CHANGEABILITY TEST OF AQUEOUS OUTFLOW RESISTANCE*†

A TONOGRAPHIC STUDY OF NORMAL AND GLAUCOMATOUS EYES
EFFECT OF GANGLIONIC BLOCKING AGENTS
ANALYSIS OF INITIAL PART OF TONOGRAPHIC TRACING

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IN recent investigations a regulation of the resistance to aqueous outflow has been demonstrated. Important experiments by Bárány (1954, 1955, 1956), Bárány and Scotchbrook (1954), and Bárány' and Woodin (1955) showed various factors causing a change in the resistance to aqueous outflow in enucleated eyes from different species of animals. The enzyme hyaluronidase caused the resistance to aqueous outflow to fall to about 50 per cent. of the initial value. Various influences *in vivo* were shown to produce changes in outflow resistance, which were not due to a regulation by means of hyaluronic acid. An increase in resistance was observed after ligation of the common carotid artery. A decrease was demonstrated after elevation of the episcleral venous pressure by obstruction of the venous circulation. Injection of an extremely pure preparation of hyaluronidase into the anterior chamber *in vivo* produced an increase of the hyaluronidase-insensitive part of the outflow resistance. This increase could be partly prevented by giving the animals a ganglionic blocking agent, showing thereby the participation of the autonomic nervous system in the regulation of outflow resistance.

When the method of tonography was shown to be applicable with reasonable accuracy to rabbit eyes, it became possible to study the aqueous humour dynamics of one eye. Ligation of the common carotid artery was found to increase the outflow resistance in rabbits (Kornbluth and Linnér, 1955), and a similar increase in resistance was demonstrated after administration of acetazoleamide (Becker and Constant, 1955).

On the other hand the resistance was found to decrease under general anaesthesia with urethan (Bárány, 1955), pentobarbital or paraldehyde (Stone and Prijot, 1955), or thiopental sodium (De Roetth and Schwartz, 1956).

In perfusion studies of human eyes, François, Rabaey, and Neetens (1956) found a decrease in resistance after administration of the enzyme hyaluronidase, but this was less marked than in animal eyes.

If the intra-ocular pressure in normal human eyes happened to be low, the outflow resistance measured by tonography seemed to be rather high, but if the same eyes were examined when the intra-ocular pressure was higher, the outflow resistance was lower, showing a compensatory mechanism in normal eyes. In glaucomatous eyes, on the other hand, this compensatory change could not take place and the outflow resistance remained high (Ballantine, 1956; Becker, 1956a).

A method of studying changes in the rate of aqueous flow in human eyes by means of a suction cup was developed by Rosengren (1956a, b). Using this method, Ericson (1957) measured the diurnal variations in normal human eyes. During the night he found that the rate of aqueous flow fell to about one-third of the daytime value, but the intra-ocular pressure fell by only about 20 per cent. Assuming that the episcleral venous pressure remained unchanged, the reduction of outflow pressure during the night was thus about 50 per cent. The discrepancy between the diurnal variation of the aqueous flow and that of the outflow pressure could be explained by a nocturnal increase in outflow resistance. A tonographic study of the same group of human beings revealed an increased outflow resistance during the night (Linnér and Ericson, 1957). A change in the outflow resistance was found during the menstrual cycle and during pregnancy (Becker and Friedenwald, 1953).

The pharmacological influence of various drugs on aqueous dynamics has been the subject of many investigations (Becker, 1956b; Grant, 1956). A decrease in resistance after the administration of miotic drugs has been reported by several investigators (Becker, 1955b; Becker and Friedenwald, 1953; Goldmann, 1951; Grant, 1951; Prijot and Weekers, 1952a). A decrease in the rate of aqueous flow produced by different drugs was found to be followed by a compensatory increase in the outflow resistance. The carbonic anhydrase inhibitor acetazoleamide has been thoroughly investigated. The short-term administration of acetazoleamide was followed by no significant change in the outflow resistance in either normal or glaucomatous eyes (Becker, 1955a, b, c; Grant and Trotter, 1954; Sugar and Fainstein, 1955); nor was any significant change seen in advanced cases of glaucoma after long-term treatment with acetazoleamide (Becker, 1955a; Kupfer, Lawrence, and Linnér, 1955). However, Becker and Constant (1955) reported a fall in intra-ocular pressure in normal human eyes to a minimum level in 2 to 4 hours without significant change in facility of outflow; in some of these eyes the intra-ocular pressure was partly restored by an increase in the outflow resistance 6 to 24 hours later; this was followed by a return to normal of the rate of aqueous flow and of the resistance to aqueous outflow. After the administration of 250 mg. acetazoleamide every 4 hours for 24 hours, Prijot and Lavergne (1956) found an 18 per cent. increase in the resistance to aqueous outflow in normal human eyes.

Important evidence has thus been accumulated about the regulation of the

resistance to aqueous outflow.   Chronic simple glaucoma seems, however, to be characterized by impairment of the normal capacity to change the outflow resistance (Goldmann, 1951; Prijot and Weekers, 1952a; Grant, 1955; Kronfeld, 1955; De Roetth and Schwartz, 1956; Ballantine, 1956; Becker, 1956a).

It was the purpose of the present investigation to study the mechanism of this regulation in human eyes under physiological and pathological conditions.   Alterations in resistance to aqueous outflow, produced by means of pilocarpine and acetazoleamide, were utilized as a changeability test of the capacity of normal and glaucomatous human eyes to regulate the outflow resistance.   The effect of ganglionic blocking agents on this regulation was also examined.

Tonography Method.—The resistance to aqueous outflow was studied by means of tonography as described by Grant (1950, 1951).   The method in general will not be discussed here.   There are, however, inherent errors of the method rendering the evaluation of the results difficult, and special attention has been paid to these problems.   In some of the tonographic tracings the fall in intra-ocular pressure was greater at the beginning than subsequently.   Bailliart (1931) reported that the ocular tension fell after application of the tonometer; the pointer sometimes moved several scale units below the initial value within the first half minute, after which it stopped or moved further down very slowly.   Grant (1950, 1951), using an electronic tonometer connected to a Sanborn recorder yielding a rather narrow chart, did not report any special observations concerning the initial part of the tracing.   Kronfeld (1952) found the coefficient of facility of outflow calculated for three or four consecutive 2-minute periods to be fairly constant. Similar results were reported by Prijot and Weekers (1952b).   On the other hand, a steep initial fall in the tonographic curve was observed by Becker and Friedenwald (1953), using an electronic tonometer connected to a Brown potentiometer; the initial steep fall seemed to be correlated with blood pressure changes.   Studies of the diastolic blood pressure recorded simultaneously with tonography revealed that the greater fall seen in the first part of the tracing could occur without a corresponding change in the blood pressure. Fig. 1 (opposite) shows simultaneous tonographic and diastolic blood pressure tracings obtained on a normal eye at the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital, Baltimore.   In this case the initial fall is not correlated to a corresponding change in the diastolic blood pressure.

This initial steep fall was noticed in Baltimore as well as in Gothenburg, and was in most cases limited to the first 30 to 60 seconds.   Any possible error in the estimate of the facility of aqueous outflow which might be caused by this fall could be reduced by excluding the initial part of the curve. In the present study the first minute was omitted, and an estimate based on the following 4 minutes was compared with the results from the same curves in the first two minutes.
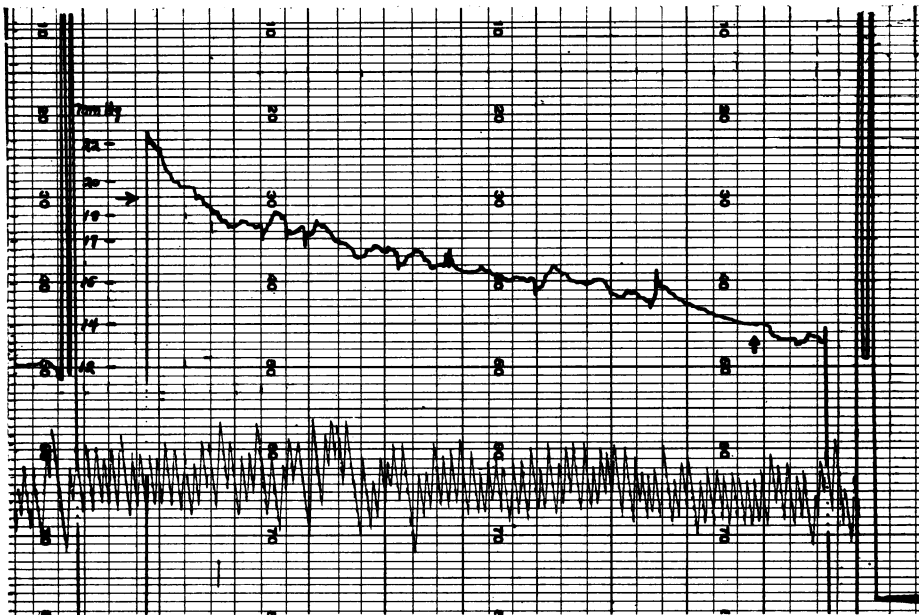
FIG. 1.—Upper tracing represents tonography of normal human eye.   Each top of lower tracing represents diastolic blood pressure.

This proposal to ignore the first part of the curve was also made by Roberts (1957) and Leydhecker (1957).

Goldmann (1957a), working with an applanation tonometer, reported that the tension went up some mm. Hg when the contact surface was 5 mm. in diameter; during the first minute the tension went down to approximately its initial value and in the next 4 minutes it changed very little.

According to Goldmann (1955a, 1957a, b) the load of the tonometer resting upon the eye caused a gradual scleral distension, or "creep", which seemed to be effective for practical purposes only during the first minute of tonography; its influence during subsequent minutes was very small.   Goldmann (1955a) reported that this "creep" effect is often considerable in young people.   Calculating the facility of aqueous outflow from the end of the first minute, Goldmann (1957b) found good agreement with the values obtained by the fluorometric method.   According to Goldmann (1957a), in the living eye the influence of the displacement of blood and "creep" cannot be dissociated.   The influence of "creep" on tonographic results was discussed by van Beuningen (1956) and van Beuningen and Fischer (1957).

Friedenwald (1955) reported that he found no evidence of "creep" with pressures up to about 60 to 70 mm. Hg, but he thought that hysteresis phenomena probably appeared at pressures of 100 mm. Hg and above.

Variations in scleral rigidity can introduce large errors.   The measurement of outflow resistance is greatly influenced by using different weights

on the tonometer (Goldmann, 1955a, b; Weekers, Watillon, and de Rudder, 1956; Wirth, 1956). Friedenwald's estimate of the average scleral rigidity was accepted because no reliable method for determining the scleral rigidity of each individual eye was available during this study.

The errors introduced by using mean values instead of individual values were reduced by comparing the results obtained from the same eye using the same tonometer weight.

There have been discussions as to which pressure should be considered to be the true end-point of the aqueous outflow system; a measurement of the overall resistance to aqueous outflow is obtained if the episcleral venous pressure is taken as the end-point.

According to Goldmann (1957a), the most important part of outflow resistance is located in the upper part of the flow system down to the aqueous veins. The pressure in an aqueous vein varies linearly with the actual intra-ocular pressure and is influenced by which tonometer weight is used. Consequently there must exist a considerable resistance between the aqueous vein and the episcleral vein, and no constant value of the pressure for the end-point can be utilized in the calculations.

In this study the overall resistance to aqueous outflow down to the episcleral venous level was utilized. No significant change was found in the episcleral venous pressure after the administration of pilocarpine or acetazoleamide (Linnér, 1956). The results in each individual eye under varying experimental conditions were compared. The intra-ocular pressure was essentially unchanged and the 5·5-g. tonometer weight was used throughout. In these circumstances the use of an average value for the episcleral venous pressure was not considered to increase significantly the errors in the estimated changes in resistance to aqueous outflow.

In the new calibration scale, Friedenwald (1957) corrected the scale of 1954 and eliminated certain discrepancies, but he pointed out that there can never be a final and absolutely correct tonometric calibration.

It was considered important to minimize the error due to the calibration scale. If the tonographic results in each individual eye were utilized on a comparative basis under various conditions in order to measure the changes, true, absolute figures of outflow facility were not essential. The level of the intra-ocular pressure might influence the estimate of outflow facility because of inaccuracies in the calibration scale. Results obtained at an essentially unaltered level of intra-ocular pressure were therefore compared.

In human beings as well as in rabbits, tonography on one eye was found to produce a decrease in the intra-ocular pressure and rate of aqueous flow in the second eye, but the outflow resistance remained unchanged (Kornbluth and Linnér, 1955). A similar change was found after tonography by Stone (1956) and after compression with a Bailliart ophthalmodynamometer on the first eye by Prijot and Stone (1956). A short measurement of the intra-ocular pressure in the two eyes was therefore made just before tonography.

Material

A group of human beings with normal eyes aged between 17 and 88 yrs was chosen for this investigation. These subjects were divided into three groups according to age in order to examine the possible influence of age on the results.

A special group of patients with arterial hypertension but with no changes in the eyes other than those that could be attributed to their hypertension was referred from the department of internal medicine. Most of them were receiving Rauwolfia preparations and hydralazine for their hypertension.

Among these patients, 23, aged between 40 and 70 yrs (average 58), were also given ganglionic blocking agents: fifteen were treated with pentolinium tartrate* in daily dosage as high as 450 mg., and the other eight received mecamyla-minhydrochloride† in daily dosage as high as 30 mg.

Eighteen patients aged between 56 and 88 yrs (average 70) with newly discovered untreated simple glaucoma were also examined. In twelve patients aged between 46 and 74 yrs (average 60) with a suspected but not clearly established diagnosis of chronic simple glaucoma, the disc and the visual field were found to be normal, but occasionally the intra-ocular pressure was found to be on a borderline level.

Technique

The tonographic examination was carried out with an electronic tonometer (Mueller) connected to a galvanometer and a recorder (Lange). The original pen writing with ink, however, was exchanged for a pen writing with an electric current on Teledeltos paper.‡ Each scale unit on the tonometer in the range in use corresponded to about 1·5 cm. on the recorder.

In a quiet room the patient was placed in a recumbent position and asked to look at a fixation target on the ceiling. Novesin (Wanderer, Berne) was used as local anaesthetic. The eyelids were gently retracted with the fingers, care being taken not to exert any pressure on the bulb. The tonometer was held just above the eye for from 10 to 15 seconds and very slowly lowered on to the cornea.

Before the tonographic examination a short measurement (about 10 sec.) of the intra-ocular pressure in the two eyes was performed using first 5·5-g. and then 10-g. weights. The right eye was always examined before the left one. The 5·5-g. load was used throughout the study in all the tonographic tracings except 24 untreated eyes of the glaucomatous group in which the intra-ocular pressure was found to be so high that the 10-g. load had to be used. The tonometer was allowed to rest on the eye for 5 minutes.

The intra-ocular pressure (p_0) was taken from the short measurement before tonography, if possible with the 5·5-g. load, Friedenwald's Tables (1957) being used for the calculations. The results of outflow resistance were expressed as facility of aqueous outflow (C) according to Grant (1950). A correction for the elevation of the episcleral venous pressure during tonography was introduced (Linnér, 1955a). Care was taken to accept only tonographic tracings where a reliable estimate of facility of outflow could be obtained. The changeability of aqueous outflow facility was calculated as a ratio within each individual.

Repeated tonographic examinations were performed on each patient, the first

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* Ansolysen®, May and Baker Ltd.　　　　† Mevasine®, Merck and Co., Inc.
‡ The device was built by the Department of Pharmacology, University of Uppsala.

one before treatment.   On a following day a 3 per cent. solution of pilocarpine was given topically twice with an interval of one hour, and one hour after the second administration a second tonography was performed.   At least one day later the patient was given a total dose of 1,500 mg. carbonic anhydrase inhibitor, acetazoleamide, by mouth.   One tablet containing 250 mg. and one enteric-coated capsule with delayed action containing 250 mg. were given simultaneously every 12 hours.   About 28 hours after the beginning of this medication, the third tono-graphy was performed.   All the examinations were made between 10 a.m. and 2 p.m.

Results

Errors of the Method.—Thirty-four normal human eyes were examined twice in order to determine the error of the tonographic method.   The standard error of the individual value of facility of outflow was calculated from the differences between two determinations on the same eye according to the method of Dahlberg (1940).   The tracings were performed on different days at about the same time of day.   The value was estimated as ±0·022. The extent to which these variations were due to physiological variability or inaccuracy of the method could, however, not be decided.   As a control of the electonic tonometer and the recording device, the intra-ocular pressure of 39 normal human eyes was at the same time measured by means of a certified Sklar-Schiötz tonometer.   The electronic tonometer and the Sklar-Schiötz tonometer were used first in alternate eyes in turn.   The instruments were found to give essentially the same value for the intra-ocular pressure (see Table I).

TABLE I

INTRA-OCULAR PRESSURE IN NORMAL HUMAN EYES MEASURED BY MUELLER ELECTRONIC TONOMETER, LANGE RECORDER CONNECTED TO THIS TONO-METER, AND SKLAR-SCHIÖTZ TONOMETER.

Instrument	Intra-Ocular Pressure in Scale Units		
	Mueller	Lange	Sklar-Schiötz
Arithmetic Mean	5·92	6·10	5·74
Standard Error of the Mean	0·13	0·14	0·14
Number of Determinations	39	39	39

The results of the electronic tonometer were found not to be accurate enough in the very low range.   Therefore the 10-g. load could not be used at the normal intra-ocular pressure with the accuracy necessary for a reliable estimate of scleral rigidity.

Changeability of Aqueous Outflow Facility.—Table II and Fig. 2 and Fig. 3 (overleaf) show results from normal human eyes.   Without treatment the average value of the intra-ocular pressure was 15·2 mm. Hg.   The intra-ocular pressure in the right eye, where the measurement was performed first, was slightly higher than in the left eye (right eye = 15·8 ± 0·39 and left eye = 14·6 ± 0·36 mm. Hg).   The difference calculated as the ratio between the left

TABLE II

EFFECT OF PILOCARPINE AND ACETAZOLEAMIDE ON AQUEOUS HUMOUR DYNAMICS IN NORMAL HUMAN EYES

Age (yrs)	Effect on Aqueous Humour	Before Treatment (I)		During Pilo-carpine (II)		During Acetazole-amide (III)		Ratio $\dfrac{C_{II}}{C_{III}}$	Ratio $\dfrac{C_{II}}{C_{I}}$	Ratio $\dfrac{C_{III}}{C_{I}}$
		P_0	C	P_0	C	P_0	C			
17–88	Arithmetic Mean	15·2	0·19	14·1	0·21	12·2	0·13	1·60	1·15	0·74
	Standard Error of the Mean	0·27	0·0041	0·25	0·0037	0·19	0·0030	0·034	0·021	0·016
	Number of eyes	84	82	84	87	84	87	87	81	82
58–88	Arithmetic Mean	15·9	0·18	14·5	0·20	12·2	0·12	1·62	1·14	0·71
	Standard Error of the Mean	0·36	0·0055	0·40	0·0056	0·30	0·0040	0·042	0·041	0·025
	Number of Eyes	28	23	28	28	28	28	28	23	23
43–57	Arithmetic Mean	14·9	0·18	14·3	0·21	11·9	0·14	1·58	1·17	0·75
	Standard Error of the Mean	0·54	0·0072	0·33	0·0063	0·34	0·0057	0·065	0·038	0·024
	Number of Eyes	28	32	28	31	28	32	31	31	32
17–42	Arithmetic Mean	14·9	0·19	13·4	0·22	12·4	0·14	1·62	1·16	0·74
	Standard Error of the Mean	0·49	0·0077	0·53	0·0066	0·37	0·0056	0·064	0·032	0·033
	Number of Eyes	28	27	28	28	28	28	28	27	27

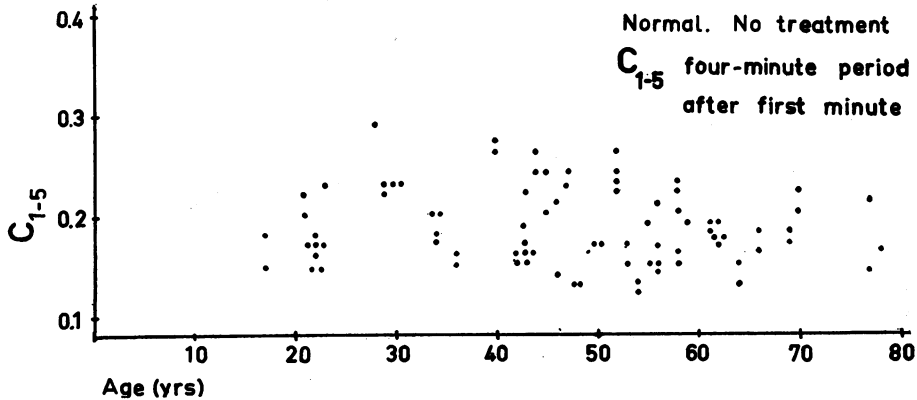P_0 Intra-ocular pressure (mm. Hg).   C   Facility of aqueous outflow (cu. mm./min./mm. Hg).

FIG. 2.—Dots represent outflow facility in normal human eyes without treatment, estimated from 4-minute period after first minute of tonography (C_{1-5}).

and the right eye was 0·93 ±0·015. This ratio is significantly different from unity ($p < 0.001$). The facility of outflow was 0·19. There was a numerical but not significant difference between different age groups ($0.1 < p < 0.2$). Assuming an episcleral venous pressure in the recumbent position of 11 mm. Hg (Linnér, 1955a, b), the outflow pressure was 4·2 mm. Hg and the rate of aqueous flow 0·80 cu. mm/min.

The facility of aqueous outflow, which was 0·19 without treatment, was increased to 0·21 during treatment with pilocarpine and decreased to 0·13 during treatment with acetazoleamide. No significant differences were
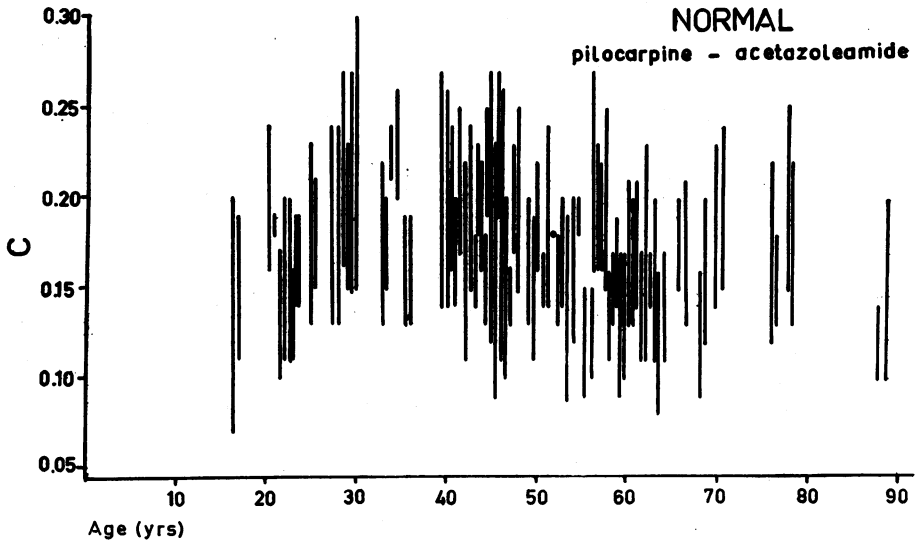
FIG. 3.—Vertical lines represent changeability of outflow facility produced by pilocarpine and acetazoleamide in human eyes. Top of each line indicates outflow facility during treatment with pilocarpine, and bottom of each line outflow facility during treatment with acetazoleamide.

revealed between different age groups. Expressed as a ratio between the pilocarpine and acetazoleamide values the total change produced in the facility of outflow was found to be 1·60. The change produced separately by pilocarpine was 1·15 and that produced separately by acetazoleamide 0·74. All these changes were statistically significant ($p < 0.001$).

The effect of ganglionic blocking agents is shown in Table III. The average intra-ocular pressure was 16·0 mm. Hg. The pressure in the right eye, where the measurement was performed first, was slightly higher than

TABLE III

EFFECT OF PILOCARPINE AND ACETAZOLEAMIDE ON AQUEOUS HUMOUR DYNAMICS IN HYPERTENSIVE PATIENTS TREATED WITH AND WITHOUT GANGLIONIC BLOCKING AGENTS

Ganglionic Blocking Agents	Effect on Aqueous Humour	Before Treatment (I)		During Pilo-carpine (II)		During Acetazole-amide (III)		Ratio $\dfrac{C_{II}}{C_{III}}$	Ratio $\dfrac{C_{II}}{C_{I}}$	Ratio $\dfrac{C_{III}}{C_{I}}$
		P_0	C	P_0	C	P_0	C			
With	Arithmetic Mean	16·0	0·17	13·8	0·19	11·8	0·14	1·36	1·14	0·85
	Standard Error	0·38	0·0060	0·39	0·0055	0·34	0·0049	0·037	0·029	0·022
	Number of Eyes	46	44	46	46	46	46	46	44	44
Without	Arithmetic Mean	16·8	0·17	15·0	0·20	13·3	0·13	1·65	1·18	0·74
	Standard Error	0·57	0·0069	0·42	0·0088	0·42	0·0052	0·063	0·044	0·033
	Number of Eyes	23	23	24	22	24	22	20	21	21

P_0 Intra-ocular pressure (mm. Hg). C Facility of aqueous outflow (cu. mm./min./mm. Hg).

in the left eye (right eye = 16.5 ± 0.57; left eye = 15.4 ± 0.48 mm. Hg). The difference calculated as the ratio between the left and the right eye was 0.94 ± 0.021, which is significantly different from unity ($0.001 < p < 0.01$). A facility of outflow of 0.17 without treatment was increased to 0.19 by pilocarpine and decreased to 0.14 by acetazoleamide. Expressed as ratios, the total changeability was 1.36, the effect caused by pilocarpine 1.14, and that produced by acetazoleamide 0.85. These changes were statistically significant ($p < 0.001$).

In comparing the normal group of the same age and that treated with ganglionic blocking agents, the difference in facility of aqueous outflow before treatment with pilocarpine or acetazoleamide was not found to be significant, nor was a significant difference found between the two groups concerning the effect produced by pilocarpine. On the other hand, the total change as well as the change caused separately by acetazoleamide was significantly reduced in the group treated with ganglionic blocking agents as compared with the normal group ($p < 0.001$).

Table III also shows the results in a group of hypertensive patients treated in the same way, except that no ganglionic blocking agents were given. No significant difference in changeability of aqueous outflow facility was found between this group and the normal one.

A group of patients with freshly-discovered untreated chronic simple glaucoma showed that the facility of outflow without treatment was significantly diminished (0.10) as compared with the normal value of 0.19 (Table IV). The total change in facility of outflow, expressed as a ratio between pilocarpine and acetazoleamide values, was significantly reduced to 1.27 as compared with 1.60 in the normal group ($p < 0.001$). The reduction in the intra-ocular pressure after administration of pilocarpine was 7.0, and that following administration of acetazoleamide 10.6 mm. Hg. There-

TABLE IV

EFFECT OF PILOCARPINE AND ACETAZOLEAMIDE ON AQUEOUS HUMOUR DYNAMICS IN HUMAN EYES WITH CHRONIC SIMPLE GLAUCOMA AND WITH SUSPECTED CHRONIC SIMPLE GLAUCOMA

Diagnosis	Effect on Aqueous Humour	Before Treatment (I)		During Pilocarpine (II)		During Acetazoleamide (III)		Ratio $\dfrac{C_{II}}{C_{III}}$
		P_0	C	P_0	C	P_0	C	
Chronic simple glaucoma	Arithmetic Mean	26·3	0·10	19·3	0·13	15·7	0·10	1·27
	Standard Error of the Mean	0·99	0·0064	0·83	0·0053	0·47	0·0042	0·039
	Number of Eyes	34	34	34	34	34	34	34
Suspected chronic simple glaucoma	Arithmetic Mean	19·5	0·14	16·0	0·15	14·5	0·12	1·30
	Standard Error of the Mean	0·59	0·0068	0·69	0·0025	0·42	0·0056	0·080
	Number of Eyes	24	24	24	24	24	24	24

P_0 Intra-ocular pressure (mm. Hg).   C Facility of aqueous outflow (cu. mm./min./mm. Hg).

fore no attempt was made to calculate the change produced by pilocarpine or acetazoleamide separately. Patients with suspected but not clearly diagnosed chronic simple glaucoma showed a reduction in changeability of outflow facility similar to that in those with chronic simple glaucoma.

Initial Part of Tonographic Curve.—The influence of the initial part of the tonographic curve on the result was studied by calculating the facility of outflow from the initial 2-minute period of the tonographic tracings. The results in normal human eyes are shown in Fig. 4 and Table V. With increasing age a trend towards a lower facility of outflow was found. A comparison between a group of old subjects (56 to 88 yrs) and a group of young subjects (17 to 41 yrs) revealed a statistically significant difference ($p < 0.001$). The same trend as that found in untreated patients was seen during treatment with pilocarpine or acetazoleamide.
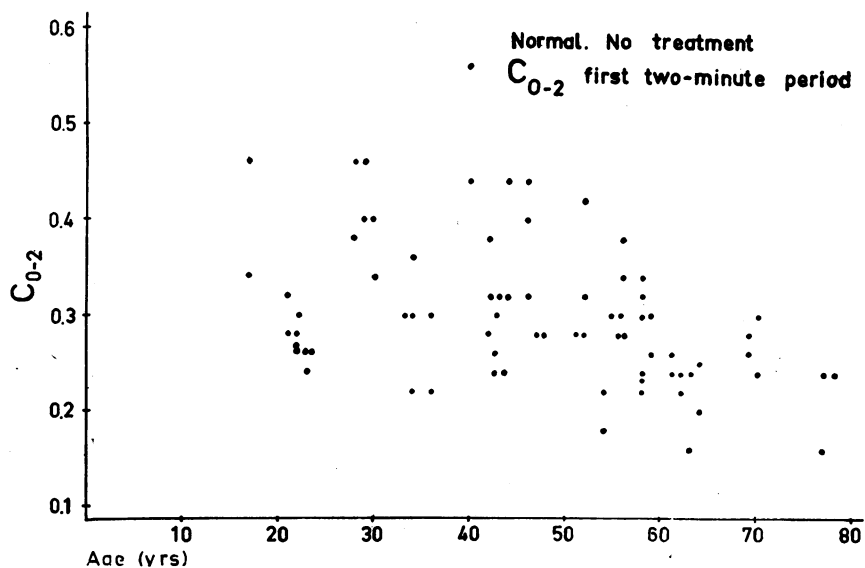

FIG. 4.—Dots represent outflow facility in normal human eyes without treatment, estimated from first 2-minute period (C_{0-2}).

Figs 2 and 3 and Table II show the facility of aqueous outflow on the same tonographic tracings during a 4-minute period not including the first minute. Using this method of estimation, no significant correlation was seen between age and facility of outflow. With increasing age outflow facility in the first part of the tracing approached the values of the 4-minute period not including the first minute. In the two younger age groups (17 to 42 yrs and 43 to 57 yrs), the difference between the two methods of estimate was statistically significant ($p < 0.001$), but in the highest age group (58 to 88 yrs) the difference was not significant ($0.05 < p < 0.1$). The same trend as that observed without treatment was found during treatment with

TABLE V
FACILITY OF AQUEOUS OUTFLOW CALCULATED FROM FIRST 2-MINUTE PERIOD OF TONOGRAPHY (C_{0-2}) IN THE SAME GROUP AS IN TABLE II.

Age (yrs)	Aqueous Outflow	Before Treatment (I) C_{0-2}	During Pilocarpine (II) C_{0-2}	During Acetazole-amide (III) C_{0-2}
17–88	Arithmetic Mean Standard Error of the Mean Number of Eyes	0·29 0·011 77	0·36 0·011 80	0·27 0·011 79
58–88	Arithmetic Mean Standard Error of the Mean Number of Eyes	0·23 0·025 23	0·30 0·015 27	0·23 0·016 28
43–57	Arithmetic Mean Standard Error of the Mean Number of Eyes	0·31 0·012 27	0·36 0·016 26	0·27 0·012 26
17–42	Arithmetic Mean Standard Error of the Mean Number of Eyes	0·34 0·017 27	0·40 0·033 27	0·32 0·024 25

pilocarpine or acetazoleamide, and all the differences were statistically significant ($p < 0.001$).

The first part of the tonographic curves had a similar effect on the estimate of facility of outflow in a separate group of hypertensive patients treated with ganglionic blocking agents (Tables III and VI). All the differences between the two methods were statistically significant ($p < 0.001$).

TABLE VI
FACILITY OF AQUEOUS OUTFLOW CALCULATED FROM FIRST 2-MINUTE PERIOD OF TONOGRAPHY (C_{0-2}) IN HYPERTENSIVE PATIENTS TREATED WITH GANGLIONIC BLOCKING AGENTS (SAME GROUP AS IN TABLE III)

Aqueous Outflow	Before Treatment (I) C_{0-2}	During Pilocarpine (II) C_{0-2}	During Acetazoleamide (III) C_{0-2}
Arithmetic Mean	0·25	0·30	0·22
Standard Error of the Mean	0·0094	0·0011	0·0094
Number of Eyes	45	46	46

In the group of patients with chronic simple glaucoma (Table IV) the intra-ocular pressure without treatment was elevated. In ten eyes only could the tonographic tracings be performed with the 5·5-g. weight. In this group the facility of outflow estimated in the first 2 minutes was $0·20 \pm 0·031$, as compared with $0·12 \pm 0·015$ in the 4-minute period after the first minute. This difference was not significant ($0·02 < p < 0·05$) but only ten eyes were tested.

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Discussion

Changeability of Aqueous Outflow Facility.—Facility of outflow in normal human eyes estimated from the 4-minute period after the first minute and the rate of aqueous flow deduced from this value were lower than the average figures reported by many other investigators. From the tonographic method alone, it was not possible to estimate how close these values were to the true values. This method was compared with others at the Glaucoma Symposium (1954) and at the XVII Ophthalmological Congress (1954).

The purpose of the present study was, however, not to give absolute figures but to study the eye's capacity to change the facility of outflow. By measuring the changeability within the same eye at essentially unaltered levels of intra-ocular pressure, the changes in facility of outflow could be expressed comparatively, thus minimizing the uncertainties involved in the tonographic method.

The capacity to change the facility of outflow was found to be considerable in normal eyes and no reduction could be detected with increasing age. The change induced by pilocarpine was in many ways different from that induced by acetazoleamide. The pilocarpine effect started rather rapidly and was not significantly influenced by ganglionic blocking agents, whereas the acetazoleamide effect developed slowly and could be partly blocked by the administration of ganglionic blocking agents, suggesting a nervous regulation of the aqueous outflow. This is one way by which a nervous regulation can influence the intra-ocular pressure.

There are other reports concerning the effect of ganglionic blocking agents on the intra-ocular pressure and its regulation mechanisms in human eyes. De Roetth and Schwartz (1956) reported a decrease in the rate of aqueous flow but no significant change in the facility of aqueous outflow in glaucomatous eyes. Rosen (1957) noted an inhibition of aqueous flow and a lowering of facility of aqueous outflow in almost direct proportion to the rate of flow in normal eyes. Böck and Stepanik (1957) also reported a reduction in aqueous flow but no significant change in facility of outflow in normal eyes. The difference in the effect on facility of outflow could be explained by the different time-intervals used in the last two studies. Rosen's tonographic determinations were carried out at irregular intervals up to 9 hours, and Böck and Stepanik's measurements were made 5 to 15 minutes after administration of the drug.

The eye seems to need time to establish changes in the facility of outflow. The compensatory decrease after administration of acetazoleamide took place some hours after the administration of the drug.

In human beings tonography of one eye was found to lower the intra-ocular pressure in the second eye (Kornbluth and Linnér, 1955; Prijot and Stone, 1956; Stone, 1956). In a series of 67 human subjects Stone reported the intra-ocular pressure to be $17·71 \pm 0·41$ mm. in the first eye and $16·14 \pm 0·40$ mm. Hg in the second eye. A similar consensual reaction was also found in rabbits (Kornbluth and Linnér, 1955; Prijot and Stone, 1956).

The group of hypertensive patients in this study did not show a complete ganglionic blockade as indicated by the fall in the intra-ocular pressure in the contralateral eye after application of the tonometer on the first eye. Rosen reported that this consensual reaction could no longer be observed after administration of the ganglionic blocking drug. Prijot and Stone (1956) were able to block the consensual reaction in systemically atropinized rabbits. It is therefore not surprising that the compensatory change in facility of outflow was diminished but not completely blocked by the drugs used in this study.

A group of hypertensive patients under treatment with drugs other than ganglionic blocking agents cannot be assumed to react as a normal group without further control, since the treatment might change the results. Administration of Rauwolfia preparations was found to lower the intra-ocular pressure in some eyes (Kaplan and Pilger, 1957), but hydralazine given by mouth did not change the intra-ocular pressure (Eberhartinger and Schenk, 1957).

This group of hypertensive patients, however, revealed no significant difference in changeability of aqueous outflow facility as compared with the normal group. The reduced capacity to change the outflow facility demonstrated in the hypertensive group of patients under treatment with ganglionic blocking agents may therefore have been produced by the blockading drug.

The group of patients with chronic simple glaucoma showed a reduced capacity to vary the facility of outflow. A similar reduction was found in the group with a suspected chronic simple glaucoma where the clinical examinations did not reveal changes other than a border-line level of the intra-ocular pressure.

That means that there was an impairment in one of the mechanisms by which the intra-ocular pressure can be controlled. The results seem to show that the changes induced by pilocarpine and acetazoleamide were much impaired, although the great differences in intra-ocular pressure rendered a detailed analysis of the separate influence of each drug uncertain. The impaired capacity to vary the facility of aqueous outflow seems to be a prodromal symptom in the development of chronic simple glaucoma, which may assist early diagnosis.

First Part of Tonographic Curve.—Calculations based on the first part of the tonographic tracing were found to influence the estimate of facility of outflow, which was significantly higher when the first minute of the curve was included. Reduction of facility of outflow with increasing age was also found when the first minute was included, but when this part of the curve was excluded from the estimate no such correlation could be detected.

Calculations based on different parts of the tonographic tracings showed no significant difference according to Grant (1950) and Prijot and Weekers (1952b), but Bailliart (1931) and Becker and Friedenwald (1953) reported an initial steep fall.

Böck, Kronfeld, and Stough (1934) studied the drop in intra-ocular pressure under the influence of prolonged tonometry in varying age groups, but did not find a tendency towards a smaller drop among older persons than among persons under 50 years of age. According to Grant (1951), age was not important. Spencer, Helmick, and Scheie (1955) reported a slight but not significant tendency towards a reduction in facility of outflow in patients over the age of 50, and Weekers and others (1956) reported a tendency towards a reduction in facility of outflow with increasing age. Goldmann (1951), using fluorometry to determine the rate of aqueous flow and a torsion balance to measure the episcleral venous pressure, reported that the outflow resistance in human eyes seemed to increase with age.

Our experience indicates that the first part of the tonographic tracing influences the estimate of facility of outflow significantly. A recording device capable of reproducing the rapid changes which occur during the first part of the tonographic procedure seems to be essential. Differences in the recording apparatus may be the reason for the discrepancies between reports concerning the role played by the first part of the tonographic tracing.

The steep initial fall emphasizes the importance of recording the truly initial deflection of the pointer so as not to underestimate the intra-ocular pressure.

This rapid initial fall cannot be explained by the present study. This effect was found in normal eyes and both after increasing and after decreasing the facility of outflow. The administration of ganglionic blocking agents did not seem to change the initial response of the eye. Scleral distension, displacement of blood from the eye, and reduction in aqueous flow could be important factors.

Summary

The capacity to change the aqueous outflow resistance (expressed as coefficient of facility of outflow) during the administration of pilocarpine and acetazoleamide was investigated by the method of tonography. The first minute of the record was excluded from the estimate.

In normal human eyes the facility of outflow was 0·19. During pilocarpine administration it increased significantly to 0·21, and during acetazoleamide administration it decreased significantly to 0·13. Ganglionic blocking agents reduced the acetazoleamide effect but did not significantly influence the pilocarpine effect.

In the early stages of chronic simple glaucoma, a reduced changeability in aqueous outflow resistance was found; this offers a means of early diagnosis. The steep initial fall seen in the tonographic tracings may influence the estimate, but this factor is less important in older patients. When the first minute of the tonographic tracing was excluded from the estimate, the facility of outflow was found to be significantly lower and no correlation with age could be detected.

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