AM-65-9

Reprinted from INVESTIGATIVE OPHTHALMOLOGY, Vol. 2, No. 2, April 1963, published by the C. V. Mosby Company, St. Louis.

Pupillary movements during acute and chronic fatigue

A new test for the objective evaluation of tiredness

Otto Lowenstein, Richard Feinberg,** and Irene E. Loewenfeld**

Spontaneous pupillary movements in darkness were recorded (1) in healthy subjects of different ages when they were rested or fatigued, (2) in chronically tired subjects without known neurological defects, and (3) in patients with various neurological lesions. In some of the experiments, local or systemic drugs were used.

While the pupils are large and quiet in darkness when the subject is alert, they oscillate under the influence of tiredness. Waves of spontaneous pupillary contraction and dilation accompany periods of increasing sleepiness and spontaneous arousal until, at the moment immediately preceding sleep, the pupils become very small.

The mechanism of these movements was analyzed and a simple test described which allows the objective determination of the degree of acute fatigue in a given subject at a given time. In the light of these results, the concepts of "normal" and of "pathologic" fatigue were discussed.

As described by us previously,[1-5] a light stimulus of a given intensity and duration will not necessarily elicit a pupillary reflex of predictable extent and speed. When normal man or animals are subjected to sensory or emotional stress, the pupils enlarge, and a light reflex elicited under such conditions will be inhibited. It can be completely suppressed if the interfering stimulus is sufficiently strong (Fig. 1, *a* → *d*). When, on the other hand, the subject is tired, and when the eye is exposed to repeated light stimuli at fairly short intervals, the pupils become smaller and the reactions less and less extensive. Finally, when the subject is almost asleep, the miotic pupil hardly reacts to light (Fig. 1, *a* → *g*).

Fig. 1 clearly shows that these changes in the pupillary reflexes are not merely a matter of amplitude. The size of the pupils and the shape of their reflexes vary with the degree of excitement or drowsiness. The characteristic square, W-shaped, V-shaped, and flattened 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; and they can be produced at will in experimental animals

This work was supported by the Harriman Fund and by a grant of the U. S. Public Health Service (Sens. Dis. B-253).

*From the Department of Ophthalmology, Laboratory of Pupillography, Columbia University, College of Physicians and Surgeons, and the Presbyterian Hospital, New York, N. Y.

**From the Georgetown Clinical Research Institute, Aviation Medical Service, Federal Aviation Agency, Washington, D. C.

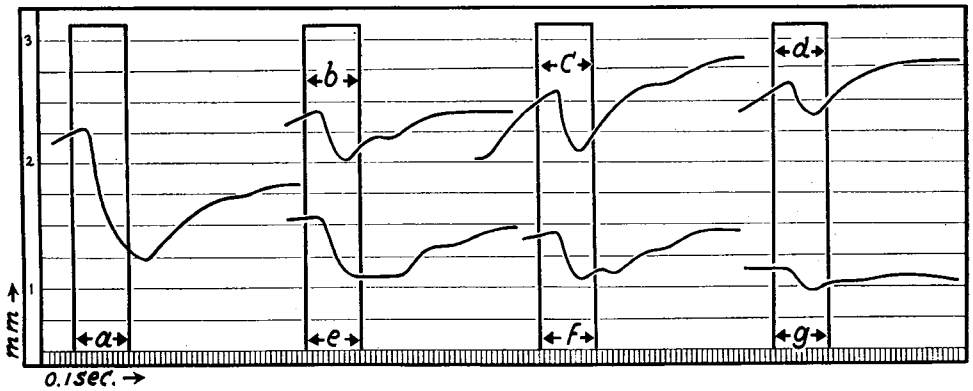

Fig. 1. Effects of emotional excitement and of fatigue upon the pupillary reflex to light in normal rats.

The pupillary diameter is plotted as the ordinate (in millimeters) against time as the abscissa (in 0.1 second units). Because of the smallness of the rat's eyes, the ordinate was enlarged by a factor of 4, as compared to the human pupillograms (Figs. 2-13). The reactions of the left eye are shown. The animals were in darkness, except for 1 second periods framed at $a \rightarrow g$, when light stimuli of about 15 footcandle intensity were presented.

The animals were young adult black rats of a tame strain which could be handled easily. For immobilization, they were sown into a small bag of cotton material, with only their heads protruding, and then held on a fairly heavy brass plate by elastic bandages. This support prevented the animals from losing their balance when they moved inside their wrappings, and appeared to make them comfortable, so that they occasionally fell asleep. Sensory stimuli consisted in sudden shouting and blowing into the animal's face.

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. They showed the characteristic W- and V-shapes found in all mammals under similar conditions.

e-g, Light reflexes elicited while the animal was sleepy. Note the square, w-, and flattened v-shapes of the reduced responses.

by electrical stimulation or surgical destruction at the same sites (Fig. 2).

The striking similarity between the reflex forms of fatigue and excitement on the one hand, and those of pathologic conditions on the other, shows that the effects of emotional or of sensory stimulation, as well as those of fatigue and drowsiness, are not diffuse or 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.[3, 4]

There is, however, one great difference between the effects of physiologic fatigue and excitement and those of pathologic conditions. While physiologic reflex changes are transitory and instantly reversible, the pathologic reaction patterns are permanent. They may deteriorate further but they cannot be restored to normal form.

In order to evaluate the extent of organic damage in a given patient, it is important to determine the degree of acute, reversible tiredness accidentally present at the time of examination and to differentiate between these fatigue symptoms and those of pathologic impairment of pupillary innervation. For this purpose we have found the following test most useful.

The patient sits, with his head comfortably supported, in complete darkness, and looks at a small, red fixation point situated at a distance of about 6 feet and approximately 15° above the horizontal

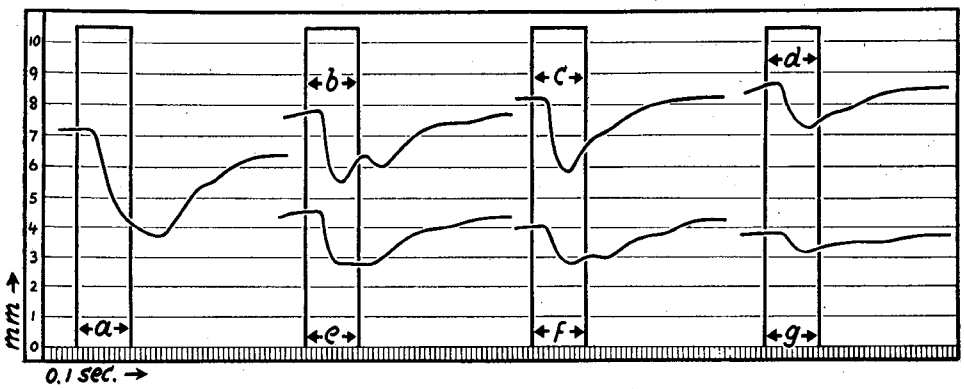

Fig. 2. Reactions to light in patients with pathologic conditions within the nervous network of pupillary control.

The patients sat in darkness and looked at a small, dark red fixation point (distance 6 foot, 15° above the horizontal plane). During the times framed at *a* → *g*, 1-second light stimuli of about 15 footcandle intensity were presented.

a, Light reflex in a normal, 66-year-old man.

b, *c*, Mydriatic pupil with inhibited, W- and V-shaped responses in a 21-year-old man who was chronically restless and excited (cyclothymic personality).

d, Very large pupil with strongly inhibited light reflex in a 20-year-old schizophrenic patient while spontaneously excited. At other times, this patient showed reactions to light of almost 4 mm. extent and of normal shape.

e, Small pupil with square, "tonohaptic" light reflex in a 51-year-old woman suffering from postencephalitic parkinsonism.

f, Flat, w-shaped light reflex of the miotic pupil in a 64-year-old man with cerebral arteriosclerosis.

g, Inextensive and slow, v-shaped light reflex in a 50-year-old woman with tabes dorsalis and miotic pupils.

plane. He has been instructed to look steadily at this point, with reasonable concentration but without excessive effort ("as steadily as you can manage comfortably"). In this condition, the spontaneous movements of the pupils are recorded.*

Results

Spontaneous pupillary movements in young, normal, alert subjects. In darkness the pupils of healthy, young, alert subjects are large, equal on the two sides, and relatively quiet. While there are differences among individuals, these are limited to a fairly narrow range. Thus, in a normal person below 35 years of age, the pupillary diameter in darkness usually does not measure less than 7 mm., and spontaneous fluctuations rarely exceed ± 0.5 mm. The pupils, however, are almost never entirely immobile. When observed for some time, they show two main types of oscillations: (1) slow waves of dilation and contraction, lasting from about 4 to 40 seconds and measuring up to ± 0.5 mm. (*a* in Fig. 3, *C*); (2) superimposed, fast and very inextensive oscillations, i.e., contractions and redilations of from 0.5 to 1 second duration and about from 0.1 to 0.3 mm. extent (*b*, *b* in Fig. 3, *C*, and Fig. 4).

Spontaneous pupillary movements in young, normal, tired subjects. When the same healthy, young subjects are tired, the large, stable pupillary diameter may be maintained for some time; but, as the subject relaxes after some minutes in darkness, the pupils become smaller and begin to oscillate. In ever deepening waves

*All records were obtained with our electronic pupillograph, an infrared-sensitive scanning device described elsewhere.[6-8]

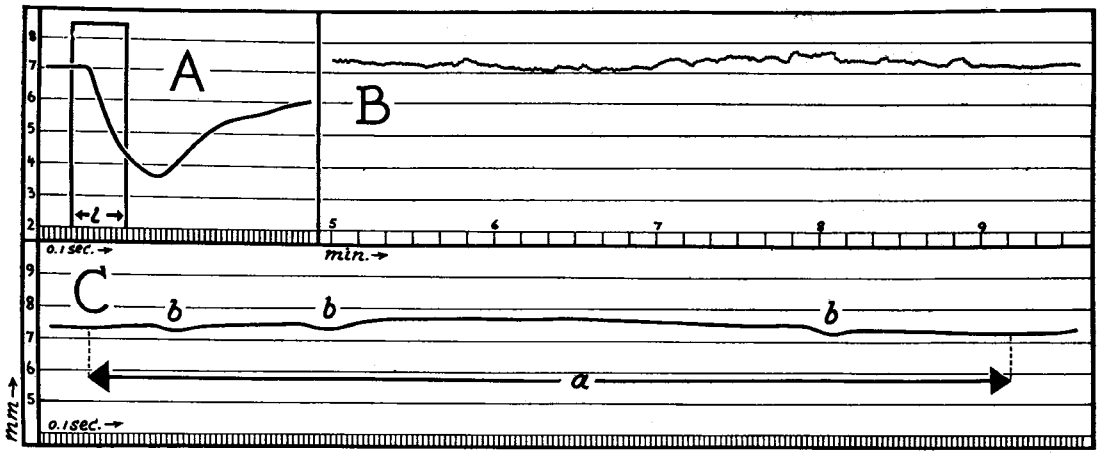

Fig. 3. Spontaneous pupillary movements in young, normal, alert subject.
The subject, a 21-year-old man, was not tired at the time of examination. The pupillograms of the right eye are shown. The eyes were in darkness, except for the time framed at *l*, when the right eye was exposed to a 1-second light flash of about 15 footcandle intensity. The pupillary diameter is recorded as the ordinate (in millimeters). In *A* and *C* the original pupillograms are shown. In these records, the abscissa represents time in 0.1 second units. In *B*, the time axis of the graph was reduced in the following manner: the pupillary diameter at the beginning of each successive second was taken from the original pupillographic record, and was plotted as a single measurement (small squares); 60 such measurements thus show the pupillary movements which occurred within each minute.
A, Normal light reflex.
B, The pupil remained large and relatively quiet in darkness. The record shows the movements during the 5th to 10th minutes of the test; the subject was able to continue the experiment for more than 2 hours without remarkable changes in pupillary behavior.
C, Slow (*a*) and fast (*b*) pupillary oscillations of small extent (see description in text).

of sudden, spontaneous arousal and gradual slipping into a doze, the pupils dilate rapidly (*a*, *a* in Figs. 5 and 6), then recontract gradually in an unsteady, wavering decline.

The more the subject is fatigued and the less he tries to suppress his sleepiness, the shorter is the time of initial mydriasis, and the deeper and more frequent the following pupillary oscillations. Eventually, the spontaneous intervals of reawakening cease altogether and the subject actually falls asleep. At the moment immediately preceding the final closing of the lids and movement of the eyes upward, the pupils are quite small. At this time a psychosensory stimulus such as a sudden sound, conversation, etc., restores the waking condition and—depending upon the type and intensity of the stimulus—may maintain it for some time (*s* in Figs. 5 and 6).

Spontaneous pupillary movements in chronically tired subjects without known neurological defect. In these times of high-pressure activity many persons habitually fail to sleep sufficiently, and it is easy for anyone to find a number of acquaintances who are chronically tired. Although these persons are neurologically in good condition, it is difficult for them to stay awake over an extended period when they are not engaged in some activity.

The pupils of such chronically tired subjects show the characteristics just described, in an exaggerated manner. After a brief, initial period of wakefulness the pupillary diameter begins to drift erratically over a wide range, the eyelids begin to droop, and fixation becomes unsteady. Soon afterward the pupils contract strongly, the eyes move upward, and the subject falls asleep (Figs. 7 and 8).

Just like the slow, extensive waves of pupillary enlargement and narrowing which accompany each wave of spontaneous arousal and decline ($a \leftrightarrow a$ in Fig. 7), the fast, superimposed oscillations may become quite marked (b in Fig. 7). Even when the tired subject forces himself by a voluntary effort to remain awake fairly steadily, these small oscillations sometimes cannot be suppressed; they are associated with minute extraocular movements and appear to be related to the growing inability of the tired subject to fixate evenly.*

Influence of age. Older persons without pathology affecting the pupillary innervation show essentially the same pupillary behavior pattern, except that the system appears, on the whole, more vulnerable. The pupils tend to be somewhat smaller in darkness, the periods of tiredness with fluctuating movements more frequent, the change from alertness to drowsiness more sudden than in normal young subjects.

It is commonly believed that the pupils become smaller with advancing age, and it is undoubtedly true that the mean pupillary diameter of a given number of arbitrarily chosen old persons will be smaller than that of an equal number of young subjects. It has not been established, however, whether this decline in pupillary size—like other conditions found with increasing frequency in the older population—is due to an aging process per se or to an increased opportunity to accumulate pathology within a longer lifetime.

The fact that individual old persons may have pupils which would be considered normal even in the young (Fig. 9, *A-C*) does not necessarily preclude the existence of an age trend even in these individuals; some young persons show pupils of very large size and greater than average mobility (Fig. 9, *D*), and the reactions of such subjects could undergo some deterioration without the development of obvious pathology. The solution to these questions will have to await the outcome of studies in which a larger number of normal subjects are followed up for an extended period.

The small, fast pupillary oscillations which accompany imperfect fixation of the tired individual tend to be less extensive in old than in young persons.

Influence of some drugs. A detailed description of the modifications of spontaneous pupillary movements under the influence of various drugs exceeds the scope of the present communication and will be given later. In connection with the problems dealt with at present it is important to note that (1) peripherally acting drugs such as instilled parasympathicolytic or sympathicolytic substances reduce the extent of the pupillary movements associated with the waves of arousal and falling asleep, by eliminating one of the effector systems (see below, "Mechanism of spontaneous pupillary oscillations," etc.). They do not, however, affect the rhythm of pupillary enlargement and contraction as such (Fig. 10, *A* and *B*); (2) in contrast, centrally acting drugs such as Benzedrine or Nembutal may alter (i.e., enhance or abolish) the waves, together with the subjective feeling of tiredness (Fig. 10, *C*, *D*).

The small, fast pupillary play which accompanies unsteady fixation is no longer recorded after administration of parasympathicolytic substances, but is relatively little affected when sympathicolytic drugs are used.

Mechanism of spontaneous pupillary movements in complete darkness.

The slow, larger waves of contraction and dilation. The pupillary sphincter muscle is activated by parasympathetic

*The unsteadiness of fixation described here does not affect our measurements of pupillary diameter by way of optical distortion, due to wandering of the subjects' eyes; the eyes are under constant observation on the oscilloscope screen, and their position is therefore controlled within narrow limits. The extraocular movements occasionally observed during unsteady fixation of the tired subject were so minute as to be barely perceptible on the screen (under ×5 linear enlargement). Since the room is completely dark and the fixation point placed at a distance of 6 feet, it is also not likely that the pupillary oscillations are *elicited* by changes in fixation or accommodation; we are inclined to regard the unsteadiness of fixation and the pupillary oscillations as parallel events, elicited together by the same central nervous mechanism (see below, "Mechanism of spontaneous pupillary movements in complete darkness").

(cholinergic) fibers running with the third nerve, the dilator muscle by sympathetic (adrenergic) nerves from the superior cervical ganglion. The possible effector mechanisms for *any kind* of pupillary movement are thus: (a) parasympathetic stimulation (contraction) or inhibition (dilation), and (b) sympathetic excitation (dilation) and relaxation (contraction).

Which of these two mechanisms is responsible for the waves of pupillary enlargement and narrowing which appear spontaneously as the tired subject sits in darkness? There is no doubt that both of them participate, activated by discharges originating in the central nervous system. This conclusion is based on the following facts:

PROOF OF THE CENTRAL NERVOUS ORIGIN OF THE PUPILLARY WAVES.

1. The pupillary waves coincide with cycles of activity in many other systems. Thus, with each moment of arousal shown by the tired subject, the palpebral fissures widen, the head is lifted slightly, the eyes are fixed in the primary position, the striated muscle tone is enhanced all over the body, respiratory and heart rates may be affected, etc. Obviously, these many effector systems cannot be brought into action simultaneously by separate peripheral mechanisms.

2. In normal man and animals the spontaneous waves of pupillary contraction and dilation in darkness are equal on the two sides.

3. When the spontaneous mechanism of arousal ceases to function and the subject falls asleep, sensory (or, in man, psychosensory) stimuli will bring about the complete awakening syndrome with all its physiologic effects. When, however, the

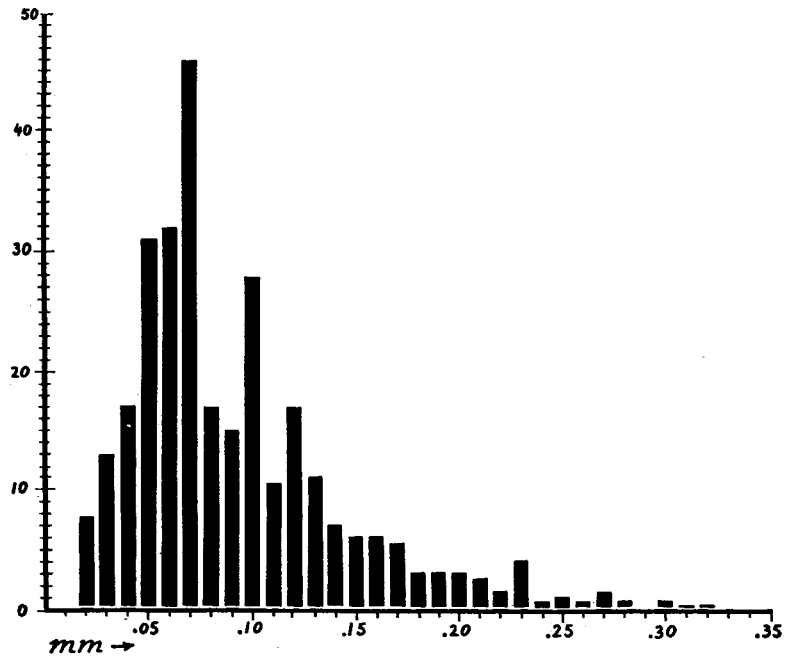

Fig. 4. Number and extent of small, fast pupillary oscillations in normal, alert subject.
The data were obtained from the same subject as in Fig. 3. The ordinate represents the number of small oscillations (*b* in Fig. 3) which occurred within a 20-minute period in darkness (average of 3 experiments). The abscissa shows the amplitude of these oscillations (in millimeters).
Most of the short pupillary oscillations were exceedingly inextensive (below 0.1 mm.), and only a few of them measured up to 0.3 mm.

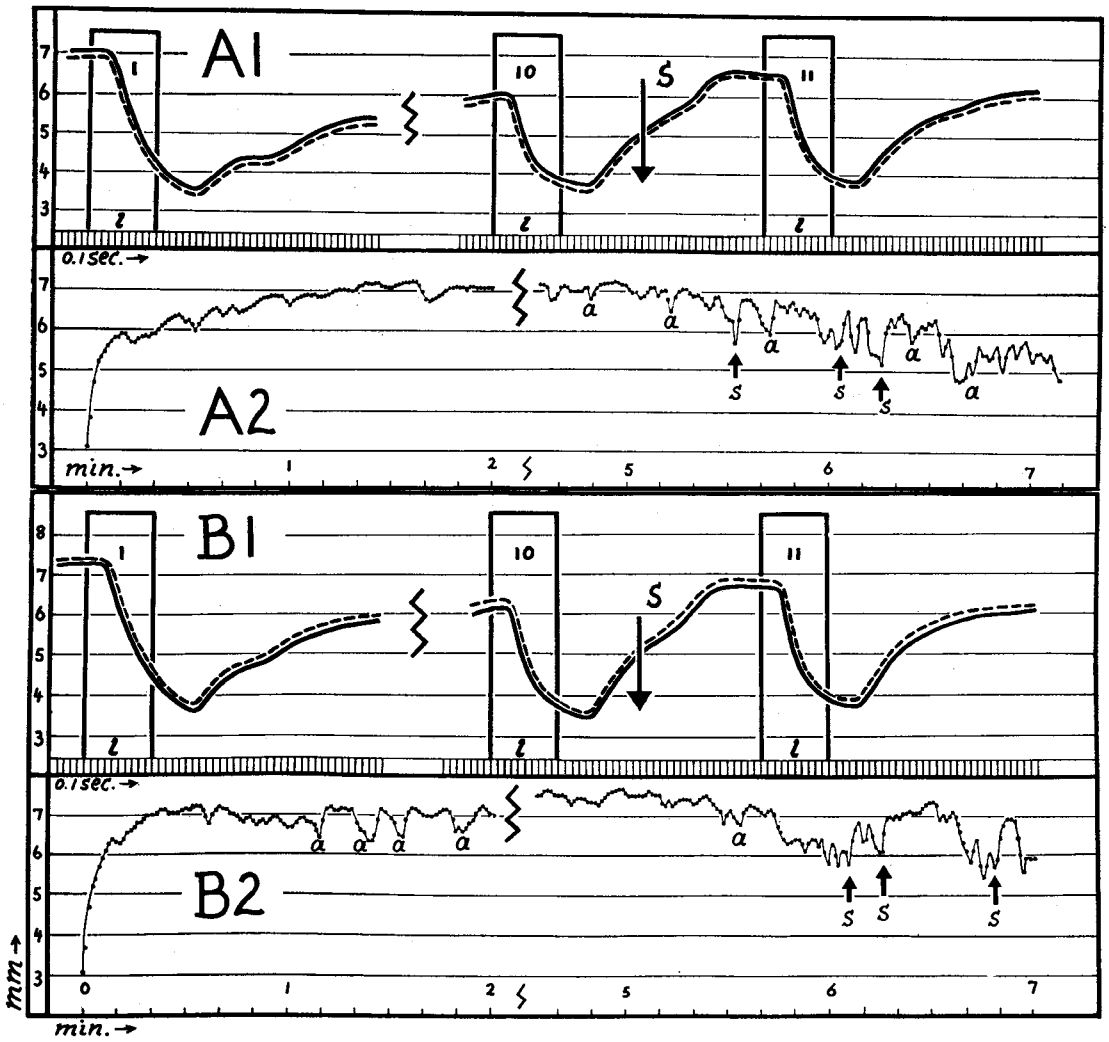

Fig. 5. Spontaneous pupillary movements in normal, young, tired subjects (identical twins). The subjects *A* and *B*, identical twin brothers, had graduated from dental school some weeks before. On the day of examination they were tired because until late the previous night, they had packed their bags preparatory to leaving for army service overseas. The tests were done in immediate succession, at 10:30 A.M. *(A)* and at 11:30 A.M. *(B)*, respectively.

In *A1* and *B1* the original pupillograms are shown. In these records, the ordinate represents pupillary diameter (in millimeters), the abscissa time (in 0.1 second units), whereby the solid lines represent the right pupils, the broken lines the left pupils. The eyes were in darkness except for the intervals framed at *l*, when the right eye was exposed to 1-second light flashes of about 15 footcandle intensity. The arrows *s* mark the time of presentation of sensory stimuli (sudden sound). Note the close similarity in the reaction pattern of the two brothers.

In *A2* and *B2* the time axis of the graphs was compressed in the manner described above (Fig. 3). At the beginning of each record, the right eye had been adapted to the stimulating light for 1 minute. The first measurement shows the pupillary diameter at the moment when this light was turned off. After the initial dilation in darkness, the pupils began to oscillate *(a,a)*. Within the following minutes, these oscillations became increasingly frequent and extensive, and, beginning with the 5th minute of examination, repeated sensory stimuli were required to keep the subjects awake (sound stimuli, marked by arrows *s*). Again, the pattern of pupillary behavior was strikingly similar in the two brothers.

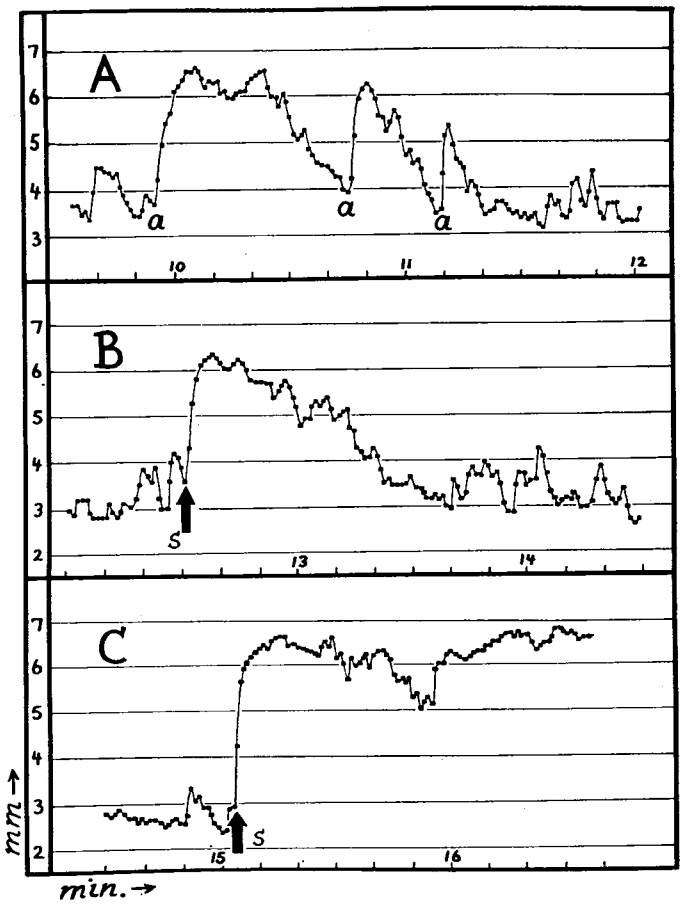

Fig. 6. Pupillary oscillations in an extremely tired normal subject.
The right pupil's movements were plotted as described above (Fig. 3). The subject, a 38-year-old man, was very tired after a strenuous series of lecture trips. In addition, he had a slight cold on the day of examination. After an initial period of wakefulness, he became drowsy. His pupils began to fluctuate wildly over a large range, in successive waves of spontaneous arousal and following decline (*a,a* in *A*). Shortly after the 12th minute of the test he fell asleep, and was awakened by a sudden, loud sound (*s* in *B*). The pupils dilated extensively, but recontracted as again he drifted toward sleep (15th minute, line *C*). A second sound stimulus was followed by continuous conversation which kept him awake during the remainder of the test (17th minute).

cortical and/or diencephalic connections are blocked, as, for example, in anesthetized animals, stimulation of sensory nerves fails to produce the awakening syndrome, and only fragmentary physiologic effects are elicited. This failure to produce the entire group of awakening symptoms is *not* caused by an interruption of the efferent outflow to the periphery but by a breakdown of transmission at the cortical and/or diencephalic level, as proved by the fact that hypothalamic stimulation readily elicits all the physiologic effects normally associated with awakening, even in deeply anesthetized animals.[9, pp. 297 ff.]

4. As mentioned above (see "Influence of some drugs"), the movements may be increased or decreased in extent and frequency by centrally acting depressant or stimulating drugs. In contrast, elimination of one of the peripheral effector mechanisms by instillation of sympathicolytic or parasympathicolytic drugs, or by surgical or clinical interruption of the peripheral

sympathetic or the third nerve, decrease the extent but do not alter the rhythm of the spontaneous movements (see below, "Spontaneous pupillary movements in patients with various neurological defects").

5. In the introduction to this paper we have described the changes in extent and form which the light reflex undergoes under the influence of emotional excitement or of fatigue (see text and Fig. 1). These reflex changes are observed when light stimuli are presented during waves of spontaneous arousal and drowsiness of a tired subject. During each period of awakening, the light reflexes of the dilating pupil are reduced and show W- or V-shapes; with each following decline, the reflex shapes reveal the increasing loss of supranuclear inhibition. As shown previously,[9, pp. 262-263] parasympathetic inhibition is a central nervous mechanism whereby supranuclear impulses act upon the oculomotor nucleus and prevent it from sending efferent parasympathetic impulses to the pupillary sphincter, while the peripheral cholinergic nerve-muscle apparatus is not inhibited at all.

THE EFFERENT MECHANISM. We have stated already that pharmacological, surgical, or clinical interference with either the sympathetic or the parasympathetic nerve supply to the iris results in reduction of the amplitude of the movements (see previous paragraph and "Influence of some drugs"). It is obvious, therefore, that *both* mechanisms participate in their production. During periods of awakening—be they spontaneous or reactive—sympathetic stimulation and inhibition of the oculomotor nucleus participate in dilating the pupil. During periods of increasing sleepiness, sympathetic activity decreases and supranuclear inhibition is gradually

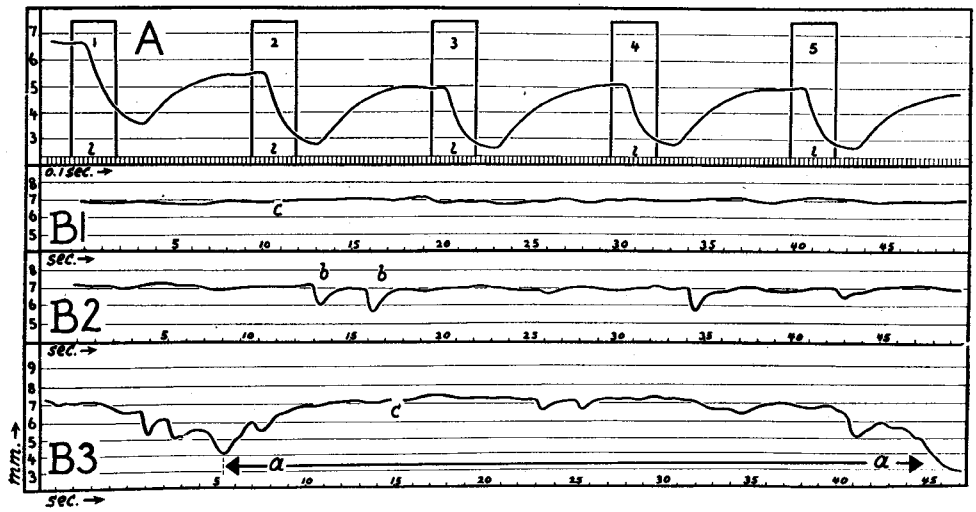

Fig. 7. Spontaneous pupillary movements in a chronically tired subject.
The right pupil's diameter is recorded as the ordinate (in millimeters) against time as the abscissa (in 0.1 second *[A]* or in 1 second units *[B]*). In *B1–B3* the graphs were reduced to one-half the size shown in *A*, both for time and for amplitude.
The subject, a 38-year-old woman who was otherwise normal, was chronically tired some months after a major abdominal operation. At the beginning of the test the pupils showed normal diameter and light reflexes *(A)*. The pupils remained relatively quiet during the first minute of the fatigue test *(B1)*. Soon, however, irregular slow fluctuations appeared and the fast oscillations became marked (*b,b* in *B2*, showing pupillary movements during the 8th minute of the test). Shortly thereafter, both types of oscillations became exaggerated; the pupils dilated and contracted in extensive waves, with frequent periods of sleep and spontaneous arousal (*B3*, recorded during the 16th minute of observation).

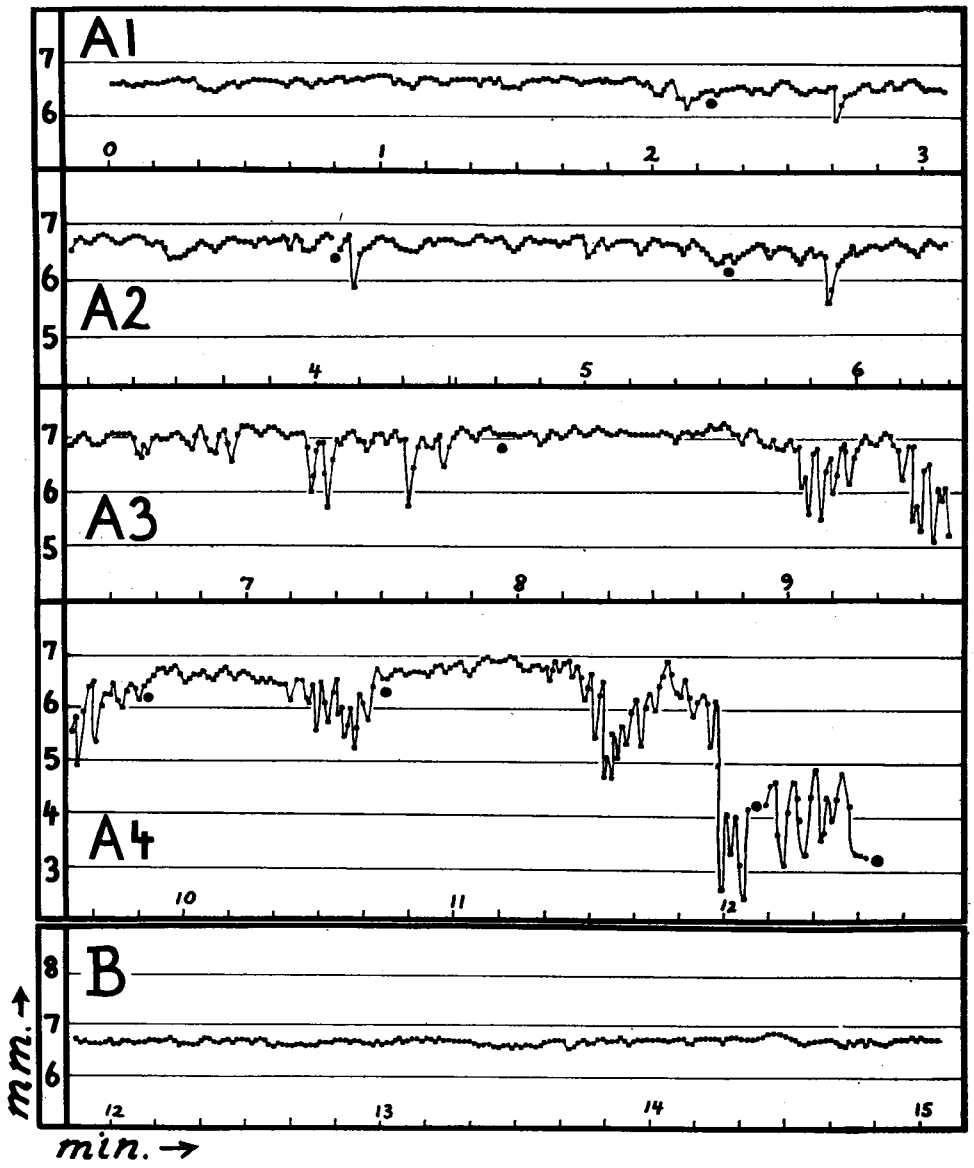

Fig. 8. Spontaneous pupillary oscillations in a chronically tired subject.
The ordinate represents the right pupil's diameter (in millimeters), the abscissa time (in minutes; cf. Fig. 3). The record was obtained from the same subject as in Fig. 7, 2 weeks later *(A1-A4)* and 2 years later *(B)*.
Intermittent periods of irregular pupillary movements appeared during the second minute of observation *(A1)*. They became more frequent and extensive with time until, finally, the subject became unable to rouse herself and the test had to be discontinued (12th minute, *A4*). It should be noted that the pupillary oscillations shown during fatigue are not related to lid-closure reactions (indicated by round dots). In complete darkness, spontaneous closing of the eyelids is not accompanied by pupillary contraction, except at the moment of falling asleep (last lid closure in *A4* of this record).
Two years later, the effects of the operation had been overcome completely; the subject felt well and was no longer chronically tired. The record shows no irregular pupillary movements (12th to 15th minutes shown in *B*), and the subject was able to continue in a series of similar experiments for several hours.

lost. The consequent relative preponderance of the parasympathetic outflow is revealed by the smallness of the pupils at the time immediately preceding sleep.

The fast, small oscillations. The small, fast pupillary movements associated with imperfect fixation of gaze are no longer recorded when the pupil has been dilated by parasympathicolytic drugs. This fact gives support to the opinion that these oscillations are cholinergic in nature, but it does not prove the point completely. Because of the small initial extent of the fast oscillations, they may escape the sensitivity of our instrument when they are reduced, without being abolished entirely. But since they are only little affected when the sympathetic innervation is blocked (see above, "Influence of some drugs"), it appears that they are, indeed, due mainly to parasympathetic impulses.

Spontaneous pupillary movements in patients with various neurological defects.

Lesions in the efferent pathways. We have, then, established that the pupillary waves of dilation and contraction of the tired subject are central nervous in origin, and that both of the available efferent mechanisms—sympathetic activation and relaxation as well as parasympathetic inhibition and activation—take part in their development. It is not surprising, therefore, that clinical lesions in the peripheral sympathetic or the third nerve paths diminish the amplitude but do not change the rhythm of the oscillations (Fig. 11).

Diencephalic lesions. Records of spontaneous pupillary movements are of diagnostic significance in those patients in whom central nervous lesions have led to the development of pathologic shapes of the light reflex such as shown in Fig. 2, $e \rightarrow g$. Because of the complete analogy in the light reflex shapes of very tired normal subjects and of patients with lesions in the diencephalic-mesencephalic region, it is often difficult to evaluate the clinical significance of the pupillary reflex pattern which a patient may show at the particular time of examination. How much of the deterioration of the reflexes is due to acute, reversible tiredness, and how much to irreversible damage?

The cases shown in Fig. 12 serve as examples. In both patients a diencephalic lesion had reduced the supranuclear inhibitory impulses to the oculomotor nucleus. The pupils were smaller than normal in darkness; the light reflexes were inextensive and showed the square form typical of this type of lesion.[2-6] But while Patient *B* was not tired and his pupils remained quiet in darkness, those of Patient *A* fluctuated extensively. Since acute fatigue was not present in Patient *B*, the pathologic light reflex pattern had to be due entirely to the organic condition. In contrast, in Patient *A*, acute tiredness may have contributed to the deterioration of the reflex pattern.

Pathologic fatigue. Every clinician encounters patients in whom constant, extreme fatigue forms a major part of the subjective complaints. In these cases, it is important to establish objectively the presence or absence of organic dysfunction, in order to differentiate between symptoms of true, physically founded fatigue and similar, physically unfounded complaints which may be voiced by patients who are, for example, mentally depressed. The cases shown in Fig. 13 serve as examples.

The first patient (Fig. *13,A*), a 16-year-old boy was a passenger on a school bus which collided with a truck. He lost consciousness and remained in a soporlike condition for about 4 days. He was difficult to rouse, and when aroused, was disoriented and excited, only to fall back into deep sleep as soon as left alone. Neurological routine examination and skull x-rays were negative. The electroencephalogram showed diffuse abnormality, more on the right than on the left side.

At the time of examination, 3 years after the accident, he was tense, restless, and jittery; his movements were slow and circumstantial. The patella reflexes were hyperactive, slightly more so on the left than on the right side, but no pyramidal symptoms were found. A slight facial paresis of central type was present on the left side. The electroencephalogram showed paroxysmal diencephalic dysfunction, and spike potentials at the

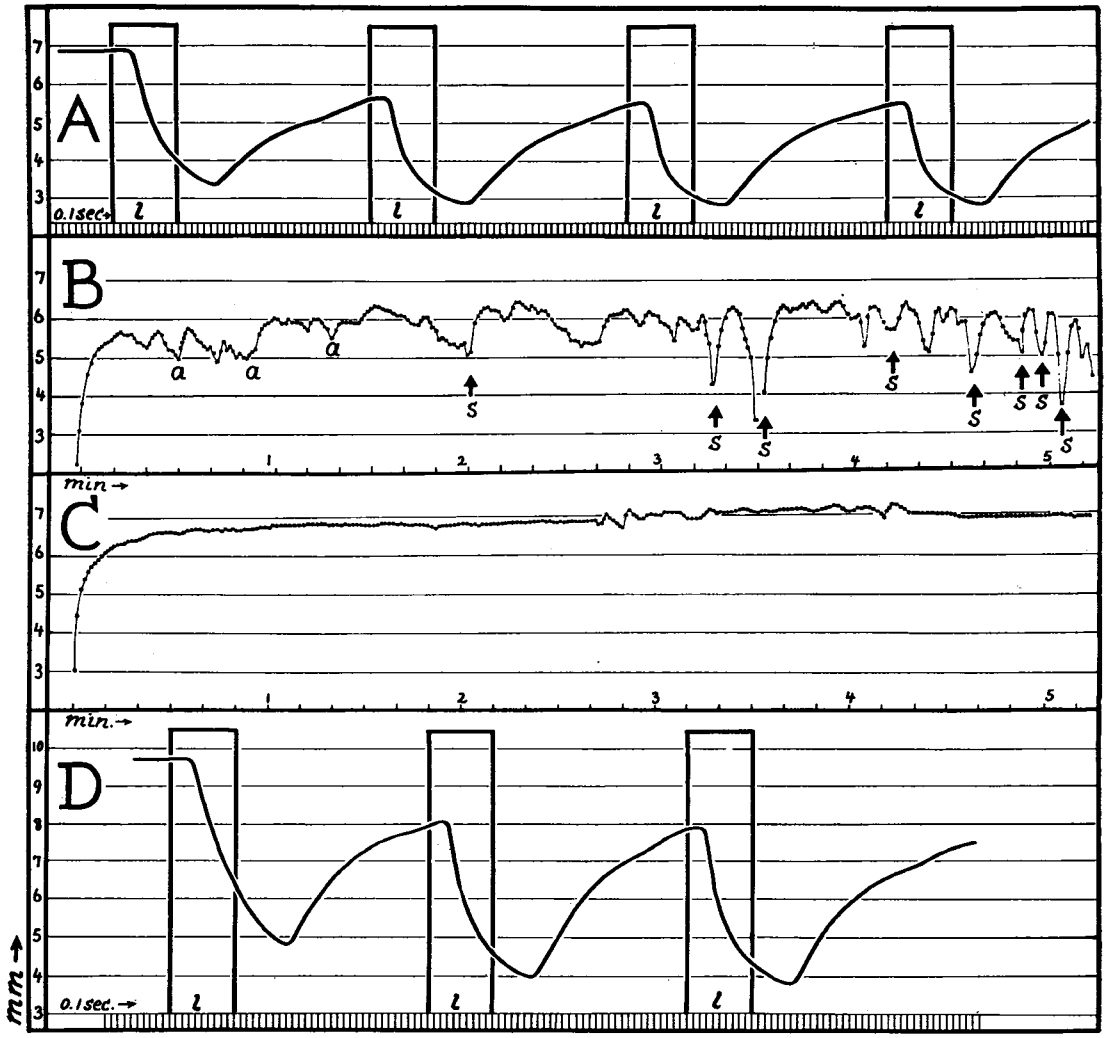

Fig. 9. Pupillary movements in a normal subject 72 years of age *(A-C)* and in his daughter aged 32 *(D)*.

In each record, the right pupil's diameter is shown as the ordinate (in millimeters) against time as the abscissa (in 0.1 second units *[A,D]* or in minutes [*B,C;* cf. Fig. 3]).

When the subject was not tired, his pupils were large and his reactions to light showed the extent and shape found in the majority of healthy young persons *(A)*. The record *B* was obtained when he was very tired (6 P.M.). At the beginning of the trace, his right eye had been adapted to light, and the first measurement represents the pupillary diameter at the moment when this light was turned off. After the initial, fast dilation in darkness, the pupils started to oscillate, and, beginning during the second minute of the test, intermittent sensory stimuli were required to keep the subject awake (sound stimuli, marked by arrows *s*). After the 6th minute, he was unable to continue the test. He was given an opportunity to rest and he slept for about an hour. The second record, taken at 8 P.M. under the same experimental conditions, showed no pupillary irregularities for more than 20 minutes (first 5 minutes shown in *C*).

The subject's daughter, who resembled him in personality and temperament, had unusually large and reactive pupils (*D;* see discussion in text).

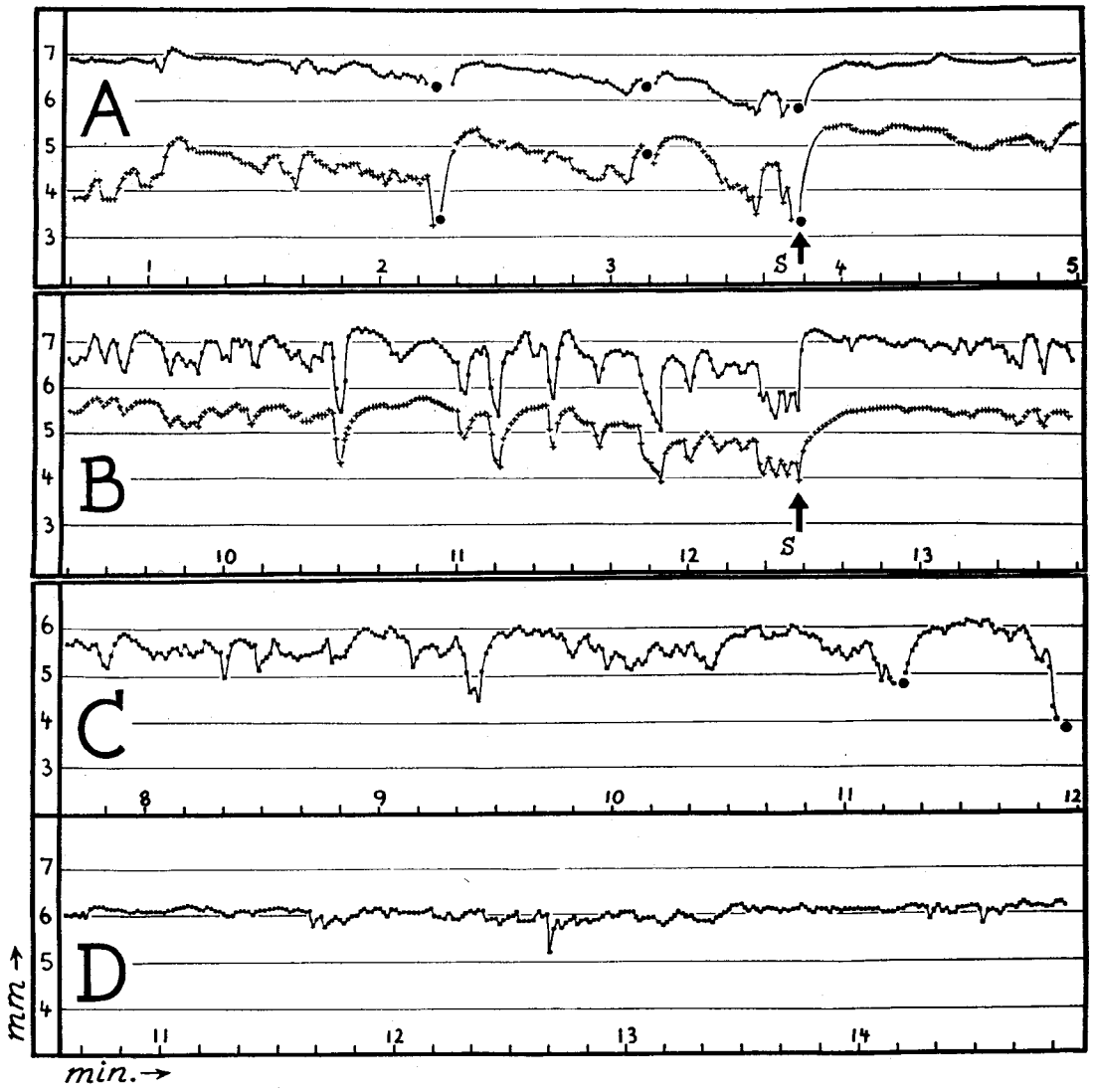

Fig. 10. Influence of some drugs upon spontaneous pupillary oscillations of tired subjects. Pupillary diameter is plotted as the ordinate (in millimeters) against time as the abscissa (in minutes; cf. Fig. 3), whereby the dotted lines represent the right pupils, the lines of crosses the left pupils *(A,B)*. In *C* and *D*, only the right pupil's movements are shown. The round dots in *A* and *C* indicate lid closures.

A, The subject, a 51-year-old man, had been chronically fatigued all his life, without a definitely established cause, except for a congenital heart condition. On the day of examination he was tired; his pupils were small and showed irregular fluctuations. Occasionally, he closed his eyes and appeared to go to sleep but roused himself spontaneously. When his right pupillary sphincter was paralyzed by conjunctival application of 2 drops of a ½ per cent solution of Cyclogyl, the pupillary oscillations were reduced in extent but their rhythm was not altered.

B, The subject was the same as in Figs. 3 and 4. On the day preceding the examination, his left eye had been treated with 2 drops of a 5 per cent solution of guanethidine (Ismelin), and on the morning of the test a complete temporary Horner's syndrome had developed on the left side. He felt sleepy, and his pupils showed extensive oscillations. They were reduced in extent and speed but otherwise unaltered by the sympathicolytic drug. Note especially the slowness of the pupillary dilation following a sensory *(continued on next page)*

anterior temporal and the ear lobe electrodes. Vision was normal except for total loss of convergence for near, unaccompanied by exophoria.

His chief subjective complaint was constant, overwhelming fatigue. He slept restlessly at night, had headaches and was always tired, forgetful, and unable to learn. While he had been a good student before the accident, he now had to force himself constantly to stay awake in school, was too tired to follow the teaching, and inevitably fell asleep after some time.

The pupillary fatigue test showed that the patient was unable to remain alert when sitting quietly in darkness. After 2 minutes his pupils began to fluctuate, and after 3 minutes he began to fall asleep. It was thus clear that the extreme tiredness of which the patient complained was organically founded.

The second patient, a 36-year-old man, was suffering from an atypical form of multiple sclerosis. For 5 years, periods of transitory spastic paralysis of the left upper and lower extremities, diplopia, and paresthesias had alternated with periods of seemingly complete remission. About a year before the onset of the degenerative central nervous disease, the patient had first complained of constant fatigue, and this fatigue had continued since then, persisting even during the periods of remission. He always felt tired, and no amount of rest appeared to help; he was even more tired when he awoke in the morning than when he went to bed in the evening, and he dragged himself painfully through the day.

This condition of extreme fatigue was expressed clearly in his pupillary movements. The reflexes to light—quite normal during moments of alertness—deteriorated markedly within seconds (Fig. 13,*B1*, *B2*). When the patient sat quietly in darkness, the pupils fluctuated wildly, and, almost from the beginning of the test, repeated sensory stimuli were required to keep the patient awake (sound stimuli at *s* in Fig. 13,*B3*).

Discussion

Mechanisms of fatigue. The spontaneous pupillary oscillations described in this communication were found in human subjects under the influence of that degree of fatigue which is commonly referred to when man is conscious of being tired (see following section under "Physiologic versus pathologic fatigue" for further definition). This kind of fatigue differs from the condition of exhaustion of experimental animals under the influence of severe stress, which brings about an outpouring of epinephrine, hypertrophy of the adrenal glands, and other anatomical changes. These mechanisms do not play a role in man under the usual conditions of civilized life, and it is our opinion that the physiologic responses to catastrophic stress situations should not be confused with the events which take place as we gradually tire during an ordinary working day.

The fatigue dealt with by us also differs from that referred to in texts on the physiology of work, in which physical symptoms such as an accumulation of waste products in muscle, increased heart rate and volume, accelerated respiration, increased oxygen consumption, and other biochemical changes are dominant features. While the type of stress used in those experiments, and the acute condition elicited, certainly are important features in human existence, they are not identical with the kind of fatigue we mean when we say "I am tired," although, of course, this may be their ultimate result.

The kind of fatigue which causes us to say "I am tired" is not necessarily associated with muscle fatigue, and need not be connected with other symptoms of physical stress; it can be reversed from one

stimulus (sound stimulus, marked by arrow *s*) which is typical for the sympathectomized pupil.

C and *D*, The same subject as in Figs. 7 and 8 was used at a time when she was in good general condition. On the evening of the test she was tired after a 13 hour day, preceded by only 3½ hours of sleep. Waves of pupillary dilation and contraction accompanied the waves of drowsiness and awakening. Since the subject made no effort to stay awake, she fell asleep after 12 minutes (*C*). At this time, 10 mg. of *d*-amphetamine sulfate (Benzedrine) was given orally. One hour later, the subject felt wide awake and slightly tense and excited. The pupils showed practically no oscillatory activity (*D*, showing the 11th to 15th minutes of the test).

moment to the next by psychosensory stimulation. When we are weary after prolonged, monotonous activity, and are gradually drifting toward sleep, an unexpected pleasant or unpleasant event which touches our emotions, a sudden idea which stimulates our imagination, instantly reverses the fatigue process; the condition of alertness is restored, and it may be maintained for a long time.

Alertness and sleepiness depend, then, not only on the amount of energy spent, or the time elapsed since a previous period of sleep, but also upon the degree of corticodiencephalic activity evoked by sensory or emotional stimuli—provided by the environment—or by spontaneous mental activity.

In this connection, it is interesting that normal monkeys, when examined at any time during the day, are almost completely unable to maintain alertness when left in darkness, provided that they are seated comfortably and are prevented from moving around by having their extremities tied by elastic bandages. While these vivacious animals react most vigorously to sensory stimulation, they appear to be devoid of spontaneous corticodiencephalic activity. When they are in darkness, and

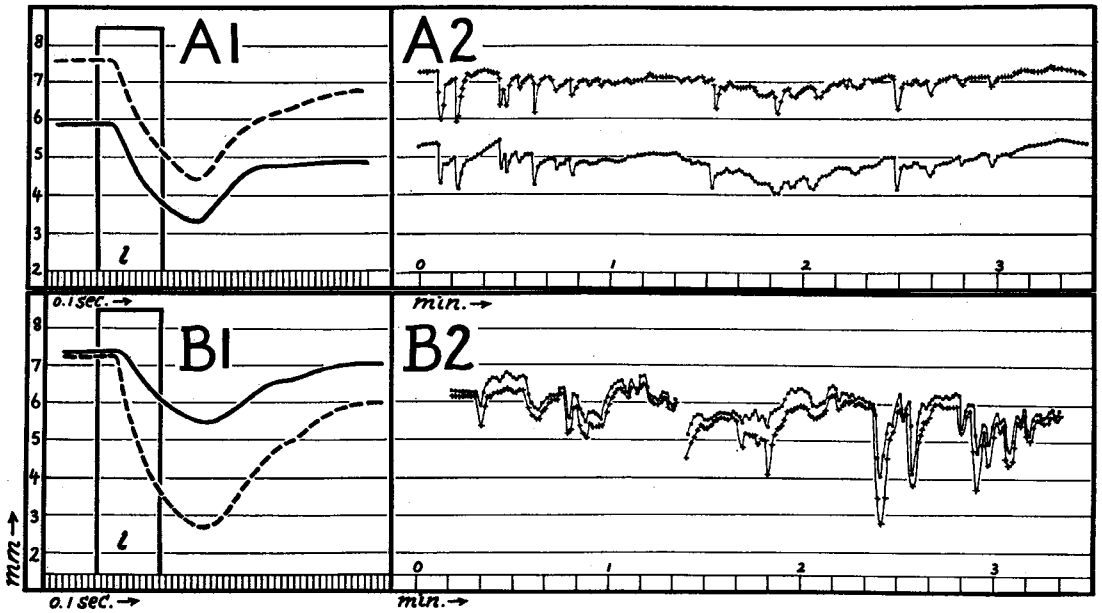

Fig. 11. Pupillary movements after damage to the peripheral sympathetic chain *(A)* or to the third nerve *(B)*.

Pupillary diameter is recorded as the ordinate (in millimeters) against time as the abscissa (in 0.1 second units *[A1, B1]* or in minutes [*A2, B2;* cf. Fig. 3]). In *A1* and *B1*, the solid lines represent the right pupils, the broken lines the left pupils. In *A2* and *B2* the movements of the right pupils are shown by dots, those of the left pupils by crosses.

A1 and *A2*, The patient was a 28-year-old man. His right sympathetic chain had been injured surgically when a tumor was removed in the area of exit of the sympathetic fibers from the spinal cord (C_8—T_2). The right pupil was smaller than the normal left one; the second redilation phase of the light reflex was missing, as is typical for sympathetic lesions *(A1)*. Spontaneous pupillary fluctuations in darkness were reduced only slightly *(A2)*.

B1 and *B2*, The patient, a 9-year-old boy, had been unconscious for 3 months after an automobile accident. Among many other sequelae of his injuries, the right third nerve was impaired intracranially. The right pupil's light reflex was sluggish and much less extensive than that of the left pupil *(B1)*. Pupillary oscillations, which appeared after a short time in darkness, were reduced in extent but not altered in character on the injured side *(B2)*.

otherwise unstimulated for only a few minutes, they appear bored; their eyelids droop, their pupils contract, and soon they fall asleep.

We have proved in detail that the changes in pupillary reaction pattern, which are among the physiologic expressions of these events, are central nervous in nature[3, 4] (see also preceding section, "Mechanism of spontaneous pupillary movements in complete darkness").

Physiologic versus pathologic fatigue. In the patients represented in Fig. 13, the light reflexes elicited at moments of alertness were normal. There was, then, no organic lesion present within the nervous network of pupillary control, and the pathologic reflex shapes shown so frequently were all due to reversible, acute tiredness. What, then, distinguishes the findings in these patients from physiologic fatigue in normal subjects? And further, can we ever speak of "normal fatigue"?

"Fatigue" has, unfortunately, become a rather overworked word, its precise meaning eroded by multiple use. At this point, we should define our meaning of the term. According to *Webster's Dictionary,* its general meaning is "weariness from labor or exertion, exhaustion of strength, loss of power due to continued work but removable by rest," and the physiologic definition "condition of cells or organs which have undergone excessive activity with resulting loss of power or capacity to respond to stimulation,"[10] and these definitions agree closely with the one used by us in earlier work, namely, "the reversible reduction and eventual exhaustion of a living function during its repeated activation."[3, p. 2]

Enclosed within these definitions is, then, the answer to the first question asked above. The patients represented in Fig. 13 were *always* tired; their condition of exhaustion was *not* preceded by activity, and it was *not* removable by rest. These features distinguish pathologic from physiologic fatigue.

As is usual in life, conditions are not always marked off as clearly. There are many individuals who, though not actually ill, fatigue more quickly than they should; that is, they become tired after activity which in the majority of healthy persons is not adequate to produce a like degree of exhaustion. Where, then, shall we draw the line between physiologic and pathologic fatigue?

Three main groups of individuals make up the vast army of the chronically tired, namely, (1) those who are tired because of a habitual lack of adequate rest, (2) patients in the incipient or convalescent stages of acute illness and patients with chronic pathologic conditions, and (3) those in whom the cause of chronic fatigue is unknown.

When excessive fatigue is part of an acute or long-lasting pathologic condition, it is reversible insofar that it disappears when the disease has been overcome. This type of fatigue is, then, a physiologic accompaniment of the condition; while *indicating* the presence of a pathologic state it is itself no more "abnormal" than the rise in temperature which accompanies infectious diseases. There are, however, central nervous conditions in which fever is a localizing sign, just as pathologic as hemiplegia. Idiopathic chronic fatigue may, like "central fever," be a primary sign of diencephalic dysfunction. If, in a given case, the organic nature of the chronic tiredness can be established by the pupillary behavior, it should be treated as the danger signal which it is.

Since we have established that the pupillary symptoms that accompany fatigue are central nervous in origin (see previous discussion), must we then assume that in every case of general disease the brain is affected, and that fatigue is due to disorganization of corticodiencephalic activity, i.e., that it reveals an only milder and still reversible degree of pathologic disintegration?

We would answer this question in the negative. Fatigue and alertness, sleep and waking are part of normal homeostatic

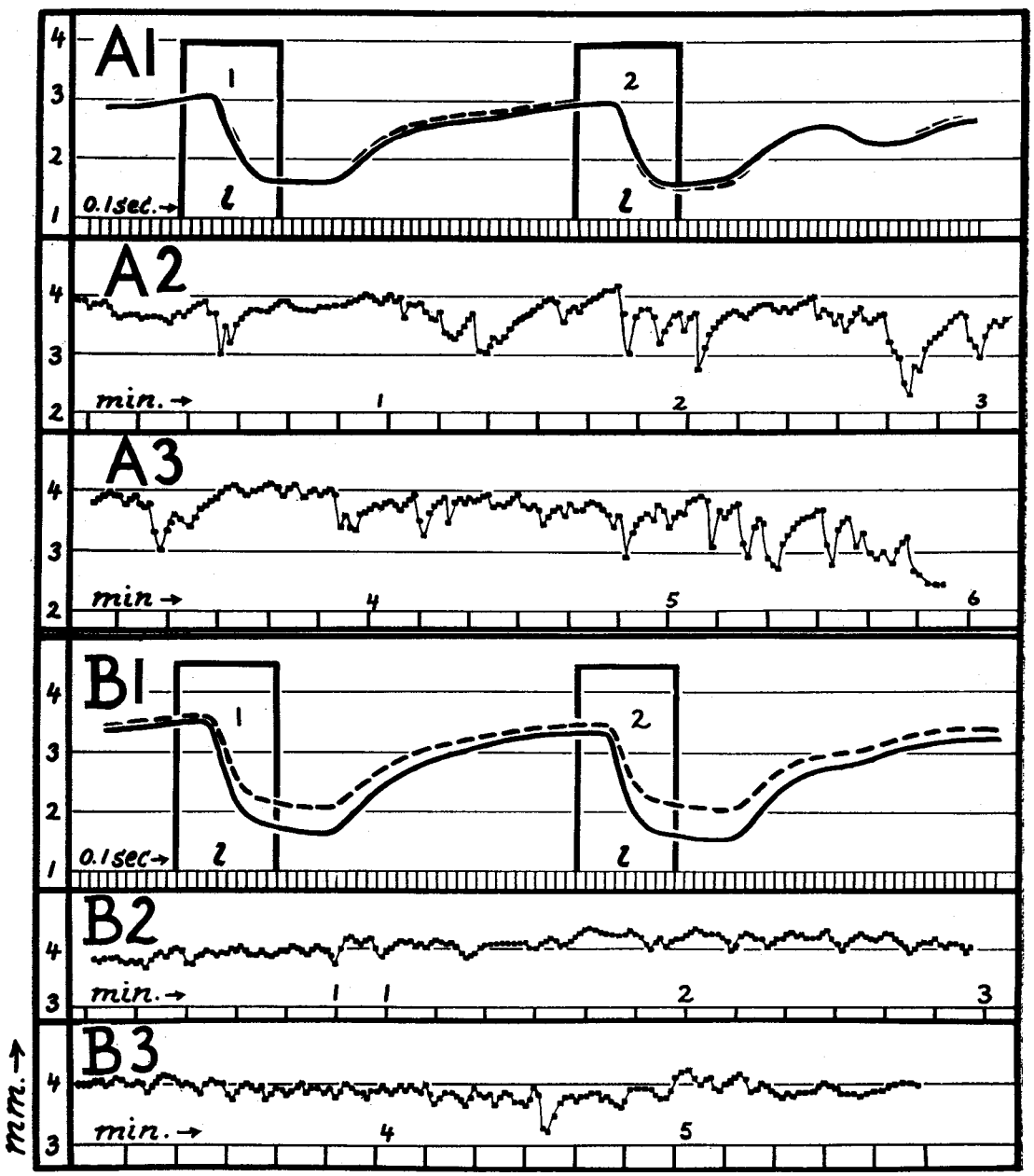

Fig. 12. Pupillary movements in two patients with diencephalic lesions.
Pupillary diameter is shown as the ordinate (in millimeters) against time as the abscissa (in 0.1 second units [*A1* and *B1*] or in minutes [*A2, A3,* and *B2, B3;* cf. Fig. 3]). In *A1* and *B1,* the solid lines represent the right, the broken lines the left pupils. In *A2, A3,* and *B2, B3,* only the right pupils' movements are shown.

A, The patient was a 58-year-old woman who had shown high blood pressure for 20 years. At the time of examination she had suffered for about 5 weeks from mental depression with constant feelings of fatigue. Her pupils were small, with square, "tonohaptic" light reflexes, indicating loss of supranuclear inhibitory impulses to the oculomotor nucleus.[3, 5, 6] In darkness, the pupils oscillated almost at once, and during the 6th minute of the test the patient fell asleep *(A2, A3).* *(Continued on next page.)*

REFERENCES

1. Lowenstein, O.: "Der Psychische Restitutionseffekt. Das Prinzip der Psychisch Bedingten Wiederherstellung der Ermüdeten der Erschöpften und der Erkrankten Funktion," Basel, 1937, Benno Schwabe & Co.
2. Lowenstein, O., and Loewenfeld, I. E.: Mutual role of sympathetic and of parasympathetic in shaping of the pupillary reflex to light, Arch. Neurol. & Psychiat. **64**: 341, 1950.
3. Lowenstein, O., and Loewenfeld, I. E.: Disintegration of central autonomic regulation during fatigue and its reintegration by psychosensory controlling mechanisms, J. Nerv. & Ment. Dis. **115**: 1, 121, 1952.
4. Lowenstein, O., and Loewenfeld, I. E.: Types of autonomic innervation and fatigue, A. M. A. Arch. Neurol. & Psychiat. **66**: 580, 1951.
5. Lowenstein, O.: Pupillary reflex shapes and topical clinical diagnosis, Neurology **5**: 631, 1955.
6. Lowenstein, O., and Loewenfeld, I. E.: Electronic pupillography. A new instrument and some clinical applications, A. M. A. Arch. Ophth. **59**: 352, 1958.
7. King, G. W.: Recording pupil changes for clinical diagnosis, Electronics **32**: 67, 1959.
8. King, G. W.: An improved electronic pupillograph for clinical use, Proc. Nat. Electronics Conf. **16**: 672, 1960.
9. Loewenfeld, Irene E.: Mechanisms of reflex dilatation of the pupil. Historical review and experimental analysis, Doc. Ophthal. **12**: 185, 1958.
10. Webster's New International Dictionary of the English Language. ed. 2, Springfield, Mass., 1960, G. & C. Merriam Co.
11. Hess, W. R.: Vegetative Funktionen und Zwischenhirn, Helv. physiol. acta, Suppl. IV, 1947.

Discussion

Dr. Gerhard A. Brecher, Atlanta, Ga. The authors are unquestionably the world's leading pupillographists. They have refined their measurement technique by means of modern technology to such a high degree of precision that it can now be used for various quantitative investigations. One of them concerns the present study in which the effect of fatigue on the pupillary reflex response is described. Changes in the pupil reactions are only one of the numerous parameters which are affected during fatiguing. The greatest difficulty experienced in the past has been that changes characteristic for tiredness have been elusive when measurements were attempted. Volitional, short-lasting periods of arousal from encroaching fatigue usually result in a level performance of tasks during long-term testing, even when marked subjective tiredness is experienced. Thus the degree of innate fatigue remains practically unmeasurable because it is masked by volitional efforts until a sudden breaking point is reached beyond which sleep supervenes. The pupillary reaction is one of the few reflexes which in ordinary people cannot be influenced by will. It is solely the result of autonomic nervous system outflow. It lends itself easily to measurements of the time course and extent of the response. The patterns of pupillary reactions during fatigue which were described and analyzed in great detail by the authors can therefore serve in future studies on fatigue as an objective criterion permitting a quantitative measure of innate tiredness. The comprehensive material presented here is most valuable. The basic concepts concerning the effect of the central nervous processes on the pupillary reflex are thoughtfully and almost philosophically developed. The work is superbly executed.

Dr. Loewenfeld (closing). We can only thank Dr. Brecher for his kind words.