and amplitude. Under the influence of barbiturates, the near point of convergence recedes, the distance phoria changes in the direction of esophoria, and the near phoria changes to exophoria. Accommodation remains unaffected. These changes are found with moderate therapeutic doses and have a time course that suggests that they are good indicators of the level of intoxication.

A study of the accommodation-convergence synkinesis reveals that it is quite drastically reduced by barbiturates. On the other hand, amphetamines enhance it while leaving all other oculo-motor responses substantially unchanged.

References

Rashbass, C. Barbiturate nystagmus and the mechanism of visual fixation. Nature, 1959, 185, 897-898.

Westheimer, G. Amphetamines, barbiturates and the accommodation-convergence synkinesis. AMA Arch. Ophthalmol., in press.

Westheimer, G., & Rashbass, C. Barbiturates and eye vergence. Nature, 1961, 191, 833-834.

THE EFFECTS OF DRUGS ON VISION

Leon S. Otis
Stanford Research Institute

The excellent papers presented by Drs. Potts, Arden, and Breinin illustrate how drugs may be used as tools to explore the physiology and structural characteristics of the visual apparatus. The emphasis, however, has been on the peripheral organ—the eye. To a behavioral psychologist, the eye is part of a larger system—the individual. When drugs are used, it is the possible alteration of the information-gathering function of the eye and the behavioral consequences that may attend such alteration that are of primary interest. That is, the psychologist would like to know to what degree drugs change how well the eye can see, what it sees, and the adequacy of the individual's performance within his visual world.

These comments in no way detract from the importance of the excellent work reported by the previous authors. They are meant, however, to point up the vastness of the chasm that exists between knowledge of how the eye works, and knowledge of how the individual processes and utilizes visual information in performance. The problem is difficult enough in its own right; it is especially complicated when drugs are introduced.

A literature relating drugs to changes in visually dependent behavior is practically non-existent; a brief review of some recent papers illustrates the paucity of good experimental data. The articles are discussed in terms of five categories that reflect, in descending order, the degree to which the experimental design included attempts to correlate performance with visual functions, or with underlying neural or chemical mechanisms.

The first and by far the most voluminous category (also the least satisfying from the point of view of controlled observation) consists of clinical reports of side effects when drugs are used in medical practice. Illustrative of such reports is the following excerpt from a recent paper (Murray, 1961).

> A patient, described by the author as "a man who had a previously unblemished record of over 20 years' driving connected with his work . . ." (p. 168) was involved in a series of relatively serious automobile

> collisions during a 90-day period following his release from the hospital. During this period he was on a maintenance dosage of 75 mg. of Librium daily. As a consequence of the accidents, ophthalmological evaluation was performed and the patient was diagnosed to be suffering "from a mild anisometropia unequal accomodation, esophoria for distance, and exophoria for near vision and poor depth perception." Librium was discontinued for seven days and he was again tested for ocular function, using the Maddox-Rod muscle balance test, and the Howard-Dolman depth perception test. Without the drug, the patient's responses were completely normal. The medication had affected his depth perception as well as his eye muscle balance. (This occurred in 2 other patients who showed similar reversible changes. One of them was on a 30 mg. daily dosage and the other on a 50 mg. daily maintenance dosage. Ten other patients who complained of visual difficulty and found to require new lens prescriptions.) Mr. L.K.'s daily dosage of Librium was reduced to 25 mg. daily and on retesting, his vision was within normal limits. Since then he has had no further automobile accidents or driving offenses. (p. 169).

Clearly, this report leaves much to be desired. One wonders to what degree the deterioration in driving skill was due to postdrug alteration of visual functioning, and to what degree it was due to other causes -- for example, changes in motor functioning, emotional reactivity, judgement processes, and the like.

Be that as it may, the clinical literature has implicated a number of drugs as causing altered visual functioning, with attendant behavioral impairment. Among those most frequently mentioned are the phenothiazines, certain of the monoamineoxidase (MAO) inhibitors, and the psychotomimetic drugs. Chlorpromazine and related phenothiazines are frequently reported to precipitate oculogyric crises and blurred vision (Affleck, Booth, Forrest, & Mackay, 1962; Apt, 1960; Kozinn & Weiner, 1960). Structural changes have also been reported. One phenothiazine (NP-207), that happily did not reach the market, has caused impaired dark adaptation, loss of acuity, and retinal pigmentary degeneration (Apt, 1960); damage to retinal elements has also been reported after thioridazine (Weekley, Potts, Reboton, & May, 1960). Pheniprazine, an MAO inhibitor recently removed from the market, has been reported to induce toxic amblyopia, decreased ability to discriminate colors (especially reds and greens), blurred vision, and impaired depth perception (Jones, 1961; Lear, Browne, & Greeves, 1962; Palmer, 1963). Perphenazine has also been reported to produce transient blindness (Apt, 1960; Johnson, 1960), and disturbance of color vision may occur after tridione (Cox, 1961). Mescaline, lysergic acid diethylamide (LSD), and

psilocybin have been implicated in impaired color discrimination, blurred vision, and, of course, visual hallucinations (Hollister & Hartman, 1962); LSD also caused overestimation of the apparent horizon (Wapner & Krus, 1959) and increased variability of size consistancy judgements (Weckowicz, 1959). Acute myopia has been reported for prochlorperazine (Yasuna, 1962); and altered depth perception, poorer accomodation, and blurred vision have been reported after chloriazepoxide therapy (Murray, 1961). Amitriptyline causes disturbances in accomodation (Lambert, Charriot, VuDinh, & Versmée, 1962). The widely used compound, imipramine, may result in poorer accomodation, blurred vision, and hallucinatory disturbances (Fleming & Groden, 1962; Friedman, DeMowbray, & Hamilton, 1961; Höhn, Gross, Gross, & Lasagna, 1961; Pollack, 1962).

As these drugs have a potent effect on the central nervous system, it is, perhaps, not surprising that the visual system is so vulnerable, including, as it does, about 12 per cent of the cerebral cortex.

Little can be said for the remaining categories. Too few research papers exist to justify more than a passing recognition of pioneering efforts in a neglected field.

The second category includes papers that report the effects of drugs on visual (or perceptual) functions, per se, using relatively simple indicator responses as performance measures. Postdrug impairment of dark adaptation (Apt, 1960), size constancy, depth perception, apparent motion, spiral after-effect and after-images (Costello, 1960a; 1960b; 1960c), brightness perception (Weiner & Ross, 1962), visual discrimination (Fuster, 1959), and visual thresholds (Blough, 1957; Carlson, 1958; Krill, Wieland, & Ostfield, 1959) have been reported in both man and animal.

The third category involves studies that measure drug effects on relatively complex visuo-motor performance. The classic studies of Payne & Hauty (1955; 1958) on the facilitating effects of amphetamine and other stimulants on visual monitoring, and those of Mackworth (1950), Kornetsky (Kornetsky, Mirsky, Kessler, & Dorff, 1959), and others on vigilance, practically exhaust this category.

Papers comprising category 4 attempt to relate postdrug changes in visual response to higher order theories of behavior or brain functioning. Costello (1960a; 1960b; 1960c) has reported changes in apparent movement, after-images, and spiral after-effects following clinical doses, 400-600 milligrams (mg), of meprobamate which have no effect on visual threshold (Melikian, 1961). He relates these changes to Eysenck's general theory of brain functioning which states that depressant drugs decrease brain excitability potential and increase inhibitory potential; stimulus drugs are presumed to have the opposite effect (Eysenck, 1957). Unfortunately, meprobamate was the only drug investigated. It would

have been desirable to include other depressant-type drugs, e.g., chlorpromazine and pentobarbital, in the design as well as a stimulant for comparative purposes.

Hollister and Hartman (1962), using a Latin square design, reported that LSD-25, psilocybin, and mescaline reduced color discrimination of normal subjects and increased the frequency of reports of color experiences after non-adequate stimuli, i.e., tones and/or an anchromatic visual flicker stimulus. These findings tend to support their hypothesis that the heightened and unusual perception of colors following psychotomimetics may be due to excitation of the central "color response" by non-adequate stimuli. The mechanism, however, remains to be specified.

Studies by Krill et al (1959), Fuster (1959), and by Carlson (1959) are illustrative of papers that attempt to relate changes in visual performance to underlying mechanisms (Category 5).

Krill et al studied the electroretinogram (ERG) and dark adaptation after low and high doses of two hallucinogens, LSD-25 and JB-318.[1] Control drugs were nonhallucinogenic analogues, Methysergide (UML) and JB-808.[1] Fifteen subjects hallucinated after 75 micrograms (μg) LSD and 7.5-15 mg JB-318, and significant changes in ERG, increase in scotopic b-wave amplitude, or in dark adaptation, elevation of the entire rod threshold and a delay in rod-cone break, were observed. The analogues had no discernible effect on vision. The authors suggest that the visual disturbances associated with the hallucinogens may have been due to the hypoxia or to toxic retinal effects, possibly induced by LSD and JB-318.

Fuster trained five monkeys in the WGTA to discriminate visually a cone from a 12-sided pyramid. LSD at 2-8 μg decreased the accuracy of discrimination and increased the latency of response—findings that are at variance with Blough's report that LSD improved visual discrimination in the pigeon (1957). Fuster (1959) correlates these findings with known excitatory effects of LSD on axosomatic fibers, i.e., sensory fibers or fibers that carry information to the brain, and inhibitory effects on axodendritic fibers, i.e., fibers which emanate from the diffuse thalamic system and reticular formation and which control "activation" of the brain.

Carlson (1958) reported that photopic threshold was raised more than scotopic threshold after non-hallucinatory doses of LSD—findings that are consistent with the occurrence of inhibitory effects on cortical processes as reported by Purpura (1956); elevation in threshold was shown to be unrelated to possible inattention and inability to concentrate.

This then, is the present state of the art; a fair number of clinical reports implicate at least some drugs in the deterioration in visual processes and performance, but few "hard" experimental studies have been done. The challenge should and, hopefully, will be met.

[1] JB compounds are experimental drugs of Lakeside Company.

References

Affleck, J. W., Booth, J. C. D., Forrest, A. D., & Mackay, K.J. The effect of thioproperazine administered by a continuous method on long-term schizophrenic patients. J. ment. Sci., 1962, 108, 862-864.

Apt, L. Complications of phenothiazine tranquilizers: ocular side effects. Survey Ophthal., 1960, 5, 550-5.

Blough, D.S. Some effects of drugs on visual discrimination in the pigeon. Ann. N. Y. Acad. Sci., 1957, 66, 733.

Carlson, V. R. Effect of lysergic acid diethylamide (LSD-25) on the absolute visual threshold. J. comp. physiol. Psychol., 1958, 51, 528-531.

Costello, C. G. The effects of meprobamate on perception. I. apparent movement. J. ment. Sci., 1960, 106, 322-326. (a)

Costello, C. G. The effects of meprobamate on perception. II. the visual after-image. J. ment. Sci., 1960, 106, 326-330. (b)

Costello, C. G. The effects of meprobamate on perception. III. the spiral after-effect. J. ment. Sci., 1960, 106, 331-336. (c)

Cox, J. The effect of tridione on colour vision. Brit. J. Physiol., 1961, Opt. 18, 79-84.

Eysenck, H. J. Drugs and personality: I. theory and methodology. J. ment. Sci., 1957, 103, 119-131.

Fleminger, J. J., & Groden, B. M. Clinical features of depression and the response to imipramine ("tofranil"). J. ment. Sci., 1962, 108, 101-104.

Friedman, C., DeMowbray, M.S., & Hamilton, V. Imipramine (tofranil) in depressive states: a controlled trial with in-patients. J. ment. Sci., 1961, 107, 948-953.

Fuster, J. M. Lysergic acid and its effects on visual discrimination in monkeys. J. nerv. ment. Dis., 1959, 129, 252-256.

Hauty, G. T., & Payne, R. B. Effects of analeptic and depressant drugs upon psychological behavior. Amer. J. publ. Hlth., 1958, 48, 571-577.

Höhn, R., Gross, G. M., Gross, M., & Lasagna, L. A double-blind comparison of placebo and imipramine in the treatment of depressed patients in a state hospital. J. psychiat. Res., 1961, 1, 76-91.

Hollister, L. E., & Hartman, A. M. Mescaline, lysergic acid diethylamide and psilocybin: comparison of clinical syndromes, effects on color perception and biochemical measures. Compr. Psychiat., 1962, 3, 235-241.

Johnson, W. Toxic amblyopia from perphenazine (fentazin), J. ment. Sci., 1960, 106, 352-354.

Jones, O. W. Toxic amblyopia caused by pheniprazine hydrochloride (JB-516, catron). Arch. Ophth., 1961, 66, 29-36.

Kornetsky, C., Mirsky, A. F., Kessler, E. K., & Dorff, J.E. The effects of dextro-amphetamine on behavioral deficits produced by sleep loss in humans. J. Pharmacol., 1959, 127, 46-50.

Kozinn, P. J., & Wiener, H. Oculogyric crisis after a small dose of perphenazine. J.AMA, 1960, 174, 166-167.

Krill, A. E., Wieland, A. M., & Ostfeld, A. M. The effect of two hallucinogenic agents on human retinal function. AMA Arch. gen. Psychiat., 1959, 1, 417-419.

Lambert, P. -A., Charriot, G., VuDinh, G., & Versmée, A. A propos d'un nouvel antidépresseur: le Ro4-1575. J. de Medecine de Lyon, 1962, 1008, 635-640.

Lear, T. E., Browne, M. W., & Greeves, J. A. A controlled trial of cavodil (pheniprazine) in depression. J. ment. Sci., 1962, 108, 856-858.

Mackworth, N. H. Researches on the measurement of human performance. London: (HMSO) Medical Res. Council Spec. Rep., 1950, Series No. 268.

Melikian, L. The effect of meprobamate on the performance of normal subjects on selected psychological tasks. J. gen. Psychol., 1961, 65, 33-38.

Murray, N. Covert effects of chlordiazepoxide therapy. Amer. J. Psychiat., 1961, 118, 168-170.

Palmer, C. A. L. Toxic amblyopia due to pheniprazine. Brit. med. J., 1963, No. 5322, 38.

Payne, R. B., & Hauty, G. T. Factors affecting the endurance of psychomotor skill. J. exp. Psychol., 1955, 50, 382-389.

Pollack, B. Imipramine-promazine therapy for depression. Amer. J. Psychiat., 1962, 118, 842-845.

Purpura, D. P. Electrophysiological analysis of psychotogenic drug action. II. General nature of lysergic acid diethylamide (LSD) action on central synapses. AMA Arch. neurol. Psychiat., 1956, 75, 132-143.

Wapner, S., & Krus, D. M. Behaviorial effects of lysergic acid diethylamide (LSD-25). AMA Arch. gen. Psychiat., 1959, 1, 417-419.

Weckowicz, T. E. The effect of lysergic acid diethylamide (LSD) on size constancy. Canad. psychiat. Assoc. J., 1959, 4, 255-259.

Weekley, R. D., Potts, A. M., Reboton, J., & May, R. H. Pigmentary retinopathy in patients receiving high doses of a new phenothizaine. AMA Arch. Ophth., 1960, 64, 65-76.

Weiner, H., & Ross, S. Effects of d-amphetamine sulfate on time and brightness perception in human subjects. Psychopharmacologia, 1962, 3, 44-50.

Yasuna, E. Acute myopia associated with prochlorperazine (compazine) therapy. Amer. J. Ophth., 1962, 54, 793-796.

SOME POTENTIAL OF RESEARCH ON DRUGS AND VISION

Richard Trumbull
Office of Naval Research

The author's interest in the effects of drugs on vision goes back to some experiences of the early 1950's while testing anti-seasickness drugs. A number of the more promising, based on laboratory studies, were taken to sea in a "double blind" evaluation in the operational situation. They were standard compounds, available to the public. Troop transports with 10,000 subjects available provided an ideal situation.

Although anyone would expect individual differences to appear in response to the drugs and their effectiveness, it was surprising to find that the range reported ran from decrement to actual improvement in vision. One man apologized for not filling out the questionnaire card because he couldn't read the print. Indeed, his pupils were so dilated that "sack-time" was his only occupation. Others commented on ability to see farther and more clearly. Similar comments were made about improved auditory function.

This situation necessitated checking the literature to see just what history had to offer (Trumbull & Maag, 1958). There are the rather dramatic instances where mescaline has produced artistic products judged by experts to be far superior to those normally produced. Certainly, anecdotal claims of this type are well known, as are those related to contrast enhancement. The improved sense of timing gained has been one reason for drummers, and others seeking exotic off-beats or new rhythms becoming addicts. Then there are more reliable data where the laboratory and control are found. It is surprising how many times researchers have reported improvements in sensory modalities resulting from drugs. The author's interest was purely on the positive side, where performance was improved, maintained, or restored from deficit by ingestion of some biochemical. Here are a few examples of what were found.

1. "(0.6 - 1.) mgm. of carcholin was administered to human subjects with a resultant lowering of dark adaptation threshold and improved dark adaptability corresponding to the dosage." (Fang, Hwang, & Hall, 1953)

2. A study of caffeine influence on color naming—"...stimulation at all doses but better at lower." (Hollingworth, 1912)

3. "It can be concluded that the decline of important elements of pilot skill can be delayed for at least four hours by pharmacological techniques." (Payne & Hauty, 1953)

4. Mescaline and lysergic acid produced "...greater sensitivity to sounds and most striking effects of visual stimuli. Colors had added 'purity,' 'vividness' and 'brilliance'." (Berlin et al., 1950)

There are many additional items (Trumbull & Maag, 1958) where there is direct reference to the sensory modalities. If one considers the multitude of performance studies where separation of sensory, central, and motor aspects is impossible, one is impressed with the potential of this area of research. By that is meant the large number of studies in which ability in mathematics, coordination, and complex reaction time might have improved as much from a simple visual improvement as it would from a central or motor one. Color naming, where time is not an element, is easier to claim. In studies of stress or fatigue, there is a major requirement for more knowledge as to just what influence these conditions have on sensory systems—the base from which it is desired to produce improvement.

This experience caused the authors to try to induce the Navy and the Department of Defense to concern themselves with "positive psychopharmacology," seeking some fraction of the money now spent to degrade or destroy man for purposes of realizing the full potential of his systems. The Stanford Research Institute became a keystone in this effort by doing a critical review of various scientific disciplines which had relevance to the problem. Leon Otis' presence in this effort has been a vital factor in seeking the more promising techniques and researchers, and developing a sensitivity to the problems and holes in present knowledge. His paper presented in this section has highlighted much of what has been learned. There is no reason, after this review, (Plotnikoff, Birzes, Mitoma, Otis, Weiss, & Laties, 1960) to be any less enthusiastic about the potential that can be made available by this means.

The three papers and two discussions preceding this presentation serve to underscore the fact of this potential while warning of the demand for improved methodology, adequate control, and more basic work on the biochemistry operating at every point in the human system involved. Research on drugs and the muscle system of the eye has also been presented. Obviously, anything which influences ocular shape, motion, transmission, or other functions can be used to further the knowledge and use of vision. Thus, the history and potential of drugs that produce these effects merit similar consideration as those to which reference has been made. It is hoped that pharmacologists will turn some attention to sensory modalities. It is urged that those interested in sensory and perceptual capabilities of man can broaden their research approach, or seek pharmacological co-investigators to answer some of the challenge and seek realization of some of the potential of this area.

References

Berlin, L., et al. Studies in human cerebral functions: the effects of mescaline and lysergic acid on cerebral processes pertinent to creative activity. J. nerv. & ment. Dis., 1955, 122, 487-491.

Fang, H. S., Hwang, T. F., & Hall, A. L. Effects of carcholin on dark adaptation and visual purple regeneration. Pensacola: USN Sch. av. Med. Rep., 1953. (Proj. No. NM 001 059.30.02)

Hollingworth, H. L. The influence of caffeine on mental and motor efficiency. Arch. Psych. (N.Y.), 1912, 3, 22.

Payne, R. B., & Hauty, G. T. The pharmacological control of work output during prolonged tasks. Randolph AFB: USAF Sch. av. Med. Rep., 1953, No. 2. (Proj. No. 21-1601-0004)

Plotnikoff, N., Birzes, Lucy, Mitoma, C., Otis, L., Weiss, B., & Laties, V. Drug enhancement of performance. Menlo Park: SRI, 1960.

Trumbull, R., & Maag, C. An annotated bibliography and critical review of drugs and performance. Washington: ONR Rep., 1958, No. ACR-29.

CONCLUDING REMARKS BY THE CHAIRMAN

Arthur Jampolsky
Eye Research Institute
Presbyterian Medical Center

Drs. Potts and Arden have pointed out how the biochemist and the electrophysiologist seek to determine the sites and modes of action of drugs on the visual apparatus. Toxic effects, and the consequent visual decrements, are valuable ways to get at the sensory side of the picture. This information is basic to the problem of maintenance and enhancement of visual performance. The different electrophysiological tools tap off different parts of the visual input system.

Dr. Breinin has emphasized the similarity in drug effects on the extraocular muscles and other skeletal muscles, and indicated the mode of action of drugs on the accommodative-convergence relationship.

Dr. Westheimer has related some of the examples of the visual psychophysical investigations in this field, an area in which there is a relative paucity of work.

Dr. Otis has stated that despite the large literature on the behavioral aspects of the problem, there is a lack of acceptable experimental evidence to elucidate specifically the performance changes. The factors of inattention, excitation by non-adequate stimuli, and the multiple sites of drug action, make it a difficult task to unscramble the variables.

Dr. Trumbull has presented a background picture of the past history, the present status, and the future potential of research seeking to answer some of the specific problems in practical terms, especially the maintenance and enhancement of man's systems. Some important monographs in this field have been brought to the attention of this group: they relate and coordinate different disciplinary approaches that point out some of the basic needs and practical problems.

From the above discussions it appears that the psychophysicist and the behavioral scientists will have difficulty in evaluating the response effects, judgmental changes, and performance results. Controls are difficult to establish, since drugs may decalibrate the subject for visual psychophysical determinations. It is often difficult to determine whether one is affecting the visual apparatus, per se, or the subject generally in

his response to the visual performance task. Double blind studies do not avoid the effect of a drug or placebo administration.

The biochemist and electrophysiologist have the unique opportunity of assessing nervous-tissue function in terms of the eye as a peripheral brain.

Computer techniques materially aid the detection of faint signals that are all but lost in the roar of biological noise. Multiple stimuli add another analytical dimension.

Electrophysiological techniques do not always avoid the limitation of drug-altered neurophysiological recording, which may be monitored by polarographic electrodes to assess blood flow and metabolic effects.

More must be known about the specific drug alterations of neuronal conduction time, neuronal recovery time, synapse blocking, shuttling, myoneural junction, storage-resynthesis, etc.

There is a unique opportunity to assess the retina as a plug of central nervous system tissue, with blood vessels and human responses attached. There is a need to know much more specifically how drugs affect the visual apparatus, per se, especially with respect to the sensory input and motor output visual systems, which lend themselves to easier direct analysis than does "that messy, raveled knot of pinkish jelly."