DIURNAL TONOGRAPHY IN NORMAL AND GLAUCOMATOUS EYES*

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THE DAILY FLUCTUATIONS IN OCULAR TENSION were first noted by Sidler Huguenin[1] in 1899 using tactile tension. The observation was confirmed by Maslenikow[2] in 1904, using applanation tonometry. Since then the topic has been widely studied and the 1961 review of Ourgaud and Etienne[3] contains over 300 references.

The terminology has caused confusion both in the literature and in the experimental design of studies. Diurnal has been used to mean either a day of 24 hours or the hours of daylight (the antonym of nocturnal). Halberg, *et al.*[4] introduced the word circadian (*circa*: about; *dies*: day) to describe continuously operating biological oscillations having a frequency of about 24 hours.

Rhythmic fluctuations characterize a number of functions in addition to the ocular pressure. More than fifty rhythmically changing cellular and fluid constituents, functional activity and behavioral elements have been studied in man.[5] Oscillation occurs at all levels of cellular complexity in biology and may well characterize all living material.

The widespread interest in oscillations is evidenced by the abundance of recent publications on this subject, including a large number of reviews,[5] two monographs,[6,7] and the proceedings of two symposia.[8,9] Some of the rhythms described include those involved in the function of unicellular organisms, in the orientation of insects, the growth of plants, and a variety of functions in vertebrates.

In man, a 24-hour, or circadian, cycle is one of the frequently occurring rhythmic patterns, but cycles ranging from a period of seconds

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(ultraradian), such as respiratory and cardiac cycles, to a period of one month (infraradian), such as the menstrual cycle, are known. Among the circadian patterns studied in humans are those for body temperature, blood pressure, psychological mood, heart rate, urinary flow rate, urinary excretion of sodium, potassium, and phosphate, electrical skin resistance (in infants), electrical activity in the brain, plasma corticosteroid levels, circulating eosinophils and lymphocytes, and serum iron concentration. Periodicity may characterize not only normal functions, but certain diseases in the human[7] and the susceptibility of the individual to certain environmental agents.[10]

Rhythmic properties are found throughout the plant and animal kingdom. A circadian rhythm was described for leaf movements in 1729.[11] It appears that even the simplest cells may manifest rhythmic behavior, the mitotic activity in tissue cultures, for example. Such observations are entirely consistent with the known periodicity of anabolism and catabolism involved in the physiologic function of the cell. Circadian rhythms characterize quite diverse phenomena ranging from the luminescence of photosynthetic organisms and bacterial population dynamics to the activity of the clam. This rhythmic property is thus an attribute of all living matter. A rhythm is characterized by its amplitude and frequency. In many instances of biological rhythm, the periodicity may be obscured either by random phenomena ("noise") or by the superimposed rhythms of other functions. Under these circumstances classical techniques of statistics and Fourier analysis are not applicable, and long-term study is necessary before one can be certain that periodicity exists.

In view of the general acceptance of a 24-hour rhythm for intraocular pressure, it is of interest that Mercer[12] has stated that to determine the periodicity of a function having a frequency between 20 and 30 hours, it is necessary to record every six hours for a total of 3,000 hours to obtain marginally adequate results. The majority of studies of ocular tension have been directed not to learning the period or the frequency of the oscillation, but rather to the amplitude of oscillation in a 24-hour period.

Rhythms which are imposed by external environmental changes are called exogenous; rhythms which are inherent to the organism and are not dependent upon some external periodic stimulus are called endogenous. Factors in the environment which cause an exogenous rhythm are called *Zeitgeber* (time-givers), synchronizers, or entraining agents. A 24-hour rhythm is usually considered to be exogenous in origin; one of consistently greater or lesser duration is usually endogenous. The

chief environmental influence is the rotation of the earth and, with it, the cycles of night and day, which are also combined with a periodicity of several physical events ranging from terrestrial magnetism to cosmic showers. Alteration in surrounding temperature is also an important synchronizer. In the experimental laboratory the external synchronizer may be as simple as the sound of a key being turned in the lock as a night watchman makes his rounds, or the rhythm of animals feeding. Intraocular pressure measured at a particular time each day may constitute such a synchronizer. A rhythm which persists after the removal of an exogenous synchronizer is called free running.

In order to establish a rhythm as endogenous, all environmental factors must be carefully controlled (particularly those of activity, light and dark alternation, and ambient temperature). The photoperiodism of plants, which has been studied for the past 200 years, can be delayed or accelerated by exposure to one minute of light a day. Endogenous rhythms may be peripheral in origin or under the control of central or humoral factors. In intact animals the adrenal cortex cycle is thought to be the most important factor controlling many endogenous circadian rhythms. However, since the adrenal cortex is under the control of both the pituitary and diencephalon, these have been considered responsible for many variations in rhythm. It has been shown that the pituitary is not essential for periodicity in all systems inasmuch as circadian rhythms persist in the hypophysectomized animal whether or not there is supplementation by hormones.[13] The adrenal functions may be changed by alternation of light and dark, but a rhythmic cycle persists even in a blinded mouse.[4]

The variation of intraocular pressure in both normal and glaucomatous individuals has been widely studied. In many of the studies the type of glaucoma has not been defined and it is difficult to compare various data. In addition, exogenous influences have frequently not been removed and those interested in circadian rhythms would find the evidence for a diurnal rhythm unacceptable.

Most studies describe the maximum ocular tension that occurs in normal subjects between 6:00 A.M. and 8:00 A.M. In glaucoma several rhythms have been described. Duke-Elder[14] has described three types of curves in wide-angle glaucoma: (1) a falling curve with the peak shortly after waking (20 per cent of cases); (2) a rising curve with a peak between 4:00 P.M. and 6:00 P.M. (25 per cent of cases); and (3) a double curve with the initial peak between 9:00 A.M. and 11:00 A.M., and a second peak between 4:00 P.M. and 6:00 P.M. (55 per cent of cases). In addition, a flat curve has been described in which the tension

is the same during a 24-hour period (with occasional rises).[15–17] A variable or irregular curve has been reported in which the tension is usually highest during the day, but no regular rhythm is noted. It is rare for the tension to be highest after 6:00 P.M. in untreated wide-angle glaucoma eyes. However, Hager[17] concluded after many studies that early morning tonometry, even in combination with two or more measurements during the daytime, does not guarantee adequate information concerning the course of intraocular pressure even though the maximum tension in glaucoma is frequently in the early morning. Hager also believes that each individual may have a characteristic curve of intraocular pressure as unique as his fingerprints.

The fundamental character of the cycle of the ocular tension is not clear from previous studies. Although the amplitude of a cycle can be modified by simple changes in environment such as placing the subject in a hospital, the period and frequency of the cycle are not known. Nor is the cause of ocular tension fluctuations known although this subject has received considerable attention. It is of primary interest to determine whether these tension fluctuations reflect local ocular changes in aqueous dynamics or changes initiated outside the eye. In this latter category both exogenous and endogenous factors have been considered.

At one time the principal exogenous synchronizer for ocular tension was considered to be the alternation of light and dark.[3] This theory was abandoned when tension fluctuations were shown to persist in patients remaining in complete darkness for 24 hours, or in those remaining in a lighted room.

The central endogenous regulation of ocular tension through the sympathetic division of the autonomic system has had numerous advocates.[14,18,19] The center for tension control was considered to be the diencephalon and it was thought that changes in sympathetic tone were reflected by changes in the caliber of blood vessels in the eye. In favor of this theory was the demonstration by Miller[20] that blocking the sympathetic supply (either at the ciliary ganglion in the orbit or at the stellate ganglion in the neck) would abolish tension fluctuations, and the discovery of a relation between episcleral venous circulation and diurnal tension fluctuations. Both Thomassen[21] and Bain[22] showed that measurable changes in the episcleral venous pressure preceded changes in ocular tension caused by the diurnal rhythm of the patient, or the use of miotics. Dobree[23] found an association between dilation of the venous side of the episcleral circulation and lowering of the ocular tension. Entirely different conclusions were reached by Linner. He found that preganglionic cervical sympathectomy in rabbits pro-

duced no significant change in ocular tension, outflow facility, or rate of aqueous flow.[24] He also showed that the episcleral venous pressure was rather stable and not affected by changes of tension or aqueous inflow induced by miotics and Diamox.[25]

Direct stimulation of the diencephalon has produced a variety of results including increases, decreases, and no change in ocular tension.[26,27] The results are inconclusive in regard to the site and nature of receptors and effectors and also in regard to the independence of tension changes from frequent associated blood pressure changes.

Although the intraocular pressure may be raised or lowered temporarily by changes in systemic arterial or venous pressure, it is unlikely that either factor is of great significance in diurnal tension fluctuations. Magitot[28] showed the complete independence of arterial pressure and ocular tension fluctuations. Boles-Carenini[29] found no relation between general venous pressure and ocular tension, although the venous pressure can have a diurnal rhythm.

Recent studies have suggested that intraocular pressure is regulated by the adrenal cortex. It has been shown that marked damping or cessation of diurnal tension fluctuations occurs in rabbits[30] or humans[31] with adrenal cortical insufficiency (through surgery or disease) or when the rising phase of plasma corticosteroids is suppressed by the use of an aldosterone antagonist.[32] A relation has been demonstrated between maximal and minimal levels of diurnal tension measurements and plasma levels of 17-hydroxycorticosteroids.[32,33] In addition, one worker found a relation between the diurnal variation of circulating eosinophils and ocular tension,[34] but this latter relation could not be confirmed in a subsequent study.[35]

Results of aqueous inflow studies are conflicting. Hodgson[36] used a fluorescein instillation technique to study aqueous flow and found that changes of aqueous inflow did not parallel changes in ocular tension. On the other hand, Ericson[37] used a suction cup technique to study diurnal inflow patterns in normal subjects. He found a marked decrease in aqueous inflow during sleep and noted a constant level of secretion during the day. Since the ocular tension can vary considerably in normal subjects during waking hours (variations up to 10 mm. have been recorded[38,39]) these findings cannot account for diurnal tension fluctuations.

De Roetth[40] has been the most recent advocate of the theory that osmotic changes in the blood might play a role in diurnal pressure variations through changes in aqueous inflow. However, diet, fasting, rest, or exercise do not alter the tension curve.[3] Conversely, there is

retention of urine during sleep and osmotic blood changes cannot be excluded.

The possibility that changes in ocular rigidity contribute to and produce apparent rather than real changes in ocular tension is unlikely since the tension fluctuations have been demonstrated with applanation as well as indentation tonometry.

Von Sallmann and Deutsch[39] showed that strict bed rest did not modify the tension curve; it is therefore unlikely that changes in intraocular volume are of importance in ocular tension fluctuations.

Several workers have searched for a relation between the daily tension curve and outflow facility (C). Kronfeld[41] in a study of secondary glaucoma following delayed restoration of the anterior chamber found marked variation in intraocular pressure associated with a relatively constant outflow. In a recent evaluation of a large number of patients, Drance[42] included two tonographic studies along with several tonometric measurements during the day. He found a daily fluctuation of C but no correlation between C, the fraction P_0/C, and the peak of intraocular pressure.

Three studies have been reported with measurement of three or more daily tonograms. De Roetth[43] found only minor diurnal outflow facility fluctuations in both normal subjects and patients with chronic simple glaucoma, and could show no relation between a fairly constant C and a variable ocular tension. In another study, diurnal tonograms were recorded without an automatic recording device,[44] and the authors reported variations in C as marked as those in ocular tension. In 23 eyes the diurnal tension variations could be correlated to diurnal changes in C; an increase in ocular tension was associated with a decrease in C and a fall in tension with an increase in C. In 16 eyes there was no relation between the ocular tension and C. Stepanik[45] obtained six daily tonograms in a group of normal and glaucomatous subjects and found a great variability of outflow resistance in both groups. In glaucomatous eyes the highest resistance (the lowest C) was noted at the peak of the diurnal pressure curve, but in the normal eyes variations in outflow resistance corresponded more to aqueous inflow than to tension fluctuations.

Thus, results are conflicting in regard to the absence or presence of daily outflow facility fluctuations, and the relation of such fluctuations, if present, to diurnal ocular tension rhythms in both normal and glaucomatous subjects.

The purposes of this study were: (1) to further investigate the question of daily outflow facility fluctuations; (2) to determine

whether there is any type of relationship between possible outflow facility and known ocular tension fluctuations; and (3) to note which features of daily outflow facility patterns distinguish glaucomatous from normal eyes.

METHOD

Sixty-seven subjects, 30 with normal eyes and 37 with glaucoma, were tested in this study. The glaucoma subjects were characterized by intermittent or constant measurement of tension greater than 24 mm. Hg and intermittent or constant measurement of outflow facility less than .13. Thirty-two of these subjects had open-angle glaucoma, two had a juvenile type of glaucoma, and three had secondary glaucoma in one eye and a normal second eye. The 32 subjects with open-angle glaucoma included 12 with characteristic visual field and optic nerve changes in one or both eyes, and 20 with no evidence of these changes in either eye. An eye with definite optic nerve or visual field changes was said to have overt glaucoma, and an eye with no such changes to have tonometric glaucoma. All eyes were gonioscoped to learn the appearance of the angles.

All glaucomatous and most normal subjects were hospitalized during the period of testing in order to approach steady-state conditions. The subjects were always admitted to the hospital at least one day before testing, and any topical medication used by a patient with glaucoma was discontinued at least three days prior to hospitalization.

Each subject was studied by tonography, usually at least three times during 24 hours separated by intervals of at least four hours. In a few instances it was not possible to obtain three satisfactory tonograms on every test day in the hospital. A few subjects were not tested in both eyes on all test days. Thirteen subjects were tested four, and ten subjects five times in 24 hours. All testing preceded meals. When only three tonograms were obtained, an attempt was made to distribute

TABLE 1. PRESSURE AND OUTFLOW CHARACTERISTICS

Group	*No. of subjects*	*No. of tonograms both eyes*	$P_0 >$ 21 *mm. Hg*	$P_0 >$ 24 *mm. Hg*	$C <$ 0.18	$C <$ 0.13	$P_0/C >$ 100
Normal	30	575	2%	0	18%	1%	5%
Tonometric Glaucoma	18	360	27%	14%	33%	35%	77%
Overt Glaucoma	12	219	10%	22%	33%	47%	77%
Other Glaucoma	7	94	12%	38%	28%	63%	89%

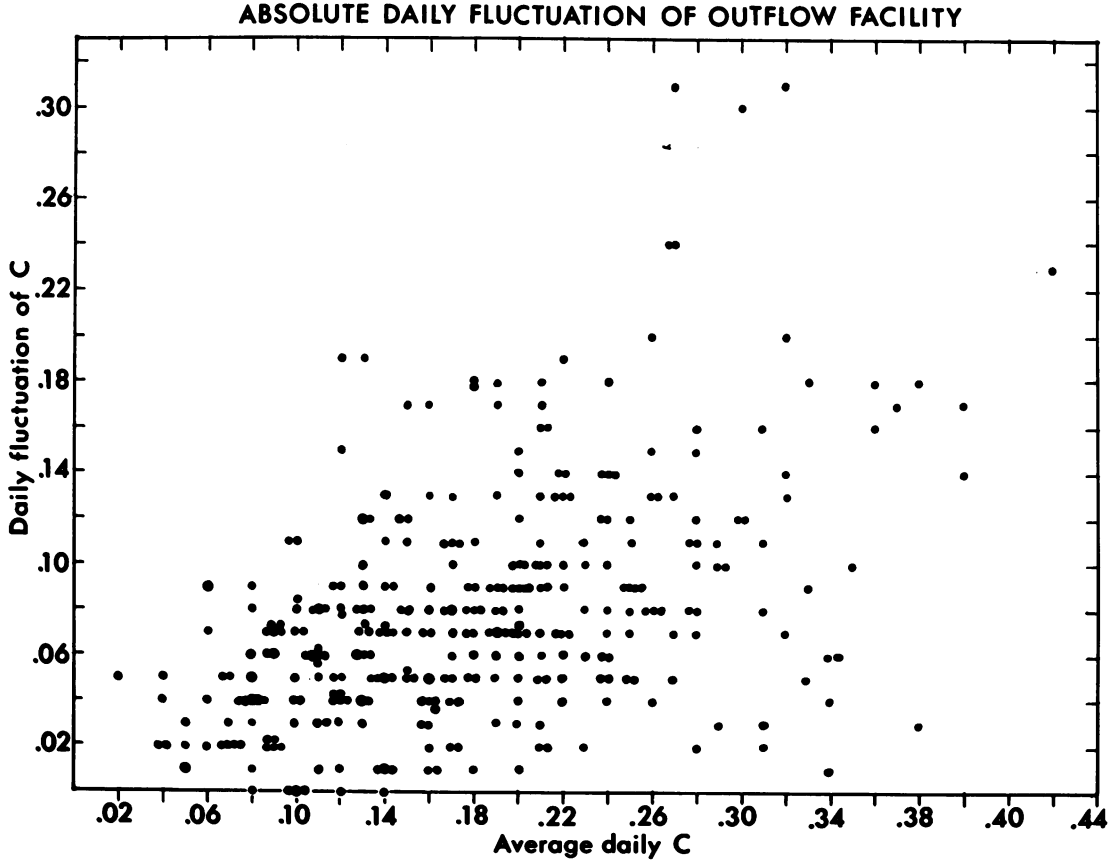


FIGURE 1

For each eye the total fluctuation of outflow facility (C) each day is plotted against the average daily outflow facility. Eyes with the smallest average C (the glaucomatous eyes) showed the least daily fluctuation of C.

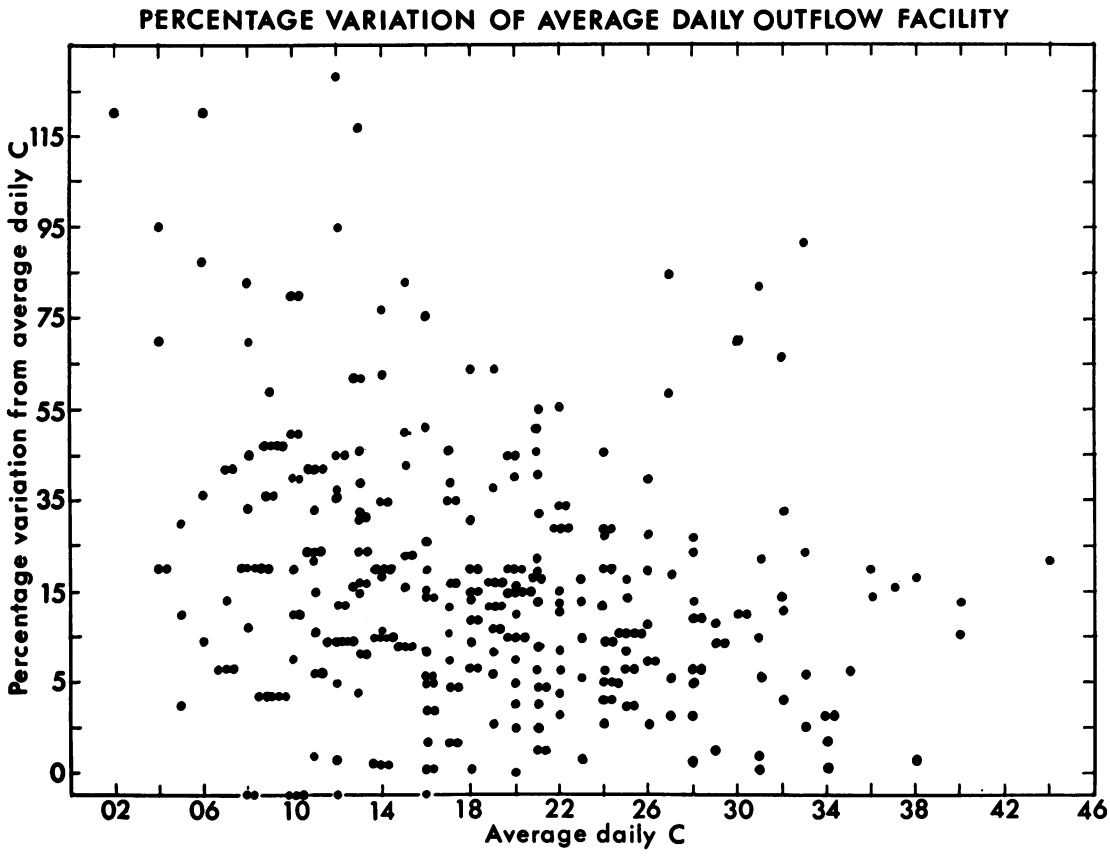


FIGURE 2

For each eye the percentage variation each day from the average daily C is plotted against the average daily C. There is no significant difference between any of the eyes.

these over the 12-hour period most likely to show a maximal tension reading (from about 6:00 A.M. to 6:00 P.M.[14,17,46]). Applanation tonometry always preceded tonography. Testing was done for at least two days. The total number of acceptable tonograms obtained from each group is shown in Table 1. All tonographies were done by the same technician, who had four years' prior experience. Tests were done in a quiet room according to accepted principles. Because of the frequency of tonographic recordings, most subjects were initially checked twice daily for corneal abrasions; however, this proved an infrequent problem. The tonographic records were rejected if deemed inadequate by either of two observers.

RESULTS

Evaluation of Data in Relation to Each Test Day

FLUCTUATIONS IN FACILITY OF OUTFLOW (C)

Fluctuations in C were observed in all eyes. The total daily fluctuation of C for each eye is shown in Figure 1 and the percentage fluctuation from the mean daily C is shown in Figure 2. The total daily fluctuation was proportional to the mean daily C. Eyes with the smallest C values (the glaucomatous eyes) showed the least and those with the largest C values (the normal eyes) showed the greatest daily fluctuation. On the other hand, the daily percentage fluctuation from the mean daily C was about the same in all groups (Figure 2).

FLUCTUATIONS IN OCULAR TENSION

Tension fluctuations between 6 to 10 mm. Hg were noted on some days for each group (Table 2). However, only the glaucomatous eyes showed daily fluctuations greater than 10 mm. Hg. The overt glaucoma group had the highest percentage of days (17 per cent) with fluctuations greater than 5 mm. Hg.

TABLE 2. DIURNAL TENSION FLUCTUATIONS

Group	*No. of Eyes*	*No. of Days*	*Diurnal tension fluctuation**	
			6–10	11 *or more*
Normal	60	172	5%	0
Tonometric Glaucoma	36	117	11%	3%
Overt Glaucoma	24	83	6%	11%
Other Glaucoma	14	32	22%	9%

*mm. Hg.

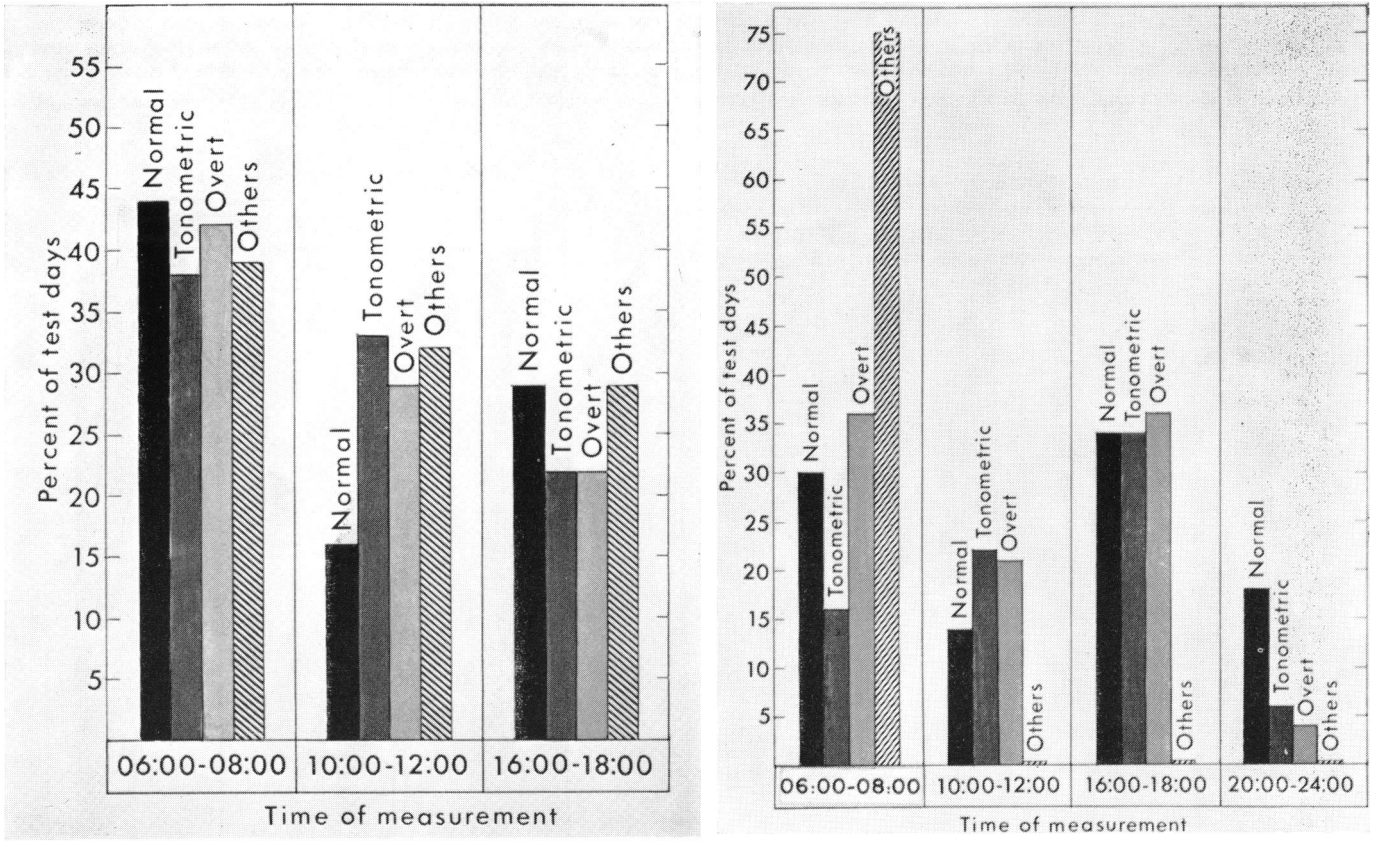


FIGURE 3. FOR ALL SUBJECTS THE PERCENTAGE OF TEST DAYS WITH MINIMUM C AT EACH OF THE TEST PERIODS IS SHOWN. A, In subjects with three daily tonograms most minimum C values were recorded during the 06:00 to 08:00 test period. B, In subjects with four or five daily tonograms most minimum C values were recorded during the 16:00 to 18:00 test period (except for the miscellaneous group). Subjects with two or more identical minimum outflow facility values in one day (a biphasic or flat curve) were omitted from these figures.

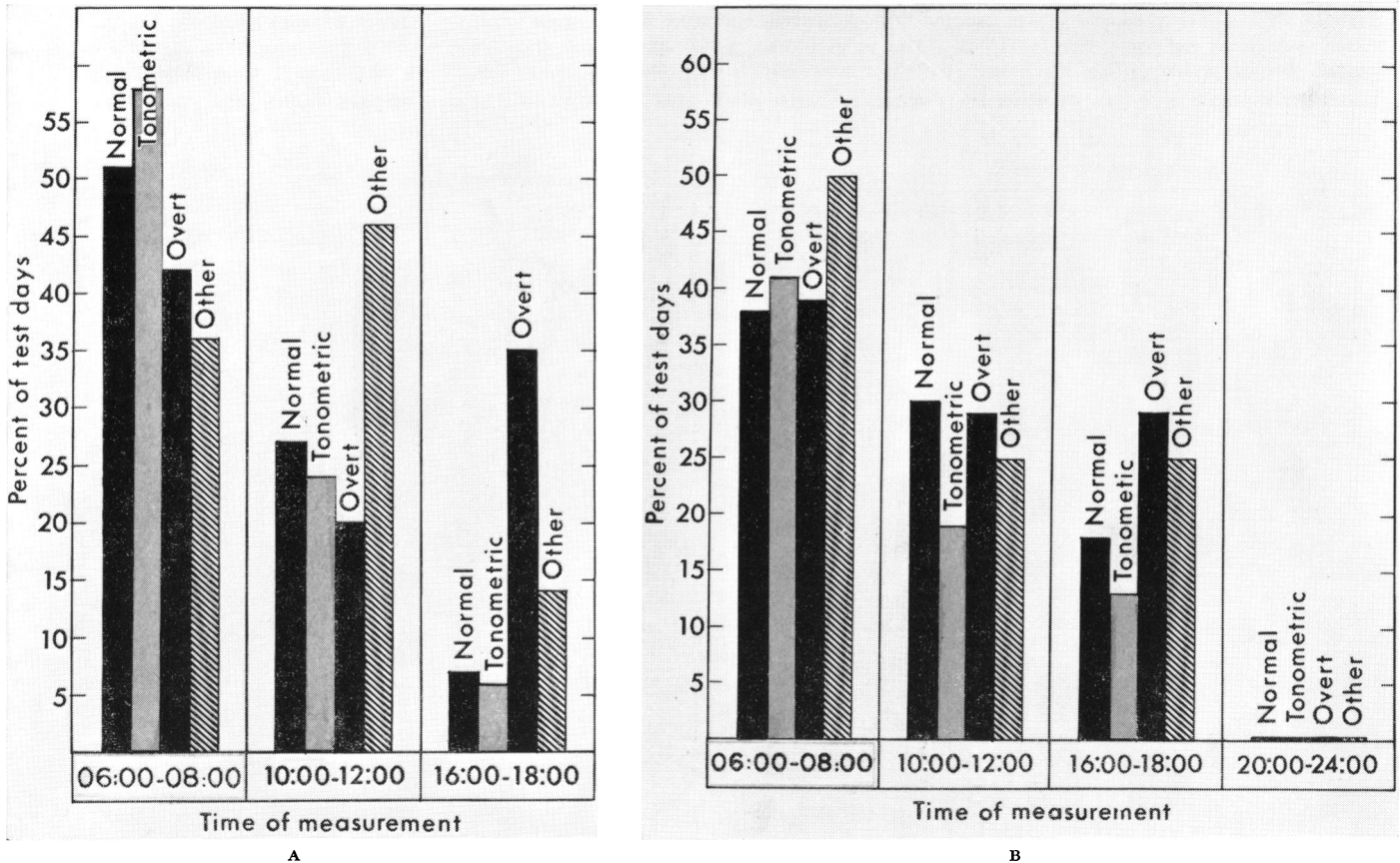


FIGURE 4. FOR ALL SUBJECTS THE PERCENTAGE OF TEST DAYS WITH MAXIMUM PRESSURE AT EACH OF THE TEST PERIODS IS SHOWN. The greatest frequency of maximum tension readings was between 06:00 to 08:00. A, However, when three daily measurements were made, the miscellaneous glaucoma group showed the greatest number of maximum tensions at 10:00 to 12:00. B, Note the scarcity of maximum tension readings from the 20:00 to 24:00 period when tensions were taken during this period. Subjects with two or more identical maximum tensions during the day (biphasic or flat curve) were omitted from these figures.

Each group of subjects was evaluated for a possible relation between daily tension fluctuations and average daily C. The data were separated to determine a relation independent of the type of eye (it is already known that eyes with glaucoma have, on the average, both higher diurnal tension fluctuations and lower C values than normal eyes). There was no apparent relation between diurnal tension fluctuations and average daily C in any group.

FLUCTUATION RHYTHMS

For compiling of daily maximum pressure and minimum C times each group of subjects was divided into two subgroups: one subgroup with three tonograms recorded between 6:00 A.M. and 6:00 P.M., and a second subgroup with four or five tonograms recorded between 6:00 A.M. and 12 midnight. In all subgroups most minimum C values were recorded during the 6:00 A.M. to 8:00 A.M. or 4:00 P.M. to 6:00 P.M. periods (Figure 3). In subgroups with more than three tonograms in 24 hours (Figure 3B), 18 per cent of the test days from normal subjects and 6 per cent or less of those from glaucomatous subjects had minimum C values during the 8:00 P.M. to midnight period.

The normal and two open-angle glaucoma groups had the greatest frequency of maximum tension readings between 6:00 A.M. and 8:00 A.M. (Figure 4). The miscellaneous glaucoma group had the greatest frequency of maximum tension readings between 10:00 A.M. and noon with three daily measurements, and 6:00 A.M. to 8:00 A.M. with four or five daily measurements. The second greatest frequency of maximum tension readings was between 10:00 A.M. and 12:00 noon in the normal and tonometric glaucoma subjects, and between 4:00 P.M. and 6:00 P.M. in the overt glaucoma group. Only two maximum tensions were recorded between 8:00 P.M. and midnight when one or two readings were taken in that period (Figure 4B). One was from a normal subject and one from a patient with overt glaucoma.

If a 24-hour rhythm exists for facility of outflow then the maximum and minimum values of this parameter should occur at about the same hour each day. An evaluation was made of the consistency of the time of minimum C in each subject. On the average each subject showed 50 to 54 per cent of all daily minimum C values at the same time (Table 3). An identical analysis was made for the time of maximum pressure. Each subject showed an average of 60 to 68 per cent of all daily maximum pressures at the same time. These findings suggested that a 24-hour cycle is more likely to exist for ocular tension. However,

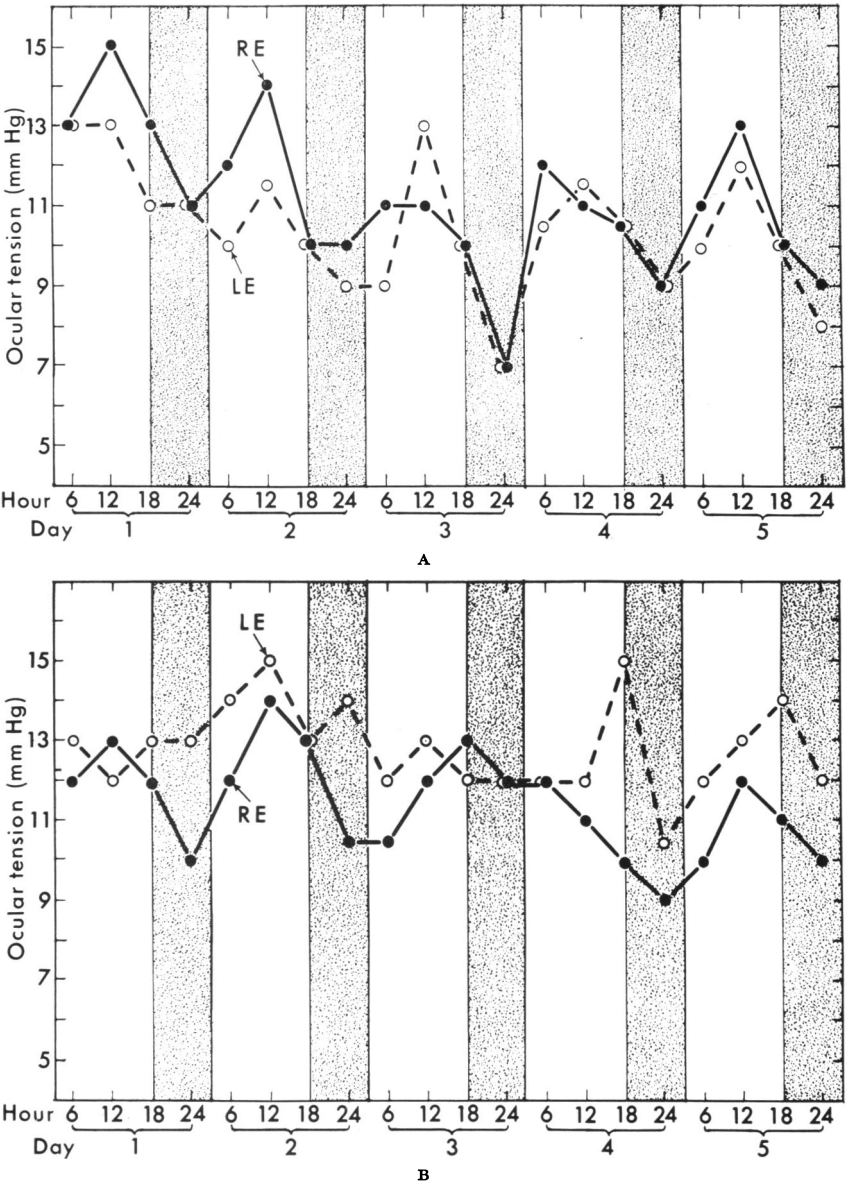
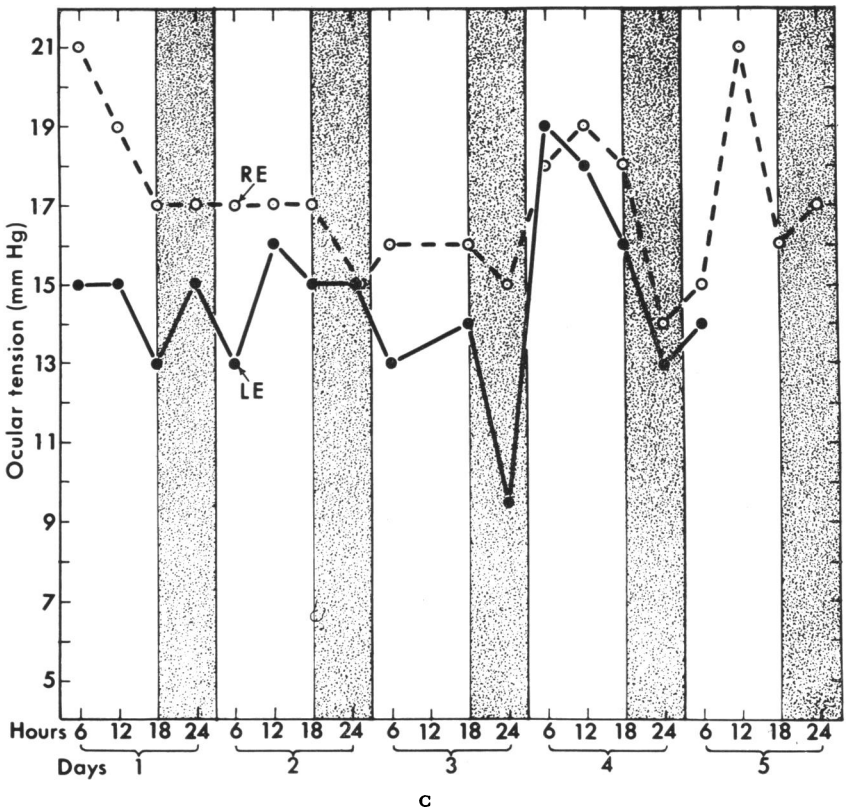


FIGURE 5. OCULAR TENSION FLUCTUATIONS OVER FIVE DAYS ARE SHOWN FOR NORMAL SUBJECTS A.S. (A), M.M. (B), AND R.I. (C).

Four measurements were usually made in each 24-hour period. Note the irregularity of the fluctuations in subjects M.M. and R.I. The fluctuations of subject A.S. showed the greatest degree of regularity. In all subjects the two eyes were frequently out of phase.



C

TABLE 3

Group	*No. Eyes*	*Frequency with which maximum pressure occurred at same hour*	
		Max. P_0	*Min.* C
Normal	58	60%	52%
Tonometric Glaucoma	36	63%	50%
Overt Glaucoma	24	68%	54%

this hypothesis could not be confirmed by the use of a *t* test.* Even subjects hospitalized at least one week prior to testing (to attain a steady state) showed variation of the times of maximum tension and minimum C values. The data from three subjects studied four times in 24 hours for five successive days are shown in Figures 5 and 6.

**P* is less than .05 for data from tonometric glaucoma group, but *P* is greater than .05 for both normals and overt glaucoma group.

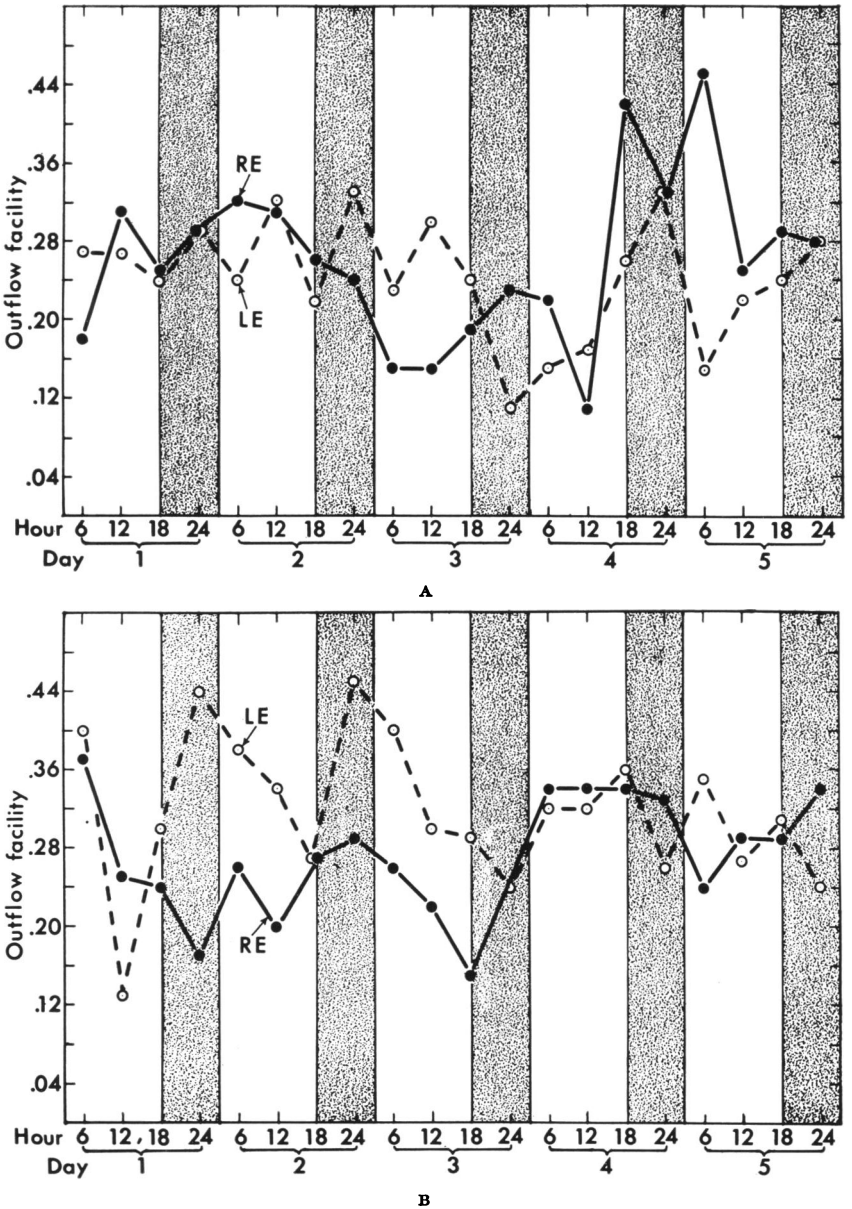
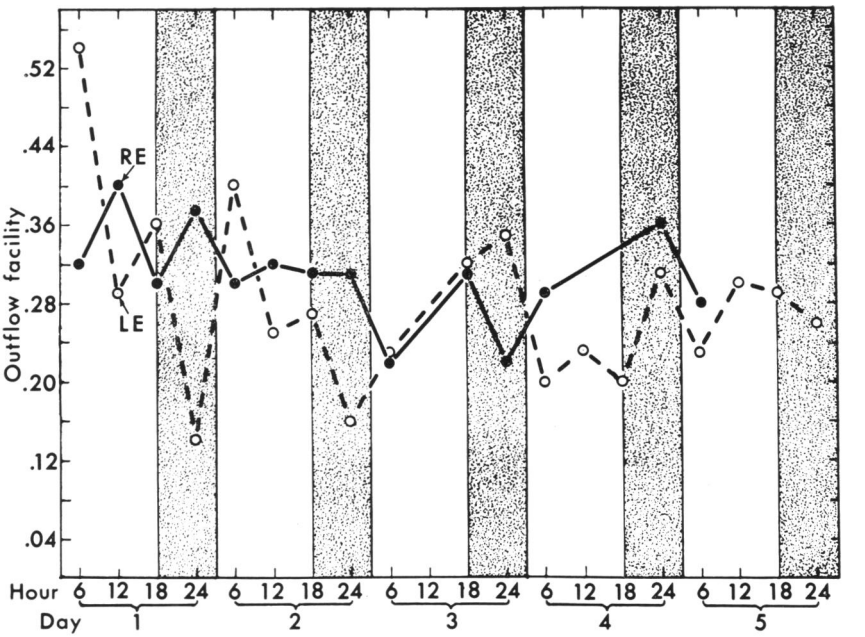


FIGURE 6. OUTFLOW FACILITY FLUCTUATIONS OVER FIVE DAYS ARE SHOWN FOR NORMAL SUBJECTS A.S. (A), M.M. (B), AND R.I. (C).

Four measurements were usually made in each 24-hour period. Note the irregularity of the fluctuation in all subjects and the asymmetry of the two eyes of each subject.



C

There was no consistent relation between fluctuation of outflow facility and intraocular pressure. However, the normal eyes tended to have the daily maximum C at the time of the daily maximum pressure, whereas glaucomatous eyes more frequently had the daily minimum C at this time (Table 4).

TABLE 4. RELATIONSHIP BETWEEN MAXIMUM PRESSURE AND C

		Glaucoma	
	*Normal**	*Tonometric**	*Overt**
Maximum P_0 with minimum C	23	44	42
Maximum P_0 with maximum C	60	36	38
Maximum P_0 with intermediate C	17	20	20

*Per cent of all days.

Comparison of Two Eyes at each Test Time

A difference greater than 5 mm. Hg between the two eyes was more frequent in the glaucoma groups than in the normal group (Table 5).

The difference in facility of outflow between the two eyes of a subject was tabulated for all subjects to see if normal eyes could be distinguished from glaucomatous eyes. The findings were inconclusive.

TABLE 5. AGREEMENT OF MEASUREMENTS FROM BOTH EYES OF AN INDIVIDUAL

Group	*Days maximum* P_0 *in both eyes was at the same hour**	*Days minimum* C *in both eyes was at the same hour**	*Difference between two eyes greater than 5 mm. Hg*
Normal	37	26	2
Tonometric Glaucoma	43	29	31
Overt Glaucoma	48	39	20
Other Glaucoma	43	7	40

*Per cent of all days.

The frequency with which the maximum tension occurred in both eyes at the same hour was analyzed. The hour of maximum pressure was identical in the two eyes 37 to 48 per cent of the test days. The same analysis was made for minimum outflow facility. It was found that the hour of minimum C was identical in the two eyes 29 to 36 per cent of the test days.

Frequency of Selection Criteria of each Group in Hospital

Inasmuch as the glaucoma patients were selected on the basis of intraocular pressure and coefficient of outflow criteria, it was anticipated that absolute values obtained in this study for these parameters would correlate with selection criteria. However, C values less than .13 occurred about twice as frequently in glaucoma subjects as did ocular tensions greater than 24 mm. Hg (Table 1). On the other hand, 32 per cent of the tonograms from tonometric glaucoma subjects and 20 per cent of those from overt glaucoma subjects were normal. Even the glaucoma index was not always abnormal in the glaucoma groups since 23 per cent of the indices of the two open-angle groups and 11 per cent of the indices of the miscellaneous glaucoma group were less than 100.

DISCUSSION

Daily fluctuations of facility of outflow occurred in all groups. The amount of fluctuation was greatest in the normal eyes, but the percentage fluctuation from the average daily C was about the same in all groups.

No circadian rhythm was evident in the C fluctuations since the time of minimum C was variable from day to day. However, a definite cycle for C (whether circadian or not) has not been excluded by this study. It may well be that a rhythm for facility of outflow has a far greater or lesser period than 24 hours and thus the period of testing was not

sufficient in either case. This might be particularly true if a minimum or maximum value occurred consistently between 12 midnight and 6:00 A.M. It should be emphasized again that to determine the absence or presence of periodicity for such parameters as facility of outflow and ocular tension requires a far greater number of observations than have been done in this or any other study.

A disturbance in the steady state of the eye from repeated tonography is always a possibility; thus, some of the tonograms obtained each day may not be true indications of the outflow facility. A time lapse of at least 3½ hours was allowed between successive tonograms, but may not have been sufficient.

Fluctuations introduced by inaccuracies of tonography (noise) may have obscured a possible relation between C and ocular tension. This would be particularly true if possible rhythms for both parameters were out of phase. However, it is likely that the large number of measurements compensated for noise effects.

The tension fluctuations observed were also quite variable. Perhaps these fluctuations, as well as those of C, do not show a circadian rhythm. Again, it is to be emphasized that many more measurements are needed. Additionally, it is necessary to control a large number of parameters which may cause temporary alterations of a possible ocular tension rhythm. Inasmuch as measurement of the intraocular pressure cannot be done remotely in man without awareness of the patient, it may well be impossible to verify or reject the existence of a circadian pattern of ocular tensions with the equipment available at this time.

It is possible that both pressure and outflow facility fluctuate randomly in response to a variety of stimuli, some of which have a circadian cycle. Bárány has proposed a mathematical formulation to show how the steady-state value of intraocular pressure depends on rate of secretion, episcleral venous pressure, outflow facility at the chamber angle, colloid osmotic pressure of the blood, systemic arterial blood pressure, pressure distribution over the vascular tree of the eye, and filtration properties of the vasculature in different intraocular regions.[47]

No definite relation was found between the daily maximum pressure and outflow facility of an eye. However, at the time of maximum pressure there was a greater frequency of maximum C values in normal eyes and a greater frequency of minimum C values in glaucomatous eyes. These data indicate that the daily maximum pressure in normal eyes is more likely to be produced by an increase in aqueous inflow and that of glaucomatous eyes by a decrease in outflow facility.

The absence of a definite relation between the daily ocular tension and facility of outflow is not surprising. Duke-Elder showed that miotics or glaucoma surgery improved C and damped the amplitude of the diurnal tension curve, but did not change the fundamental cyclic tension pattern.[14] Becker and Friedenwald noted that miotics or surgery may normalize the tension in some patients without improving the facility of outflow.[48] Drance demonstrated that marked diurnal tension variation may persist in eyes with supposedly good outflow after miotics.[49] The observation that a miotic (pilocarpine) has unrelated effects on outflow facility and ocular tension suggests an independence of the two parameters.[50] In this study it was demonstrated that the amount of daily tension fluctuation was not related to average C and that daily fluctuations of C were unrelated to the maximum ocular tension.

The data do not support the concept that central regulation is the dominant factor of either ocular tension or outflow facility. This is true because of the frequently independent cycles of the two eyes for both parameters. With central hormonal (or neurohumoral) control a parallel behavior of the two eyes would be anticipated. It may be that an underlying rhythm produced by a central regulator is frequently obscured by numerous factors operating at the level of the eye.

Although the glaucoma patients were selected by a criterion of previous tensions greater than 24 mm. Hg at some time, only 14 to 38 per cent of the ocular tensions from the three glaucoma groups were greater than 24 mm. Hg in the hospital. This damping effect has been previously noted,[5] and indicates the influence of exogenous factors on the amplitude of ocular tension. A far greater percentage of C values was in the preselected range (C less than .13) for the three glaucoma groups (35 to 63 per cent). However, the most distinctive feature of the glaucoma groups was the value of the glaucoma index ($P_0/C \times 100$). Seventy-seven to 89 per cent of the indices from glaucoma eyes were greater than 100 compared to only 5 per cent of those from normal eyes. Thus, an abnormal outflow facility and particularly an abnormal glaucoma index is a more constant feature of a glaucoma eye than an abnormal ocular tension. These data show the danger of depending only on the absolute level of ocular tension for a diagnosis of glaucoma.

As in some previous studies, diurnal ocular tension fluctuations greater than 10 mm. Hg were found only in glaucomatous eyes, and fluctuations between 5 and 10 mm. were noted in some normal eyes.[38,39] In addition, differences between the two eyes greater than 5 mm. Hg were rarely found in normal eyes at one test time. The

maximum tension in both normal and open-angle glaucoma eyes occurred most frequently in the morning. However, a greater scattering of maximum tensions throughout the day was noted in the glaucomatous eyes. Other than the absolute value of the outflow, additional criteria such as the time of minimum C, the absolute difference between the two eyes in C, and the percentage variation of C each day were of no value in distinguishing the normal from the glaucomatous group.

It is of interest that the subjects with tonometric glaucoma and those with overt glaucoma in one or both eyes were similar in regard to most tonometric and tonographic findings.

In assessing both the benefits and the difficulties inherent in this study, one concludes that there is very little need for this type of program, except possibly in the evaluation of drugs. Not only must the same technician be used to obtain valid data, but one should obtain a steady state. However, anything close to a steady state is quite unlikely in present-day hospital systems (and present-day human beings). Outpatient studies, from 8:00 A.M. to 6:00 P.M., are probably adequate for clinical diagnosis and avoid the phenomenon of damping.

CONCLUSIONS

Daily fluctuations of outflow facility are common to all eyes. These fluctuations are irregular and are not in phase with daily ocular tension fluctuations.

In this study there was also frequent irregularity of ocular tension fluctuations. It is possible that these fluctuations do not follow a 24-hour rhythm; however, the evidence is inconclusive both from this and previous studies. In addition, the two eyes were frequently out of phase in regard to both intraocular pressure and facility of outflow.

It seems likely that many factors are responsible for daily fluctuations in intraocular pressure and outflow facility. Some of these factors operate at the level of the eye.

In the hospital, glaucomatous eyes are best characterized by a reduced coefficient of outflow, an elevated glaucoma index, a markedly fluctuating tension curve, an asymmetry of tension levels in the two eyes, and a more unpredictable time of maximum tension.

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DISCUSSION

DR. A. J. ELLIOT. The work of Doctors Newell and Krill was extremely well planned and very timely. The review brings out a number of important points with regard to the basic problem of biological rhythms of which the intraocular pressure may well be one. More detailed knowledge of these phenomena may give a better understanding of the early deviations which occur in glaucoma. Study of the diurnal rhythms of the intraocular pressure variations has practical applications: firstly, to determine the height of the intraocular pressure at peak times; secondly, to ascertain abnormal lability of the intraocular pressure when the pressure is still within acceptably normal limits; thirdly, to discover the timing of peaks of pressure in regulation and supervision of therapy.

Drs. Newell and Krill have shown that approximately 40 per cent of intraocular pressure peaks occur between 6 and 8 A.M. This agreed with the findings of Dr. S. M. Drance and has its practical application because at that time people are not normally studied. Drance has shown on 220 patients (404 eyes) who did not have glaucoma and whose pressures were recorded six times during the 24 hours, a mean fluctuation of 3.7 mm. Hg with a standard deviation of $\pm$ 1.8. These figures suggest that a diurnal swing of pressure of 7 mm. Hg would be considered probably abnormal whereas a variation of 9 mm. Hg would be considered abnormal. This agrees fairly closely with the figures obtained by Drs. Newell and Krill. In 138 glaucomatous eyes without any therapy a mean intraocular pressure variation of 11 mm. Hg was found with a slight difference between those with a field defect and those without a field defect.

Another practical aspect of diurnal tonometric and tonographic studies is in the therapy of chronic simple glaucoma because of the very likely peaks which can occur. These peaks may be high enough to produce further damage and may account for one of the groups of people who are apparently controllable with regard to pressure and yet who continue to deteriorate. It was shown by Drance that approximately one-third of treated glaucoma patients whose intraocular pressure was 19 mm. Hg or less and whose outflow coefficients were .20 or more and whose P_0/C was 100 or less showed peaks of intraocular pressure to 24 mm. Hg. or more. Some of these patients rose as high as the upper 30's.

It is interesting that Drs. Newell and Krill found, in normal people, a maximum C value and a high intraocular pressure as the most common finding. This might suggest a homeostatic mechanism whereby the intra-

ocular pressure is raised due to increased aqueous production and the outflow is maximal in attempting to maintain that pressure at a normal level. In the glaucomatous eyes the minimum C value was usually found with a high intraocular pressure which suggests a failure of the homeostatic or an abnormality of the outflow channels. It must, however, be stressed that none of the work so far reported, including the work by Drs. Newell and Krill, has been designed to evaluate the relation of the outflow coefficient and the rising or falling phase of intraocular pressure. The design of such an experiment would be both difficult and time-consuming but it would give an insight into the relations of outflow to pressure.

The dampening of the intraocular pressure swing which occurs in hospital during the first three days is a well-known phenomenon. It is by no means certain whether one should be interested in the steady-state pressure when the patient has been completely isolated from his environment or whether one should be interested in the first 24 hours which might be most akin to the type of ocular dynamics which will occur at home. The multiplicity of exogenous factors which may interfere with the many parameters making up the steady-state intraocular pressure may mask any endogenous circadian patterns and this may also be masked by the circadian rhythms of other organs such as the adrenals.

It was interesting that the P_0/C was the most consistent distinguishing criterion between normal and glaucomatous eyes. The outflow coefficient was next and the intraocular pressure height last. This agrees with Drance's findings although in his study daily variation of intraocular pressure was more constantly abnormal in glaucomatous eyes than any of the other phenomena.

DR. JOHN M. MCLEAN. I believe this report is very important and basic to our understanding of the complex problems of intraocular pressure control. I would like to ask the essayists a question.

First, I wonder if in their correlation they paid attention to the sleep cycle of the patient. I noticed all the charts were a correlation with the clock. I wonder, for example, if any of their patients took long naps in the daytime, and if so, whether that made a difference. There are several physical possibilities in addition to the question of a hypothetical biological clock. For example, there is the question of possible fluid transfer by evaporation from the surface of the open eye, which does not take place when the eye is steadily closed. There is a possible temperature differential effect which would not be the same during prolonged closure of the eyes as during the waking hours. There is also the question of the effect of light and dark. I wonder if they can give us information on these possibilities. I hope they will continue their studies.

DR. NEWELL. [Slide] One of the most significant points of Dr. Elliot's discussion was that only 12 per cent of glaucoma patients had pressure of

more than 25 mm. Hg during an entire 24-hour period. It is very possible that one can miss an increased intraocular pressure with a single measurement.

Some fifty different functions in man have been studied and have been shown to have a circadian rhythm, ranging from a variety of hormones to an electrical resistance of the skin, psychologic activity, sleep, wakefulness, and the like.

We did not, in our study, look into the sleep pattern of our patients napping during the day. This, however, was done in 1930 by one of our members, Dr. von Sallmann, who found that variation in ocular tension was not related to sleep. Also, the variation is not related to being in a light or dark room.

There are a number of explanations for these variations. Unlike Dr. Elliot and Dr. Drance, we have been discouraged at the possibility of designing an experiment in which we are not imposing our own *Zeitgeber* upon the nature of the experiment. Until such time as we can telemeter intraocular pressure without disturbing the patient, I do not know that a valid study can be designed.

Even in determining temperature variations at the Cambridge State Hospital in Minnesota, it was necessary to study patients every three hours for a period of one year to determine the rhythm. Mercer, who has discussed the mathematical analysis of these studies, believes that if one believes a function has a period of between 20 and 30 hours, and wishes to learn this period exactly, it would require a minimum of 1,000 observations every six hours—a total time of 6,000 hours. This has not been done with intraocular pressure, and it is unlikely that it will be done.

I believe, too, that most of us, when we study intraocular pressure, are paying more attention to the daily fluctuations than to any particular rhythm.

We already know a dozen or more things that affect intraocular pressure, each of which probably has its own diurnal rhythm, and these changes in turn are reflected upon the intraocular pressure.