MEASURING OUTFLOW RESISTANCE/FACILITY OF AN EYE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/034,484, filed Mar. 6, 2008, the entire disclosure of which is hereby incorporated by reference in its entirety, including any appendices, for all purposes.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The invention relates generally to intraocular pressure measurement, and more specifically to medical systems and methods for measuring aqueous outflow resistance/facility of an eye.

[0004] 2. Description of the Related Art

[0005] For more than a century, tonometry has been used to evaluate intraocular pressure (IOP), or fluid pressure inside an eye, which is considered to be the most important clinical risk factor for glaucomatous eyes. Eyes produce a watery fluid, or aqueous humor, that normally enters the eye and then drains out via an aqueous drainage pathway (e.g., the trabecular meshwork, uveoscleral pathways and episcleral veins) into the bloodstream. Glaucoma, an eye disease that can damage eyes and potentially result in blindness, causes a buildup of fluid inside the eye that does not drain properly due to problems in the drainage path and puts damaging pressure on the optic nerve.

[0006] Tonometry, the measurement of tension or pressure, can be used to evaluate this intraocular pressure and detect glaucoma by application of an instrument called a tonometer. One type of tonometry, indentation tonometry, measures the depth of an indentation produced in the cornea by a small plunger-like instrument. The amount of weight needed for indentation determines the IOP of the eye. Tonography, developed based on indentation tonometry, is a continuous tracking technology for monitoring the indentation level of an eye. Tonography is used to record changes in IOP due to sustained pressure on the eyeball. Tonography has been used to assess outflow resistance (or outflow facility) in the aqueous drainage path. Relating the indentation level to both intraocular pressure (P_o) and displaced ocular volume (ΔV), the aqueous outflow resistance (R) can be estimated by: $R=\Delta P/\Delta V/\Delta t$. Accurately measuring outflow resistance could potentially lead to a better understanding of the glaucomatous pathology. However, due to the invasiveness and length of the tonography procedure, as well as its highly imprecise nature, the procedure has not been used extensively in clinical practices since its original introduction in 1950s.

[0007] Current tonography procedures also encounter an intrinsic technical hurdle. In order to measure flow resistance or facility, two measurable quantities are typically required: pressure drop (ΔP) and flow rate (Q) or rate of volume change ($\Delta V/\Delta t$). But in tonography, the only measurement made is through the reading of indentation level. Therefore, statistical correlations applied in tonography procedures relate the indentation levels to both volume change and pressure reading under a constant weight on the cornea surface. Jonas Friedenwald's early work in 1947 in this field provided the foundation of the methods. Although flow resistance can be "calculated" in this manner (under serially unreliable assumptions and limitedly studied correlations), the conclusion is neither mathematically nor physically convincing. In addition to the unreliability of the underlying principle itself, current tonography is also significantly affected by limited reproducibility. This instability of the measurement can result from that inconstant perturbing force (weight load) on the cornea surface, rapid eye movement-induced IOP variation, eyelid movement and squeezing-induced disturbances, etc.

[0008] With the recent developments in measurement sciences and polymer materials, the emerging flexible electronics and touch sensing techniques demonstrate great potential in biological and clinical applications. Accordingly, embodiments of the invention provide a safe, convenient, noninvasive and accurate measurement solution for a better assessment of aqueous outflow resistance, compared to the original concept of tonography.

SUMMARY OF THE INVENTION

[0009] Embodiments of the invention provide methods, systems, and computer products for measuring the outflow resistance/facility of an eye. One embodiment of the system includes a contact-lens device comprising a rigid outer wall, a flexible inner wall, and an inflatable bladder disposed there between. The contact-lens device has a concave shape to allow placement over the eye, and the flexible inner wall contacts the eye. The system also includes a hydraulic unit coupled to the bladder and configured to control a flow of fluid between the bladder and an external reservoir. The hydraulic unit is further configured to measure a change of volume in the bladder over time. The system also includes a pressure measurement system coupled to the bladder and configured to measure a pressure of fluid within the bladder. In addition, the system includes computer-controlled logic configured to compute the outflow resistance of the eye as a function of the pressure in the bladder and the change of volume in the bladder over time

[0010] One embodiment of the method for measuring an outflow resistance of an eye comprises applying pressure to the eye and measuring the applied pressure to the eye. The method further includes directly measuring a volume change of the eye at a plurality of times and computing an outflow rate of fluid from the eye based on the measured volume change of the eye over time. In addition, the method includes determining the outflow resistance of the eye as a function of a ratio of the applied pressure and the outflow rate.

[0011] An embodiment of the computer program product for measuring an outflow resistance of an eye comprises a computer-readable storage medium containing computer program code. The code includes instructions for receiving a pressure measurement representing an applied pressure to the eye, and receiving a set of volume measurements representing a directly measured volume change of the eye at a plurality of times. The instructions further include computing an outflow rate of fluid from the eye based on the measured volume change of the eye over time. In addition, the instructions comprise determining the outflow resistance of the eye as a function of the ratio of the applied pressure and the outflow rate, and further using a biomechanical model of the eye to model dynamic effects.

[0012] The features and advantages described in this disclosure and in the following detailed description are not all-inclusive, and particularly, many additional features and advantages will be apparent to one of ordinary skill in the relevant art in view of the drawings, specification, and claims hereof. Moreover, it should be noted that the language used in

the specification has been principally selected for readability and instructional purposes, and may not have been selected to delineate or circumscribe the inventive subject matter, resort to the claims being necessary to determine such inventive subject matter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] These and other features, aspects, and advantages of the present invention will become better understood with regard to the following description, and accompanying drawings, where:

[0014] FIG. **1***a* is an illustration of the dual measurement system for applying tonographic techniques to an eye, according to an embodiment.

[0015] FIG. **1***b* is an illustration of the dual measurement system for applying tonographic techniques to an eye, according to an embodiment.

[0016] FIG. **2** is a flowchart illustrating the steps performed by the dual measurement system, according to an embodiment.

[0017] FIGS. **3***a* and **3***b* are flowcharts illustrating other embodiments of the steps performed by the dual measurement system.

[0018] FIG. **4***a* is a depiction of the current principles of tonography.

[0019] FIG. **4***b* is an illustration of the dynamic, dual-parameter measurement (a) prior to and (b) after the ocular volume change, according to an embodiment.

[0020] FIG. **4***c* is an illustration of a lumped element circuit representation of the microfluidic model in the anterior chamber of the eye, according to an embodiment.

[0021] FIG. **5** is a high-level block diagram illustrating a standard computer system **200** for use with the invention.

[0022] FIG. **6** is a high-level block diagram illustrating the functional modules within the biomechanical modeling module **600**, according to an embodiment.

[0023] FIG. **7** is a flowchart illustrating steps performed by the biomechanical modeling module **600**, according to an embodiment.

[0024] FIG. **8***a* is an illustration of the microfabrication of the contact lens device, according to an embodiment.

[0025] FIGS. **8***b* and **8***c* are photographs of a prototype of an array of miniature pressure sensors fabricated onto a flexible contact-lens platform, according to an embodiment

[0026] FIGS. **9***a* and **9***b* are photographs of in vitro biomechanical test setups to evaluate the aqueous outflow resistance, according to an embodiment.

[0027] FIG. **9***c* is photograph of a prototype of the dynamic dual measurement system using the volume-adjustable contact-lens device, according to an embodiment.

DETAILED DESCRIPTION OF THE INVENTION

System for Outflow Resistance Measurement

[0028] The dual measurement system and method described here are generally based on the tonography principles, but with real-time, continuous and direct measurement on both intraocular pressure (P_o) and displaced ocular volume (ΔV). In comparison with the convention tonography technique that uses statistical correlations to calculate IOP and volume change from an indentation indicator, the dynamic, dual-parameter (ΔIOP-ΔV) measurement system detects both IOP and ocular volume changes simultaneously, and measures the outflow resistance directly in a short duration (e.g., a few minutes). An explanation of the principles behind tonography is provided in the appendix of U.S. Provisional Application No. 61/034,484, filed Mar. 6, 2008, which is incorporated by reference.

[0029] FIGS. **1***a* and *b* illustrate an eye **102** and further show the anterior chamber **103** of the eye **102** containing the aqueous humor, the sclera **150**, and the cornea **152** of the eye **102**. As explained above, eyes produce this watery fluid, or aqueous humor, that normally enters the eye and then drains out via an aqueous drainage pathway. However, in eyes with glaucoma, the aqueous humor typically does not drain properly creating pressure in the eye **102** that leads to vision problems. Thus, it is the properties associated with the flow of this aqueous humor that the dual measurement system and method described here will measure.

[0030] Along with the illustration of the eye **102**, FIG. **1***a* further illustrates an embodiment of the contact lens-based dual measurement system **100** comprising an inflatable bladder, referred to in FIG. **1** as a hydraulic pressure management reservoir **104**. The reservoir **104** is disposed between a rigid outer wall **111** (inelastic shell) and a flexible inner wall, referred to in FIG. **1** as a flexible membrane **110**, forming a contact lens device **112** with a concave shape that can be placed in an eye **102** in a manner similar to a standard contact lens. When placed over the eye **102**, the flexible inner wall/membrane **110** portion of the contact lens device **112** contacts the eye **102**. The inflatable bladder/reservoir **104** is designed to hold fluid, and can be filled with fluid to expand against and put pressure on the eye **102**.

[0031] A hydraulic unit **124** is coupled via the hydraulic input/output **108** (hydraulic I/O) to the bladder/reservoir **104** to control the fluid inside the bladder/reservoir **104**, and so control the pressure therein. In one embodiment, the hydraulic unit **124** is configured to measure pressure in the bladder/reservoir **104** or to work in conjunction with a pressure measurement system to measure pressure. The hydraulic unit **124** can also measure volume displacement inside the bladder **104**. For example, the hydraulic unit **124** can include volume sensors or another volume detection/measurement apparatus that measures volume changes in the bladder over time. In one embodiment, the hydraulic unit **124** coupled to the bladder is configured to control the flow of fluid between the bladder/reservoir **104** and an external reservoir of the hydraulic unit **124** that holds fluid, so the hydraulic unit **124** can manage the filling of and removal of fluid from the bladder **104** as required by the system **100**. The hydraulic unit **104** is illustrated in FIG. **1** as being separate from or external to the contact lens device **112**, but in some embodiments, at least some components of the unit **104** (e.g., volume sensors or other components) are included within the device **112**.

[0032] Although the dual-measurement system **100** can be implemented using a number of different designs, the soft contact lens design used in one embodiment system **100** allows pressure measurements to be easily taken in the clinical optometry environment. The flexibility and convenience of this hybrid, volume-adjustable, soft contact lens make it easy to be applied to the cornea surface, even by patients themselves. Thus, a tonography-style device or tonometer is implemented on a contact lens platform that takes measurements associated with the eye **102**. In one embodiment, the contact lens device **112** uses pressure sensors **106** to take these measurements. In the FIG. **1***a* embodiment, the flexible surface **110** of the contact lens device **112** is embedded with pressure mapping sensors **106** for intraocular pressure detec-

tion. Since the flexible membrane **110** is brought into contact with the eye **102** when the contact lens is inserted into the eye **102**, the sensors **106** are also placed into proximity with the eye **102**. The sensors **106** in the flexible membrane **110** are configured to measure the pressure in the bladder/reservoir **104**, allowing for noninvasive and convenient pressure and flow monitoring. In one embodiment, the pressure mapping sensors **106** function in conjunction with the external hydraulic unit **124** including external pressure and/or volume sensor (s). In some embodiments, the sensors **106** measure both pressure and volume changes. In other embodiments, the pressure and volume sensors are coupled to but are all external to the device **112**.

[0033] The flexible contact membrane **110** is made of soft elastomer materials, such as silicone (Polydimethylsiloxane or PDMS), and the contact lens device **112** is backed by a relatively rigid outer shell **111** of polymeric materials, such as acrylic (Polymethyl-methacrylate or PMMA). A hydraulic chamber/reservoir **104** is enclosed in the shell, and is directly coupled to the ocular volume upon direct contact. The net change of the volumes in hydraulic chamber/bladder **104** and the anterior chamber **103** of the eye **102**, which contains the aqueous humor or fluid to be measured, should be zero theoretically. Based on the volume correlation between the fluid in the bladder **104** and the aqueous humor in the eye **102**, nanoliter volume displacement can be precisely monitored, e.g., through a computer-controlled interface.

[0034] The device **112** is also coupled via the electrical I/O **107** (e.g., wirelessly or wired) to a computer **122** or logic configured to process the measurements of the system **100**, and a display **120** (e.g., a computer monitor or other type of information display mechanism). The computer **122** processes and stores pressure data and/or volume change data retrieved by the system **100**, and the display **120** provides information to a user visually for user review or manipulation. The computer **122** can be used in calculating the outflow rate of fluid from the eye **102** based on the measured volume change of the eye **102** over time. The computer **122**/display **120** represent the logic configured to compute the outflow resistance of the eye **102** as a function of the pressure in the bladder/reservoir **104** and the change of volume in the bladder **104** over time.

[0035] FIG. **1***b* illustrates the dual measurement system **100** for applying tonographic techniques to an eye, according to another embodiment. In this embodiment, the contact lens device **112** is designed in the same general manner as the device **112** shown in FIG. **1***a*, including an outer rigid wall/inelastic shell **111**, a flexible inner membrane **110**, and an adjustable hydraulic reservoir **104**. The contact lens device **112** sits naturally on the cornea **152**. In some embodiments, the overall footprint of the device **112** is greater than that of a regular contact lens, which covers the entire cornea surface and extends beyond the limbus area of the eye. The flexible inner membrane of the contact-lens device is in direct contact with the cornea surface, between which an ultrathin layer (e.g., a few microns) of tear film is left during the measurement.

[0036] In one embodiment, embedded nanocomposite pressure sensors (similar to those shown in FIG. **1***a* as **106**) are incorporated into the device **112** as an additive feature for high-accuracy IOP measurement, though they are not required. The system **100** of FIG. **1***b* also includes a hydraulic unit **124** that takes the form of a computer-controlled nanofluidic pump including an external reservoir **156**. In embodiments of FIGS. **1***a* and **1***b*, the external reservoir can be included in the hydraulic unit **124** or can be a separate entity coupled to the unit/pump **124**. The unit/pump **124** is coupled to the bladder/reservoir **104** to control adding or removal of fluid from the reservoir **104**. In one embodiment, the unit/pump **124** is coupled to the bladder/reservoir **104** via microtubing that manipulates the hydraulic volume of the lens device **112**. Again, a computer **120**/display **122** is illustrated in FIG. **1***b* that is in contact with the contact lens device **112**, and functions in the same general manner as the computer **120**/display **122** of FIG. **1***a*. The computer-controlled interface allows pressure information to be directly employed to control the hydraulic flow to the bladder/reservoir **104**. The FIG. **1***b* embodiment further illustrates an external pressure sensor **160** that is in contact with the reservoir **104**, and can also be in contact with the hydraulic unit/pump **124** and the computer **120**.

Method for Outflow Resistance Measurement

[0037] FIG. **2** is a flow diagram illustrating the method for measurement of the outflow resistance of an eye, according to some embodiments of the present invention. It should be understood that these steps are illustrative only. Different embodiments of the system **100** may perform the illustrated steps in different orders, omit certain steps, and/or perform additional steps not shown in FIG. **2** (the same is true for FIG. **3** and FIG. **7**).

[0038] During operation of the contact lens device **112**, the bladder/reservoir **104** is placed **202** in the eye **102**. To take the IOP measurements, the contact lens **112** can be placed **202** in the eye **102** with topical anesthetic while the patient lies back & relaxes. One or both eyes can be tested at the same time. In the embodiment of FIG. **2**, the system **100** is used to slowly fill **204** bladder **104** with fluid until the trans-membrane pressure signal is stable. Filling **204** the bladder **104** in this manner can initially expand the flexible inner wall against the eye a stable pressure is reached. This will be the baseline pressure ($P_{baseline}$). The pressure sensors **106** and/or **160** or other pressure measurement mechanism can measure the pressure applied to the eye (e.g., at set intervals or continuously) to determine when the system **100** has reached the stable pressure signal (e.g., the baseline pressure level).

[0039] The system **100** can then be used to increase the pressure applied to the eye **102** by adding **206** additional fluid to the bladder **104** to raise the IOP a fixed amount (e.g., $P_{baseline}$+20 mmHg) over the baseline pressure. The pressure sensors **106** and/or **160**, or other pressure measurement mechanism can measure the pressure applied to the eye (e.g., at set intervals or continuously) to determine when the fixed amount of pressure is reached. The bladder can thus be brought to a pressure that exceeds the starting IOP of the eye **102**, which further expands the flexible inner wall/membrane **110** against the eye **102** to place pressure on the eye **102**.

[0040] In some embodiments, during the operational run of the system **100**, the servo-controlled microfluidics maintain **208** the pressure level (e.g., $P_{baseline}$+20 mmHg) absolutely steady (±0.1 mmHg resolution/100 msec). In one embodiment, the hydraulic unit **124** increases or decreases fluid in the bladder to maintain/regulate the pressure on the eye **102** at this fixed amount for a period of time based on continuous pressure measurements by the pressure sensor(s) **106** and/or **160**. In this manner, the system **100** can account for patient squeezing, valsalva (forceable exhalation against a closed airway, etc. and other outside forces that might otherwise

interfere with the pressure readings. This increased pressure on the eye **102** is thus maintained **208** for a period of time, and the pressure on the eye **102** tends to cause fluid outflow from the eye **102** during this time.

[0041] After a pre-programmed time interval (e.g., 2 or 4 min or other time interval), the system **100** draws/removes **210** fluid from bladder **104** until the trans-membrane IOP returns to $P_{baseline}$. The system **100** thus decreases the pressure on the eye **102** to return the pressure to the baseline pressure level. The fluid outflow can be measured using the change in volume of the bladder **104** as a proxy for the change in volume of the eye **102** over time, assuming that the increased volume in the bladder **104** is directly related to a loss of volume of fluid in the eye **102**. The volume needed to fill the bladder **104** at the end of the run to return the pressure reading to $P_{baseline}$ (V2) minus the volume needed to fill the bladder at the start of the run (V1) represents the outflow volume during the run (current microfluidics technology allows this to be measured with 0.1 μL precision), so the change in volume—and thus, the outflow—has been measured **212** directly. In one embodiment, the passive pressure sensors **106** and/or sensor **160** coupled to the bladder **104** working with the hydraulic unit **124** (e.g., the volume sensors) can directly measure **212** the decreasing volume in the bladder **104** over time under the presence of a known, measured pressure. In one embodiment, the system **100** can take a plurality of measurements of the change in volume of the eye **102** over time under the increased pressure. During the procedure, time and perturbing pressure are tightly controlled. This operation can be performed on one eye or on both eyes simultaneously.

[0042] With the data collected, the time-dependent variation of ocular volume can be used to calculate **214** flow rate as $Q=\Delta V/\Delta t$. The system **100** computes **214** the outflow rate of fluid from the eye **102** based on the measured volume change of the eye over time. The resistance can then be determined **216** as $R=\Delta P/Q$. The system **100** thus determines **216** the outflow resistance of the eye as a function of the ratio of the applied pressure and the outflow rate. In some embodiments, the system **100** can also measure other ocular parameters, such as ocular rigidity, pseudofacility, or other ocular mechanical parameters related to flow or pressure.

[0043] In one embodiment, the data collected by the system **100** can be outputted to a display (e.g., computer display **122**) for viewing and/or manipulation by the user. In addition, information regarding the computations **308** performed to determine the outflow rate or the determination **310** of the outflow resistance can be provided on the display **122**. Similarly, the final results of the calculations/determinations **308**/**310** can be outputted on display **122** for the user to view/manipulate.

[0044] There can be a number of different variations on the method steps above. In some embodiments, step **208** (FIG. **2**) of the method is optional, and the pressure does not have to be maintained **208** over time. For example, the pressure could be pulsed or fluctuating over time, and so not maintained at a constant level. As another example, the pressure could be gradually increased over time or could be alternating. The method can include various other pressure waveforms, as well. Further, in the embodiment described above, the method describes changing the pressure applied and measuring the resulting volume change. However, in other embodiments, the method includes changing the volume over time and measuring the pressure, as illustrated in FIG. **3***b*.

[0045] Referring now to FIGS. **3***a* and **3***b*, there are shown flowcharts illustrating the operation of the dual measurement system **100**, according to other embodiments of the invention. Like, FIG. **2**, the methods of FIGS. **3***a* and **3***b* include placing **302**, **352** the contact lens in the patient's eye in a manner similar to that described for step **202** above. In some embodiments, the methods of FIGS. **3***a* and **3***b* include automatically adjusting the bladder volume. As one example, the hydraulic unit/pump **124** can automatically add fluid to the bladder **104** or remove fluid from the bladder **104** until the appropriate volume is reached.

[0046] Continuing with FIG. **3***a*, the method further includes applying **306** pressure to the eye **102**. As one example, the hydraulic unit **124** can add fluid to the bladder **104** which is resting against the eye **102**, causing the bladder **104** to apply **306** pressure to the eye **102**. As explained above, the pressure applied can be constant, pulsed, increasing, alternating, etc. over time. As also explained above regarding FIG. **2**, placing pressure on the eye **102** tends to cause fluid outflow from the eye **102**. In step **308** of the method, the system **100** can directly measure **308** a volume change of the eye created by the applied pressure **306** to the eye over time. With the data collected, the system can calculate **310** the outflow rate of fluid from the eye **102** based on the measured volume change of the eye over time, and can determine **312** the outflow resistance of the eye or other ocular parameter (e.g., ocular rigidity, pseudofacility, etc.), as explained above regarding FIG. **2**.

[0047] Returning to FIG. **3***b*, the method continues with the step of imposing **356** a volume change in the bladder. As one example, the hydraulic unit **124** can add fluid to the bladder **104** or remove fluid from the bladder **104** to impose this change. In some embodiments, the changing volume is constant, pulsed, increasing, alternating, or changed in some other pattern over time. The addition or removal of fluid from the bladder **104** causes the bladder **104**, which is resting against the eye **102**, to create changes in pressure applied to the eye **102**. In one embodiment, the pressure sensors **106** and/or **160** or other pressure measurement mechanism can directly measure **358** the pressure change of the eye created by the imposed **356** volume change. With the data collected, the system can calculate **360** the outflow rate of fluid from the eye **102** based on the measured pressure change of the eye over time, and can determine **362** the outflow resistance of the eye or other ocular parameter (e.g., ocular rigidity, pseudofacility, etc.), as explained above regarding FIG. **2**. Thus, using any of the methods of FIGS. **2**, **3***a*, and **3***b*, the system can detect IOP and ocular volume change simultaneously, and can measure outflow resistance directly.

Physical/Mathematical Model for the Intraocular Biomechanics and Microfluidic Dynamics

[0048] Background

[0049] To understand the mathematical model used by the dual measurement system **100**, it is helpful to first review the current tonography procedures and their deficiencies. As explained above, current tonography procedures face an intrinsic technical hurdle. In order to measure flow resistance or facility, two measurable quantities are typically required: pressure drop (ΔP) and flow rate (Q) per volume change ($\Delta V/\Delta t$). But in tonography, the only measurement made is through the reading of indentation level. Therefore, statistical correlations applied in tonography procedures relate the indentation levels to both volume change and pressure read-

ing under a constant weight on the cornea surface. Formulas typically used in current tonography procedures include the following:

$$V_1=1/K_T*\log(P_{T1}/P_{01})$$

$$V_2=1/K_T*\log(P_{T2}/P_{02})\rightarrow\Delta V=K_T/K_D*(1/K_T*\mathrm{Log}(P_{T1}/P_{T2})-V_2+V_1)$$

$$\Delta V=1/K_D*\log(P_{01}/P_{02})$$

FIG. **4***a* depicts current tonography procedures in more detail. The total change in volume due to the application of the tonometer, ΔV, is calculated using the above formula. P_{01} and P_{02}, are the pressures before and after application of the tonometer, respectively. P_{T1} and P_{T2} are the pressures during application of the tonometer at time point **1** and time point **2**, and these values are obtained from standard tonometer calibration tables (e.g., open manometer calibration tables). V_1, V_2 are the volumes before and after tonometer application, respectively, and are also obtained from the calibration tables. The average values of K_T and K_D are used. See Grant W. M. Tonographic method for measuring the facility and rate of aqueous flow in human eyes. *Archives of Opthalmology.* 44:204-214 (1950), which is incorporated by reference. Finally, the facility of outflow $C=(\Delta V/T)/(P_{Taverage}-P_{01})$, where T is the time of application of the tonometer. $P_{Taverage}$ is the average pressure over the tonometer application time. Low C values have been found in patients with glaucoma.

[0050] Problems with this approach include the fact that just one tonometer reading is used to determine both the numerator and the denominator (2 properties) in the formula for C. Moreover, the formula should read as: C=(ΔV/T)/(P−Pv), where Pv is the episcleral venal pressure and P is the intraocular pressure. The denominator is the pressure difference which is the driving force for the aqueous humor flow, and the numerator is the volumetric flow rate. C is therefore equivalent to the inverse of the resistance to this flow (compare with Ohm's law). Another issue is that P_{01} and P_{02} are obtained from closed manometer calibration, which is not reliable.

Hybrid Dual-Parameter Measurement Principle

[0051] Rather than relying on measurement of the cornea/sclera deformation under a mechanical load like conventional ocular biomechanical assessments, the dual-parameter (ΔIOP-ΔV) measurement system **100** couples, manipulates and continuously measures both ocular volume and IOP change. To accurately evaluate flow resistance (R) or facility (F) in any linear fluidic system, two measurable quantities are typically required, the pressure difference (ΔP) and the according outflow rate (Q) or volume change rate (ΔV/Δt), as indicated in the definition of flow resistance or facility in Equation 1:

$$R=\frac{1}{F}=\frac{\Delta F}{q}=\frac{\Delta F}{\Delta V/\Delta t} \quad (1)$$

[0052] FIG. **4***b* is an illustration of the dynamic, dual-parameter measurement (a) prior to and (b) after the ocular volume change, according to an embodiment. As shown in part (a), this configuration allows direct coupling of the adjustable fluidic reservoir in the contact lens to the anterior chamber. The two-way nanoliter-precision hydraulic pump **124** perfuses liquid into or out from the contact-lens reservoir **104**, which displaces the complementary volumes of the reservoir (V_l) and anterior chamber (V_o) simultaneously (part (b) of FIG. **4***b*) following the relationship described in the Equation 2:

$$V_l+V_o=\text{constant or } \Delta V_l+\Delta V_o=0 \quad (2)$$

[0053] By adjusting the ocular volume while continuously monitoring the IOP, the pressure/volume relationship (ΔIOP-ΔV) of the eye is established dynamically, enabling determination of the aqueous outflow resistance/facility.

[0054] Dynamic Dual-Parameter Measurement Modeling

[0055] To understand the intraocular biomechanics coupled with fluidic dynamics of aqueous humor (the circulation flow inside the anterior chamber), a mathematical/biomechanical model has been developed and can be used in conjunction with the dual-measurement system **100**. The dynamic, dual-parameter concept is similar to the impedance analysis in circuits, where a tiny current excitation is produced to generate a measurable voltage shift. A lumped-element model, analogous to an electronic circuit model, has been developed to understand the intraocular biomechanics coupled with fluid dynamics of aqueous humor, the circulation flow inside the anterior chamber. FIG. **4***c* shows the lumped-element model of the aqueous humor hydrodynamics for the proposed dynamic measurement techniques, according to an embodiment. As the Figure shows, it is the linear component of the aqueous outflow resistance (R) that is the primary measurand in the model, while the ocular rigidity of the eye (K), a compliance measure of the corneosclera envelope, is also included. The governing equations can be derived from Equation 1 and the biomechanical model for corneoscleral envelope.

$$R=\frac{d(IOP)}{d\left(\frac{dV}{dt}\right)} \quad (3)$$

$$K=\frac{(d\,IOP/dt)/(dV/dt)}{IOP} \quad (4)$$

[0056] Using similar approaches to the circuit analysis (Kirchhoff's current and voltage laws), the equations of conservation of mass and energy are employed to establish relationships between the ocular flows and pressures in the hybrid fluid mechanical model. Furthermore, to clinically exam the unknown ocular parameters, in particular, the outflow resistance, various excitation schemes can be explored in the dual-parameter measurement system **100**. The simplest operation schemes are the constant-flow mode and constant-pressure mode. Unlike those used in the current tonography method, the constant-pressure mode employs an invariant pressure greater than the IOP, which is applied onto cornea. Meanwhile, the coupled volume displacement of the eye is closely manipulated via the hydraulic interface of the lens. Finally, the evaluation outcomes can be used to compare with the tonography results.

[0057] Considerations for Measurement Accuracy

[0058] To guarantee accurate measurement of aqueous outflow resistance, several possible clinical issues should be considered. First, to ensure a direct and close coupling between the deformable reservoir **104** and the anterior chamber **103**, the contact-lens device **112** is held in place by the patient's eyelids in a manner similar to conventional tech-

niques of clinical retinal electrophysiology while the pressure/volume change is applied. Meanwhile, the thin tear film/membrane will induce considerable capillary adhesion (e.g., up to 200 mmHg) between the lens and the ocular surface, according to the Laplace's equation. Moreover, the flexible membrane of the lens is relatively unresistant to the pressure change, and highly adaptive to the cornea surface with slightly varied dimensions and curvatures. The altered ocular volume is relatively small in comparison with the entire volume of the anterior chamber, under which linear biomechanical analysis can be performed. Furthermore, due to existing stress in the cornea, the pressure assessed through the hydraulic reservoir **104** may not reflect the true IOP reading. Fortunately, according to the dynamic dual-parameter measurement (as illustrated in Equations 3 and 4), the IOP change, instead of absolute IOP value, is the primary concern. Under a small volume change of the anterior chamber (e.g., <2%), the measured pressure change is expected to reflect the IOP variation in the anterior chamber, which has been demonstrated the in vitro experimental investigation described below.

Computer Product for Outflow Resistance Measurement

[0059] Embodiments of the invention can include a computer product that uses this biomechanical model described above. FIG. **5** is a high-level block diagram illustrating an example of a standard computer **500** for use with the computer product. Illustrated are at least one processor **502** coupled to a chipset **504**. The chipset **504** includes a memory controller hub **520** and an input/output (I/O) controller hub **522**. A memory **506** and a graphics adapter **512** are coupled to the memory controller hub **520**, and a display device **518** is coupled to the graphics adapter **512**. A storage device **508**, keyboard **510**, pointing device **514**, and network adapter **516** are coupled to the I/O controller hub **522**. Other embodiments of the computer **500** have different architectures. For example, the memory **506** is directly coupled to the processor **502** in some embodiments.

[0060] The storage device **508** is a computer-readable storage medium such as a hard drive, compact disk read-only memory (CD-ROM), DVD, or a solid-state memory device. The memory **506** holds instructions and data used by the processor **502**. The pointing device **514** is a mouse, track ball, or other type of pointing device, and is used in combination with the keyboard **510** to input data into the computer system **500**. The graphics adapter **512** displays images and other information on the display device **518**. The network adapter **516** couples the computer system **500** to a network. Some embodiments of the computer **500** have different and/or other components than those shown in FIG. **5**.

[0061] The computer product may be performed or implemented with one or more hardware or software modules, alone or in combination with other devices. Thus, the computer **500** is adapted to execute the biomechanical modeling module **600** for providing functionality described. In one embodiment, a software module is implemented with a computer program product comprising a computer-readable medium containing computer program code, which can be executed by processor **502** for performing any or all of the steps, operations, or processes described. Embodiments of the invention may also relate to an apparatus for performing the operations herein. This apparatus may be specially constructed for the required purposes, and/or it may comprise a general-purpose computing device selectively activated or reconfigured by a computer program stored in the computer **500**. Such a computer program may be stored in a tangible computer readable storage medium (e.g., storage **508**) or any type of media suitable for storing electronic instructions, and coupled to a computer system bus. Furthermore, any computing systems referred to in the specification may include a single processor or may be architectures employing multiple processor designs for increased computing capability. In addition, the computer **500** can take the form of another electronic device, such as a personal digital assistant (PDA), a mobile telephone, a pager, or other devices. The computers can execute an operating system (e.g., LINUX®, one of the versions of MICROSOFT WINDOWS®, and PALM OS®), which controls the operation of the computer system, and execute one or more application programs.

[0062] In one embodiment, the computer product is executed as a biomechanical modeling module **600**, shown in FIG. **6**. FIG. **6** is a high-level block diagram illustrating the functional modules associated with the biomechanical modeling module **600**, according to one embodiment of the invention. In the embodiment illustrated in FIG. **6**, the biomechanical modeling module **600** includes a receiving module **602**, an outflow rate computing module **604**, and a resistance determining module **606**. Some embodiments have different and/or additional modules than those shown in FIG. **6** and the other figures. Likewise, the functionalities can be distributed among the modules in a manner different than described herein or can be incorporated into other modules.

[0063] The receiving module **602** receives the pressure measurement representing the applied pressure to the eye **102**. The receiving module **602** also receives the set of volume measurements representing the directly measured volume change of the eye **102** at a plurality of times. In one embodiment, the pressure measurement and volume measurements are obtained via a tonographic-style device, such as a contact lens device **112** similar to that illustrated in FIGS. **1***a* and *b* (though other mechanisms could be used to obtain these measurements). The measurements can be obtained automatically from the device **112** (e.g., wirelessly) or via manual input by a user into a computer, such as computer **122** in FIGS. **1***a* and *b*. These measurements can be obtained through placement of the device **112** in the eye and filling of the bladder **104**, according to the method steps described in FIGS. **2** and **3**. In one embodiment, pressure measurements are taken via one or more pressure sensors **106** and/or **160** associated with the inflatable bladder **104** of the contact lens device **112** as described above, and transmitted to module **602** for analysis. Similarly, the volume measurements can be taken by the hydraulic unit **124** (e.g., volume sensors) working in conjunction with the pressure sensors **106** and/or **160** as described above, and transmitted to module **602** for analysis.

[0064] The outflow rate computation module **604** computes an outflow rate of fluid from the eye **102** based on the measured volume change of the eye **102** over time. Where a device such as contact lens device **112** is used to obtain the pressure and volume measurements described above, the pressure sensors **106** and/or **160** coupled to the bladder **104** in conjunction with the hydraulic unit **124** can directly measure the decreasing volume over time under the presence of a known, measured pressure. Module **604** can compute the outflow rate using this change in volume of the bladder **104** as a proxy for the change in volume of the eye **102** over time, as explained in more detail above.

[0065] The resistance determining module **606** determines the outflow resistance of the eye **102** as a function of the ratio of the applied pressure and the outflow rate. The resistance can be determined as $R=\Delta P/Q$. The module **606** also uses the biomechanical model of the eye **102** described in detail above to model dynamic effects.

[0066] Referring now to FIG. **7**, there is shown a flowchart illustrating the operation of the biomechanical modeling module **600**, according to some embodiments of the invention. The module **600** receives **702** a pressure measurement representing the pressure applied to the eye **102**. The module **600** also receives **704** a set of volume measurements representing the directly measured volume change of the eye at a plurality of times. These measurements can be taken using a device, such as contact lens device **112**, and can be provided to module **600** automatically or via user input. The module **600** further computes **706** an outflow rate of fluid from the eye **102** based on the measured volume change (e.g., measured via contact lens device **112**) of the eye over time. In addition, the module **600** determines **708** the outflow resistance of the eye as a function of the ratio of the applied pressure and the outflow rate, and uses the biomechanical model of the eye **102** to model **710** dynamic effects, as described in more detail above. The data collected by the system **100** and processed by the biomechanical modeling module **600** can be outputted to a display (e.g., computer display **122**) for viewing and/or manipulation by the user. In addition, information regarding the computations **706** performed to determine the outflow rate or the determination **708** of the outflow resistance can be provided on the display **122**. Similarly, the final results of the calculations/determinations **706/708** can be outputted on display **122** for the user to view/manipulate.

Fabrication of the Contact Lens Device

[0067] Below is an example of specific embodiments for fabricating contact lens device **112**. The examples are offered for illustrative purposes only, and are not intended to limit the scope of the invention in any way. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental error and deviation should, of course, be allowed for.

[0068] The contact lens device **112** can be fabricated in a number of different manners, and by using various different materials. The device **112** integrates microfluidic control and pressure sensing capacity into a hybrid contact-lens platform to evaluate aqueous outflow resistance accurately. FIG. **8***a* is an illustration of the microfabrication of the contact lens device, according to an embodiment. The Figure illustrates the microfabrication process for a smart contact-lens device **112**. A silicone elastomer (e.g., PDMS) is used as the construct for the flexible membrane. PDMS has high optical transparency, high mechanical flexibility, excellent biocompatibility and easy processability. In particular, its Young's modulus is more than 10 times smaller than that of the corneoscleral envelope, providing high adaptability to cornea surface and low resistance to pressure/volume change. An array of miniature pressure sensors can be into this material, as described below.

[0069] On the outer shell, a much stiffer biocompatible polymer (e.g., PET or PMMA), is used, which ensures one-way volume expansion under positive pressure. A spinnable ultraviolet-curable adhesive (e.g., LOCTITE FLASH-CURE®) is used to define the hydraulic volume and seal the PDMS membrane to the plastic shell. Thickness of the flexible membrane and adhesive layer can be controlled by spinning coating, which results in the target thickness of 80 μm and 20 μm, respectively. The rigid shell of 100 μm in thickness can be purchased from the manufacturer (e.g., DUPONT®) directly. Thus, the overall thickness of 200 μm for the contact lens device **112** is similar to that of a vision-correction contact lens, with an entire footprint of 2 cm in diameter to completely cover the cornea surface for accurate volume coupling from the contact lens to anterior chamber. In the subsequent thermocompression molding, the device **112** is shaped into a spherical dome to match with the cornea curvature under an elevated temperature (the glass transition temperature) and a mechanical pressure (part (d) of FIG. **8***a*). Finally, a microtube is glued to the through-hole of the inelastic shell (part (e) of FIG. **8***a*).

[0070] In some embodiments, very flexible, nanocomposite sensors (e.g., sensors **106**) are embedded in the device **112** (e.g., as an additive monitoring feature to achieve higher accuracy for the IOP measurement). The sensors are fabricated using a photopatternable, conductive, nanocomposite polymer comprising conductive filler (e.g., silver nanoparticles) and an additional photosensitive component well dispersed into an elastomer matrix (e.g., PDMS). The PDMS-Ag nanocomposite material provides very high electrical and thermal conductivity, along with enhanced mechanical strength. The built-in photopatternability makes manufacturing process easy and very reproducible. FIGS. **8***b* and **8***c* are photographs of a prototype of an array of miniature pressure sensors fabricated onto a flexible contact-lens platform, according to an embodiment. In one embodiment, the array of miniature pressure sensors is fabricated onto a flexible contact lens platform using the nanocomposite.

[0071] Fabrication of the pressure sensing elements on the flexible membrane begins with mixing of a commercially available PDMS base with a curing agent in a 10:1 (w/w) ratio. The silicone pre-polymer is spin-coated onto a 4 inch silicon substrate at 1,000 rpm. The PDMS membrane of about 60 μm thick is thermally cured at 80° C. for one hour. The photosensitive conductive nanocomposite material is prepared from the PDMS prepolymer mixture with Benzophenone (3 wt %), the photosensitizer, and silver nanopowder (21 vol %, 150 nm in diameter), the conductive filler. It is spin-coated onto the cured pure PDMS film at 4,000 rpm to achieve a 20 μm-thick layer. The spin-coated substrate is ultraviolet exposed under a chrome photomask using proximity mode (of 50 μm separation). Unlike the regular photosensitive polymers, the conductive PDMS-Ag nanocomposite requires a heavy exposure dosage (~7000 mJ/cm^2), possibly resulting from strong ultraviolet absorption and scattering by silver nanoparticles present in the film. Subsequently, a post-exposure bake is carried out at 120° C. for 50 sec, which facilitates the further crosslink in the unexposed region. The exposed PDMS-Ag composite is then removed in toluene for 3-5 sec during the development. Finally, the wafer is rinsed with 2-propanol and blow-dried under nitrogen flow.

[0072] After fabrication of the conductive polymeric circuits, an ultrathin PDMS layer is spin-coated on top of the surface at 5,000 rpm. This PDMS layer of 12 μm thick, only half cured for the following folding bond process, serves as a pressure sensitive layer in the capacitive sensing design. Subsequently, the elastomer sensing circuit membrane is folded over and fully thermally cured to secure final packaging. The sensing circuits on each side are orthogonally crossed over and form a matrix of capacitive sensing elements in the film.

At the end, a thermal compression process on a curved surface is used to form the final contact lens shape, as shown in FIGS. **8***b* and **8***c*.

In Vitro Bench Test to Evaluate Aqueous Flow Resistance

[0073] FIG. **9***a* shows an in vitro biomechanical experiment setup that was built to evaluate the aqueous flow resistance. This example is provided to illustrate, through an in vitro apparatus, how the system **100** might function in vivo. This example (and the other examples below) is not intended to limit the scope of the invention in any way.

[0074] An elastic silicone chamber **902** with a deflectable membrane was constructed to simulate anterior chamber **103** and cornea surface. A manometer reservoir/syringe pump **904** providing a flow stream to the simulated anterior chamber **103** is connected to the inlet of the eye model through a three-way valve **906**, the other end of which directs to a computer-controlled pressure gauge **908**. The outlet of the chamber passes to a flow restrictor, which provides a linear resistance to the flow. Using the same setup, the plastic anterior model can be replaced with a cadaver eye. Based on the findings from the biomechanical analysis, the in vitro example can be used to optimize measurement design on displaced ocular volume and/or intraocular pressure.

[0075] FIG. **9***b* shows a photo of another in vitro biomechanical experiment setup that was built to simulate the anterior chamber with aqueous humor circulation. The FIG. **9***b* setup is similar to the FIG. **9***a* setup, including artificial anterior chamber (like chamber **902**), an aqueous outflow tube leading to a flow resistor, an aqueous inflow tube coming from a perfusion pump, and an ocular pressure measure to a pressure sensor. The artificial anterior chamber model of FIG. **9***b* is constructed from an acrylate polymer, which consists of a fluidic chamber in the plastic substrate, a clamping sleeve, and an artificial cornea manufactured by silicone rubbers with a similar Young's modulus to the human cornea. The designed cavity is 12 mm in diameter and 3 mm in depth and, together with the mounted artificial cornea, forms the artificial anterior chamber, of which the volume is about the same size as that in vivo. Four plastic screws secure the seal from the cornea under the clamping sleeve to the artificial anterior chamber. Furthermore, the fluidic chamber contained three through-channels from the backside. Among the three, two channels provide an inflow path from a digital perfusion pump and outflow drainage to a reservoir, respectively, and the other allows real-time tracking on hydraulic pressure inside the chamber by a digital pressure sensor.

[0076] On the outflow path, a microfluidic channel is connected to mimic the flow resistance to the aqueous outflow. The flow resistance (R) can be designed according to the geometric dimensions and fluidic viscosity, as shown in the Poiseuville's equation:

$$R = \frac{8\mu l}{\pi r^4} \tag{5}$$

[0077] where l and r indicates the length and radius of the microfluidic channel, respectively, while μ is the viscosity of the fluid. Under physiological conditions, the perfusion pump is operated at a constant flow rate of 45 nL/s (2.7 μL/min). In order to generate an artificial IOP of 2000 Pa (15 mmHg), the aqueous outflow resistance is set at 4.4×10^{13}N-s/m^5, which is used as the key design parameter for the flow resistor. Furthermore, the measured pressure changes in the contact-lens reservoir are directly compared with the true value measured by the pressure sensor connected to the inside chamber. Although little difference between the external and internal pressure variations has been experimentally observed under a small volume change of the anterior chamber (<2%), this configuration allows the further calibration of differential pressure measurements in the contact-lens device for a higher accuracy.

Prototype of the Dual Measurement System

[0078] FIG. **9***c* is photograph of a prototype of the dynamic dual measurement system using the volume-adjustable contact-lens device **112**, according to an embodiment. Through the micro tubing connection, the contact-lens device **112** with the embedded adjustable hydraulic bladder is connected to a three-way stopcock, one limb of which passes to a high-precision pressure sensor, and the other to a two-way high-precision perfusion pump, as described above. Then, both of the pressure sensor and nanofluidic pump are interfaced with a laptop computer. The two-way nanofluidic pump with cyclic infusion/withdrawal capacity (e.g., KD SCIENTIFIC 210) offers nanoliter-precision pulse-free flow to/from the hydraulic volume, which is microprocessor-controlled through the built-in TTL and RS232 interfaces. Similarly, the high-precision digital pressure sensor (e.g., OMEGA HHP 90) allows direct assessment of the hydraulic pressure in the deformable contact lens through the built-in RS232 interfaces. Furthermore, since the computer has digital access to both hydraulic flow control and pressure measurement, a software control interface uses the pressure information, which can be employed to manipulate the hydraulic flow through feedback. This interface would enable true dynamic dual-parameter measurement schemes, under which pressure-controlled excitation modes can be realized in the aqueous outflow resistance/facility assessment, e.g., the constant-pressure mode.

Ex Vivo Investigation of the Dual Measurement System

[0079] The integrated hybrid measurement system and computer-controlled interface can be validated both ex vivo and in vivo. Porcine eyes can be used since they are comparable in size to human eyes. The scale of the prototype can thus be designed to be a similar size to a device designed for clinical use. By slightly modifying the in vitro validation model, an enucleated porcine eye can be immobilized with the cornea facing upwards. Subsequently, the anterior chamber is cannulated and infused with a simulated aqueous flow at a physiological rate driven by the perfusion pump. Meanwhile, the true IOP pressure in the cannulated eye can be measured directly through a three-way stopcock using the similar setup presented in FIG. **9***b*. The outflow resistance for each individual eye can be determined by this procedure first. Afterwards, the device is mounted on the eye surface, which is treated with artificial tears right before. The dynamic, dual-parameter assessment can be performed using various computer-directed operation schemes, including the constant-pressure and constant-flow modes, and the results can be directly compared with the measurements made through the invasive cannula system described above to determine the optimal protocol and conditions. In addition, eye movement and eyelid squeezing can be simulated by touching and press-

ing on the eye globe during the measurement, for analyzing influences from the environmental disturbances, and for designing strategies to minimize the extrinsic factors.

In Vivo Validation of the Dual Measurement System

[0080] In vivo experiments can also be performed on anesthetized pigs. In a manner similar to that described above, the baseline outflow resistance in anesthetized pigs is measured through an invasive cannula system, where an artificial inflow is imposed, while the IOP is assessed by connecting to a three-way stopcock. The device described previously is sized appropriately to fit under the eyelids of a pig. During the hybrid measurement operation, the natural aqueous inflow occurring in the anesthetized animals can be assessed dynamically, instead of the simulated flow from the perfusion pump. The optimal testing protocol and parameters can be refined using the in vivo model. Moreover, in vivo IOP is a dynamic physiological parameter, influenced by eye movement as well as the ocular pulse. Various pulsed stimulations (either flow or pressure) can be used to determine whether dampening or simulating the existing ocular influences is necessary during the in vivo measurement.

[0081] The foregoing description of the embodiments of the invention has been presented for the purpose of illustration; it is not intended to be exhaustive or to limit the invention to the precise forms disclosed. Persons skilled in the relevant art can appreciate that many modifications and variations are possible in light of the above disclosure. Accordingly, the language used in the specification has been principally selected for readability and instructional purposes, and it may not have been selected to delineate or circumscribe the inventive subject matter. It is therefore intended that the scope of the invention be limited not by this detailed description, but rather by any claims that issue on an application based hereon.

1. A method for measuring an outflow resistance of an eye, the method comprising:
- applying a pressure to an eye;
- measuring the applied pressure;
- directly measuring a volume change of the eye created by the applied pressure to the eye;
- computing an outflow rate of fluid from the eye based on the measured volume change of the eye over time; and
- determining the outflow resistance of the eye as a function of a ratio of the applied pressure and the outflow rate.

2. The method of claim **1**, further comprising
- initially applying pressure to the eye until a stable pressure signal is received; and
- measuring the pressure applied to the eye to reach the stable pressure signal, the pressure applied being a baseline pressure level.

3. The method of claim **2**, wherein applying pressure to the eye further comprises:
- increasing the pressure on the eye to raise intraocular pressure a fixed amount; and
- maintaining the pressure on the eye at this fixed amount for a period of time.

4. The method of claim **3**, further comprising decreasing the pressure on the eye to return the pressure to the baseline pressure level, wherein the volume change is measured at the baseline pressure level.

5. The method of claim **3**, further comprising taking a plurality of measurements of the change in volume of the eye over time under the increased pressure.

6. The method of claim **1**, further comprising:
- placing a pressure sensor in proximity to the eye;
- continuously measuring the applied pressure detected by the pressure sensor; and
- regulating the applied pressure using the pressure sensor to maintain the applied pressure at a stable level.

7. The method of claim **1**, wherein the outflow resistance and an ocular rigidity of the eye are determined using mathematical modeling and experimental measurements from a pressure sensor placed in proximity to the eye.

8. The method of claim **1**, further comprising:
- placing a contact-lens device in the eye, the contact-lens device comprising a rigid outer wall, a flexible inner wall, and an inflatable bladder disposed therebetween, wherein the flexible inner wall contacts the eye and is coupled to a pressure sensor for measuring pressure applied to the eye; and
- filling the bladder with fluid until a stable pressure signal is received representing a baseline pressure level.

9. The method of claim **8**, wherein applying pressure to the eye further comprises:
- filling the inflatable bladder with additional fluid to increase the pressure on the eye to raise intraocular pressure a fixed amount; and
- increasing or decreasing fluid in the bladder to maintain the pressure on the eye at this fixed amount for a period of time based on continuous pressure measurements by the pressure sensor.

10. The method of claim **9**, further comprising removing fluid from the inflatable bladder to decrease the pressure on the eye to return the pressure to the baseline pressure level, wherein the volume change in the bladder is measured at the baseline pressure level, the volume change in the bladder representing the volume change in the eye.

11. The method of claim **1**, further comprising applying directly measured intraocular pressure change and directly measured volume change of the eye to determine a plurality of different ocular mechanical parameters related to flow or pressure of the eye.

12. A system for measuring an outflow resistance of an eye, the system comprising:
- a contact-lens device comprising a rigid outer wall, a flexible inner wall, and an inflatable bladder disposed therebetween, the contact-lens device having a concave shape to allow placement over an eye wherein the flexible inner wall contacts the eye;
- a pressure measurement system coupled to the bladder and configured to measure a pressure of fluid within the bladder and applied to the eye;
- a hydraulic unit coupled to the bladder and configured to control a flow of fluid between the bladder and an external reservoir, and further configured to measure a change of volume in the bladder created by the pressure applied to the eye; and
- logic configured to compute the outflow resistance of the eye as a function of the pressure in the bladder and the change of volume in the bladder over time.

13. The system of claim **12**, wherein the pressure measurement system comprises a pressure sensor embedded in the flexible inner wall of the contact-lens device for directly measuring the pressure of fluid within the bladder.

14. The system of claim **12**, wherein the pressure measurement system comprises a pressure sensor external to and coupled with the contact-lens device.

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(54) **MEASURING OUTFLOW RESISTANCE/FACILITY OF AN EYE**

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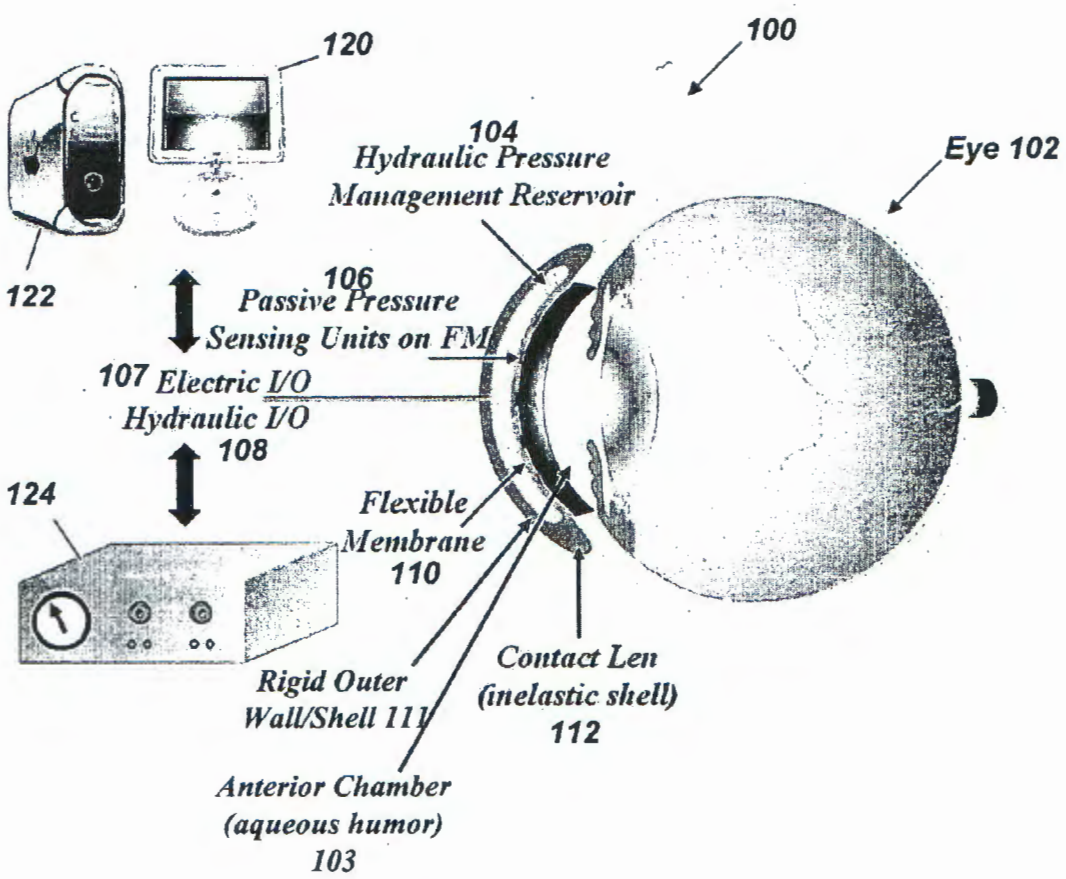
(57) **ABSTRACT**

A measurement system takes measurements of intraocular pressure and displaced ocular volume for determination of aqueous outflow resistance A device with a rigid outer wall, a flexible inner wall, and an inflatable bladder in between is placed over the eye A pressure measurement system is coupled to the bladder and is configured to measure a pressure of fluid within the bladder A hydraulic unit is coupled to the bladder and configured to control a flow of fluid between the bladder and an external reservoir, and to measure a change of volume in the bladder created by the pressure applied to the eye Both the pressure measurement system and hydraulic unit are directly controlled by and communicated with a microprocessor/computer In addition, the microprocessor computes the outflow resistance of the eye as a function of the pressure in the bladder and the change of volume in the bladder over time.



Tonography
Glaucoma Provocative Tests

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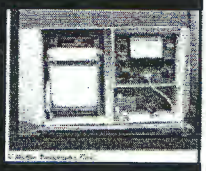
Tonography

- Estimates the facility of aqueous outflow from the eye and any possible resistance.
- Electronic tonometer is placed on anesthetized cornea for a 4-minute period.
- External force applied to the eye will cause IOP to rise and elevated pressure should force aqueous out of the eye at a faster rate than normal, resulting in a drop in IOP.
- Electric tonometer is wired to a stylus that records the pulsations of the eye.
- Gives a visible etching on a graph that can be calculated to determine the coefficient of aqueous outflow facility.



Method

- Tonography
  - Instrument is turned on and allowed to warm up.
  - Check to make sure there is enough graph paper in the recorder and that ink stylus is sufficiently moist to insure a good tracing.

Calibration

- Should be done every time the machine is turned on.
  - Voltage meter – switch will change needle position from 0 to 10. Calibration knob enables fine tuning of needle position.
  - Electronic stylus – rests lightly on graph paper.
  - Electronic Schiotz tonometer – 5.5 gram weight in place.
  - Test block – with two metal plates labeled 0 and 10

Calibration

- To calibrate, secure the 5.5 gm weight on the tonometer and place tonometer on the test plate labeled 0.
- Make sure the switch of the voltage meter is in the 0 position.
- Observe the needle of the meter scale and the stylus on the graph paper.
- Both should be aligned on 0.
- If the voltage meter needle and ink stylus do not rest on 0, rotate the calibration knob until the 0 position is obtained.

Calibration

- Now turn the voltage meter switch to 10 and place the tonometer on the test plate labeled with 10.
- Both the voltage meter and ink stylus should be aligned with 10.
- If not, rotate the calibration knob until the 10 position is obtained.
- Repeat the procedure to insure proper calibration.
- Once calibrated, the voltage meter switch should remain in the 0 position.

Technique

- Before beginning the test, the IOP should be established with an applanation tonometer.
- This is done so the appropriate weight for the electronic Schiotz tonometer can be determined.
- Use the following standards:
  - IOP readings under 20 mm Hg, use 5.5 gm weight
  - IOP readings from 20-30 mm Hg, use 7.5 gm weight
  - IOP readings over 30 mm Hg, use 10 gm weight
- Carefully explain the procedure so the patient knows what to expect.

Technique

- Restrictive clothing can alter test results, so make necessary adjustments to clothing and place patient in supine position.
- Elevate the chin slightly so the patient's face is parallel to the floor and the eyes are level.
- The technician should be comfortably seated at the head of the patient.

Technique

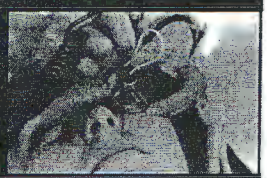
- Place a drop of topical anesthetic in both eyes and direct the patient to fixate on a target point on the ceiling large enough for the patient to easily see.
- The right eye should be tested first.
- Grasp the tonometer with one hand and retract the eyelids with the thumb and index finger of the other hand.
- Caution should be taken NOT to press on the globe, but to hold the lids firmly against the brow and cheekbone.
- Slowly lower the tonometer hand so that the heal of the hand rests on the patient's forehead making sure not to block the patient's fixation.

Technique

- Hold the tonometer over the cornea for about 10 seconds so the patient can become accustomed to the interruption of binocular fixation.
- Carefully lower the tonometer onto the cornea, allowing the sleeve of the tonometer to drop a few millimeters.
- Also, be sure to hold the tonometer so that the tonometer head floats in the middle of the handle ring with as little contact to the ring as possible.
- Avoid tilting the instrument on the cornea for a full 4 minutes.
- The ink stylus will show definite results on the pulsation tracing on the graph.

Technique

- After a 4-minute period, gently lift the tonometer off the cornea and have the patient close their eyes.
- Disassemble the tonometer and clean it.
- Reassemble (with the proper weight) and repeat the procedure for the left eye.



Calculation of Test Results

- Tonographic terms essential in calculating results.
- Po: actual pressure (mmHg) measured with applanation tonometer prior to tonography.
- Pt: initial IOP increase caused by the weight of the Schiotz tonometer when first placed on the eye.
- F: flow of aqueous into the eye per minute measured in microliters. Average is 2.4 microliters per minute.

$$F = Po - Pv \times C$$

Calculation of Test Results

- Pv: episcleral venous pressure which is 11.7.
- C: coefficient of aqueous outflow or the coefficient of facility of outflow.
- Facility of outflow (C) = increase outflow per minute from tonometer weight change during the tonography.
- C values less than 0.18 are suggestive of glaucoma.
- If the number of Po/C is greater than 125, glaucoma is suspected.

Calculation of Test Results

- The result of tonography is to determine if there is a resistance to the facility of aqueous outflow as determined by the value C.
- First identify R1 (initial reading on graph) and R2 (final reading)
- Subtract R2 from R1 to determine the change in R
- Standard tables have been established to determine the C value. Refer to the table corresponding to the correct weight used during the test.

Calculation of Test Results

- Find the value of R1 in the "initial reading" column.
- Locate the column for the change in R (Change in R = R2 – R1).
- Trace down the column to identify the value corresponding to the initial R reading.
- That number represents the C value. (C value of less than 0.18 is suggestive of glaucoma).
- Po/C is determined by dividing the C value into the Po value (initial IOP).
- Po/C values greater than 125 are suggesting of glaucoma.

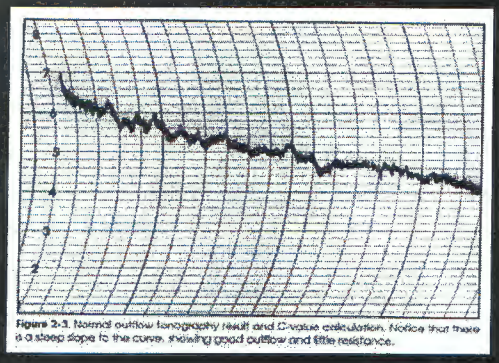


Figure 2-3. Normal outflow tonography result and C-value calculation. Notice that there is a steep slope to the curve, showing good outflow and little resistance.

Normal

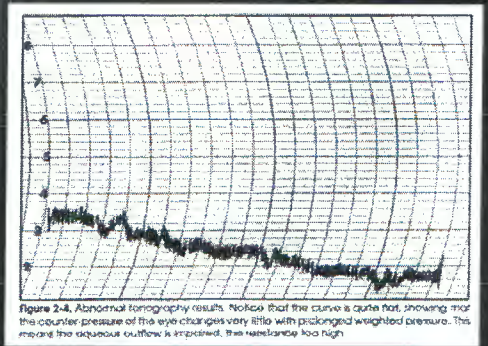


Figure 2-4. Abnormal tonography results. Notice that the curve is quite flat, showing that the counter-pressure of the eye changes very little with prolonged weighted pressure. This means the aqueous outflow is impaired, the resistance too high.

Abnormal – Flat curve

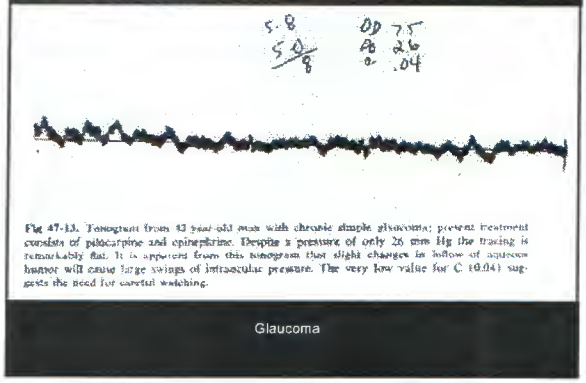


Fig 47-13. Tonogram from 83 year-old man with chronic simple glaucoma; present treatment consists of pilocarpine and epinephrine. Despite a pressure of only 26 mm Hg the tracing is remarkably flat. It is apparent from this tonogram that slight changes in inflow of aqueous humor will cause large swings of intraocular pressure. The very low value for C (0.04) suggests the need for careful watching.

Glaucoma

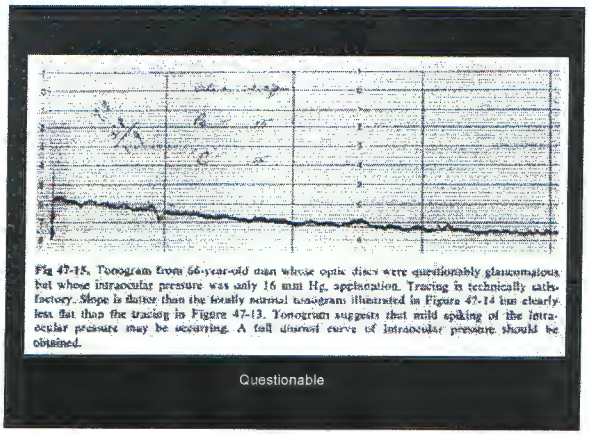


Fig 47-15. Tonogram from 66-year-old man whose optic discs were questionably glaucomatous, but whose intraocular pressure was only 16 mm Hg, applanation. Tracing is technically satisfactory. Slope is flatter than the totally normal tonogram illustrated in Figure 47-14 but clearly less flat than the tracing in Figure 47-13. Tonogram suggests that mild spiking of the intraocular pressure may be occurring. A full diurnal curve of intraocular pressure should be obtained.

Questionable

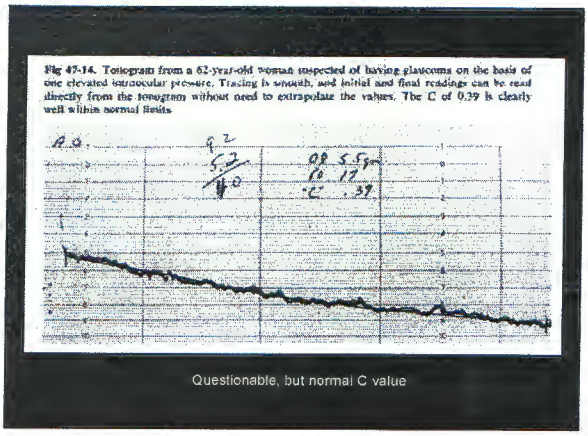


Fig 47-14. Tonogram from a 62-year-old woman suspected of having glaucoma on the basis of one elevated intraocular pressure. Tracing is smooth, and initial and final readings can be read directly from the tonogram without need to extrapolate the values. The C of 0.39 is clearly well within normal limits.

Questionable, but normal C value

Glaucoma Provocative Tests

- Water Provocative Test
  - Done to try to provoke an incompetent outflow filtration mechanism by giving a changed amount of aqueous inflow following a challenge with extra body fluid.
  - Patient is asked to drink from 2 quarts to 1 gallon of water in 15-20 minutes.
  - Over the next 1-2 hours the patient has serial IOPs taken.
  - This serial measurement shows incompetence of aqueous as the pressures rise to a peak, and then start to descend.

Glaucoma Provocative Tests

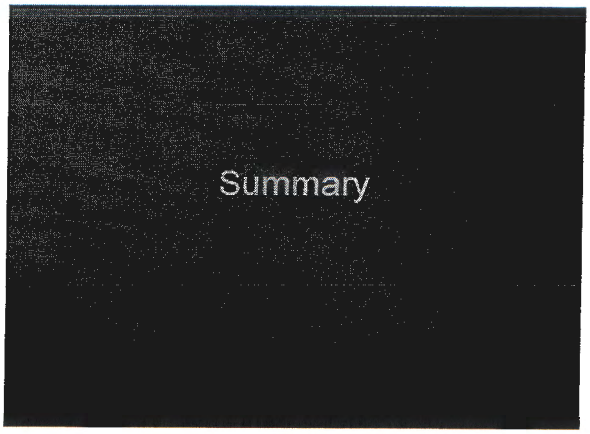
- Prone Provocative Test
  - Designed to look for angle closure and/or open angle glaucoma in whom the prone position and a shifting forward of the lens and iris when the face is down causes IOP to rise.
  - Patients are placed in a dark, quiet room and asked to sit at a table face down on folded arms.
  - Patients should be bend at the waist and head at the same height as their heart.
  - Alternatively, they can lay face down on a flat table surface.

Glaucoma Provocative Tests

- Prone Provocative Test
  - IOP is taken prior to face-down position and again after patient has been in prone position for 45 minutes.
  - Some ophthalmologists also perform gonioscopy after prone testing to see if the angle has changed.
  - Many offices do a combined prone provicative and dark room provocative test.

Glaucoma Provocative Tests

- Dark Room Provocative Test
  - Designed for patients who are angle closure suspects or when open angle glaucoma is thought to worsen related to position of the iris.
  - Room needs to be very dark.
  - Patient is told to remain in the dark with eyes open.
  - This allows the pupils to dilate maximally for an extended period.
  - After 1 hour, the IOP is checked and compared to the pretest pressure.
  - The patient may also be gonioscoped to evaluate any change in angle structure.
  - Alternatively, dilating drops can be used to provoke angle closure attacks under close supervision.


Summary


Volume Control
(by Perfusion Pump)
Pressure Sensor
Smart Contact-Lens Device
w/ Adjustable Fluidic Volume

Figure 9c

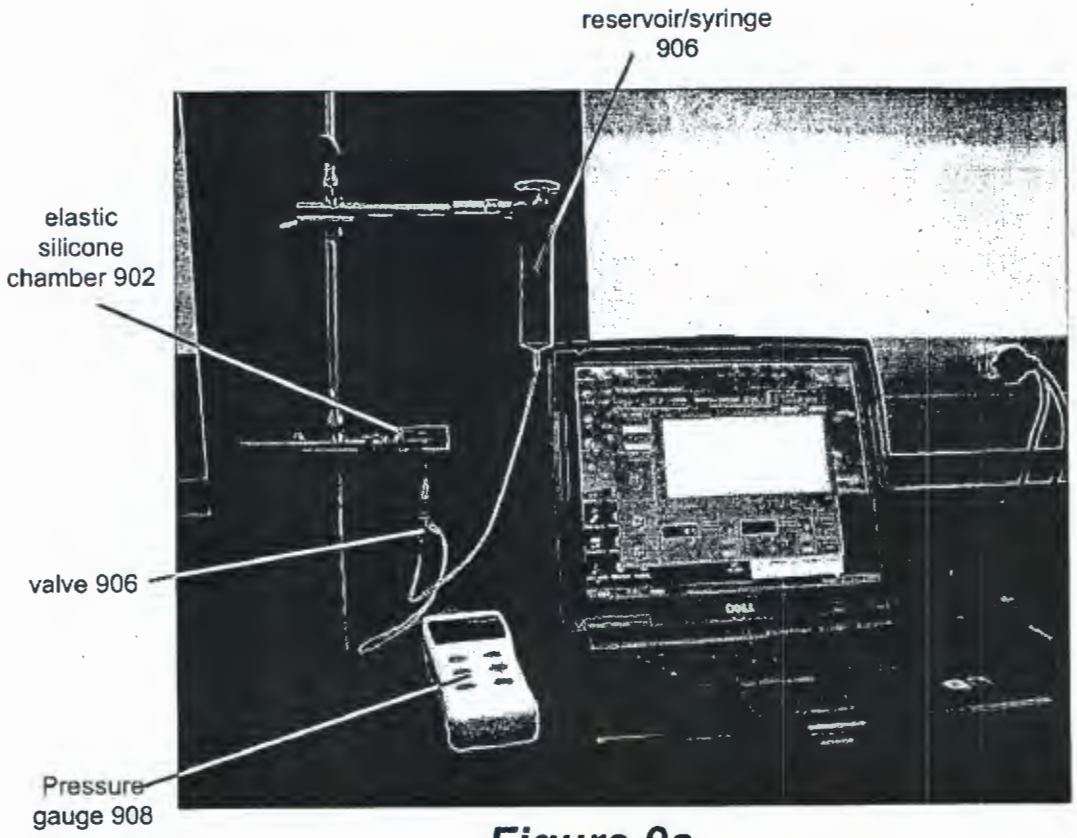


Figure 9a

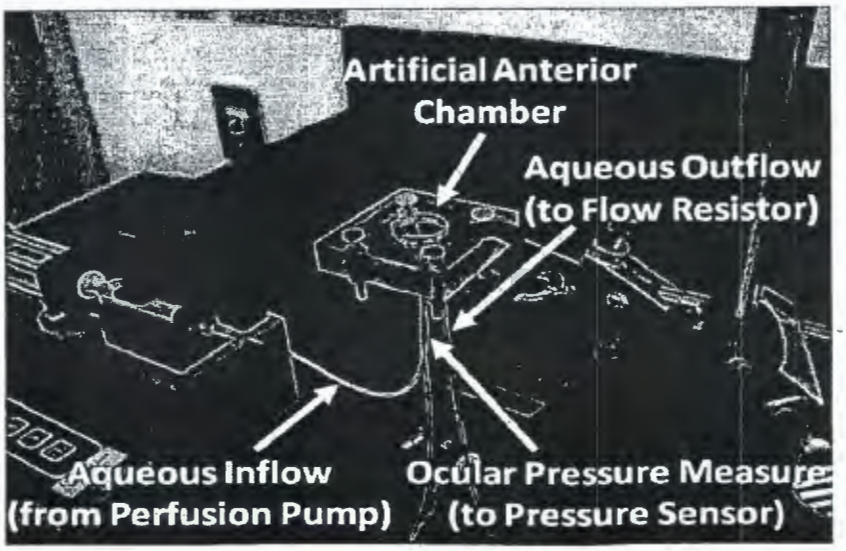


Figure 9b

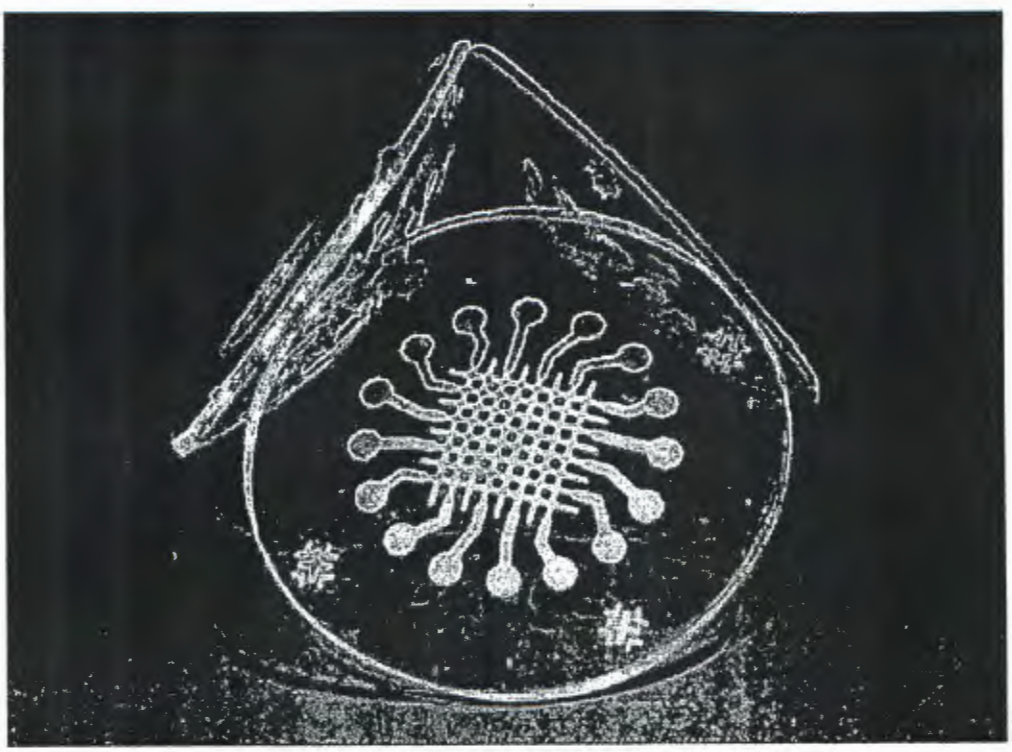


Figure 8b

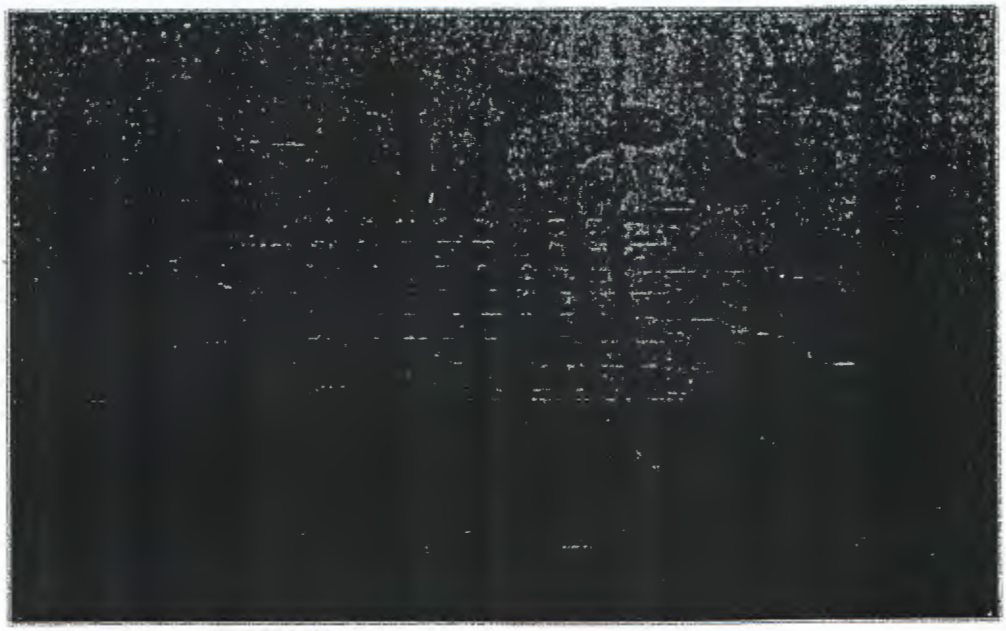


Figure 8c

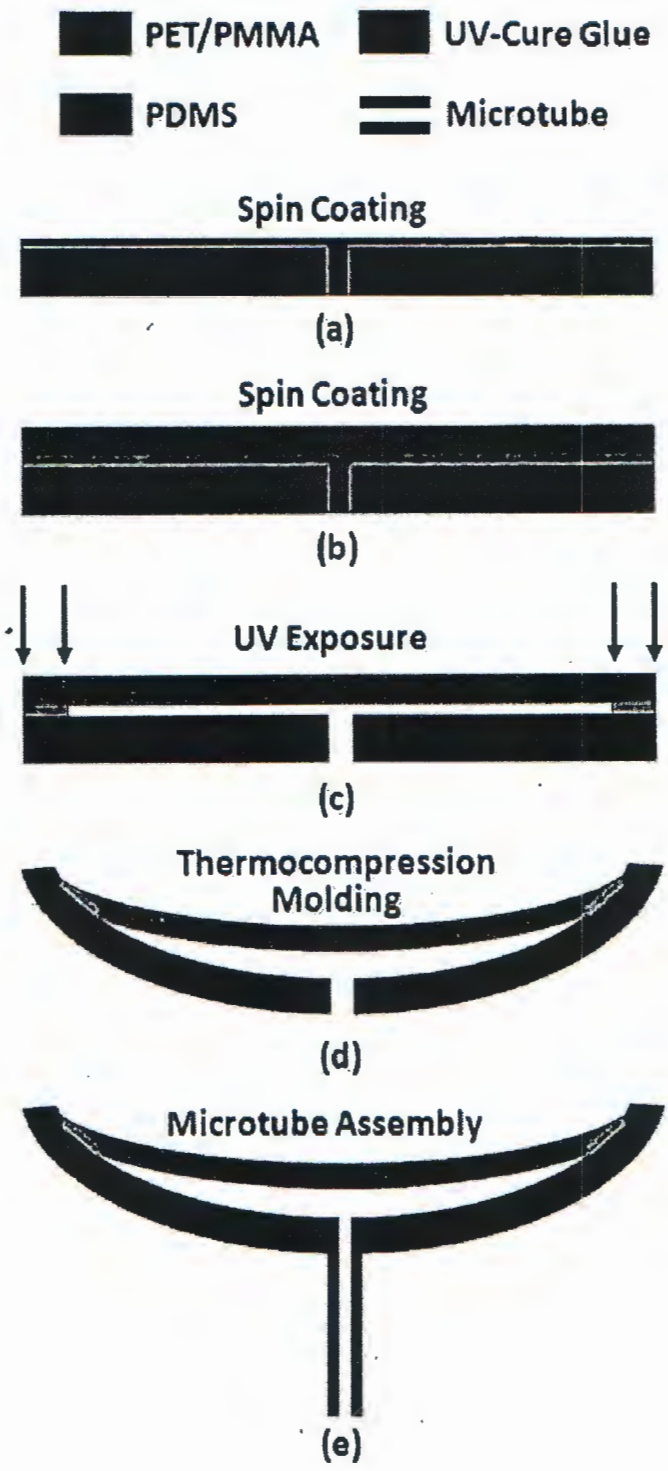

PET/PMMA
UV-Cure Glue
PDMS
Microtube
Spin Coating
(a)
Spin Coating
(b)
UV Exposure
(c)
Thermocompression Molding
(d)
Microtube Assembly
(e)

FIGURE 8a

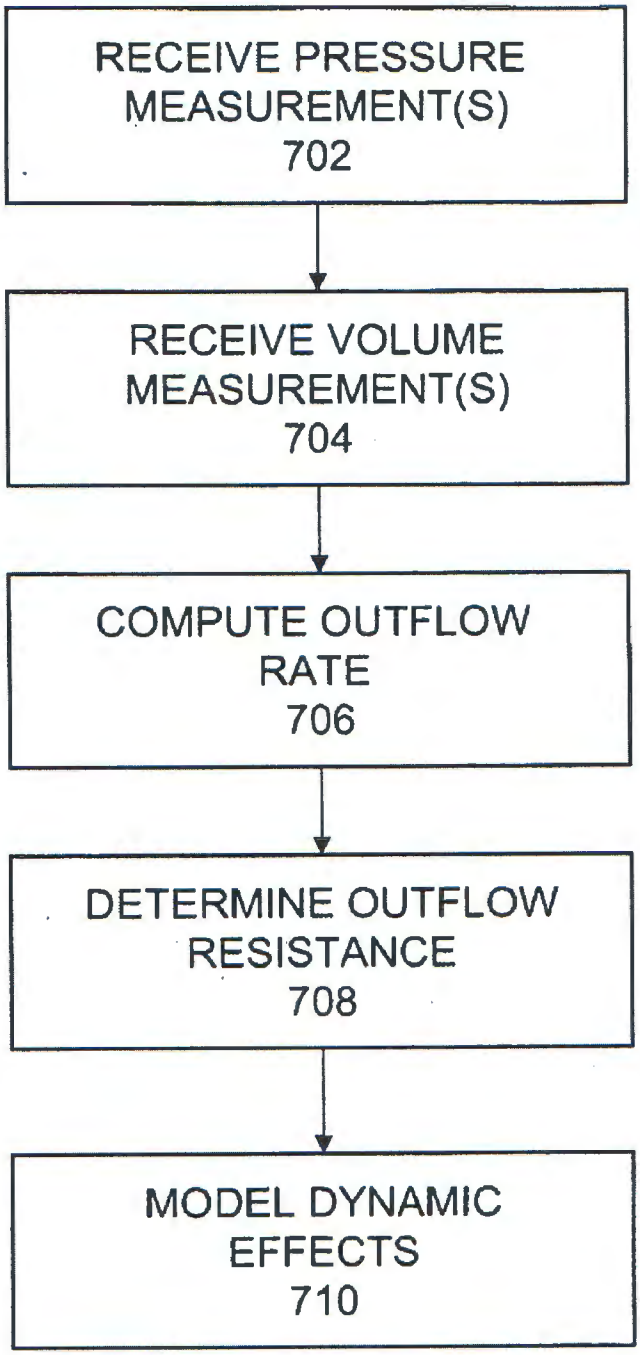

RECEIVE PRESSURE MEASUREMENT(S) 702
RECEIVE VOLUME MEASUREMENT(S) 704
COMPUTE OUTFLOW RATE 706
DETERMINE OUTFLOW RESISTANCE 708
MODEL DYNAMIC EFFECTS 710

FIGURE 7

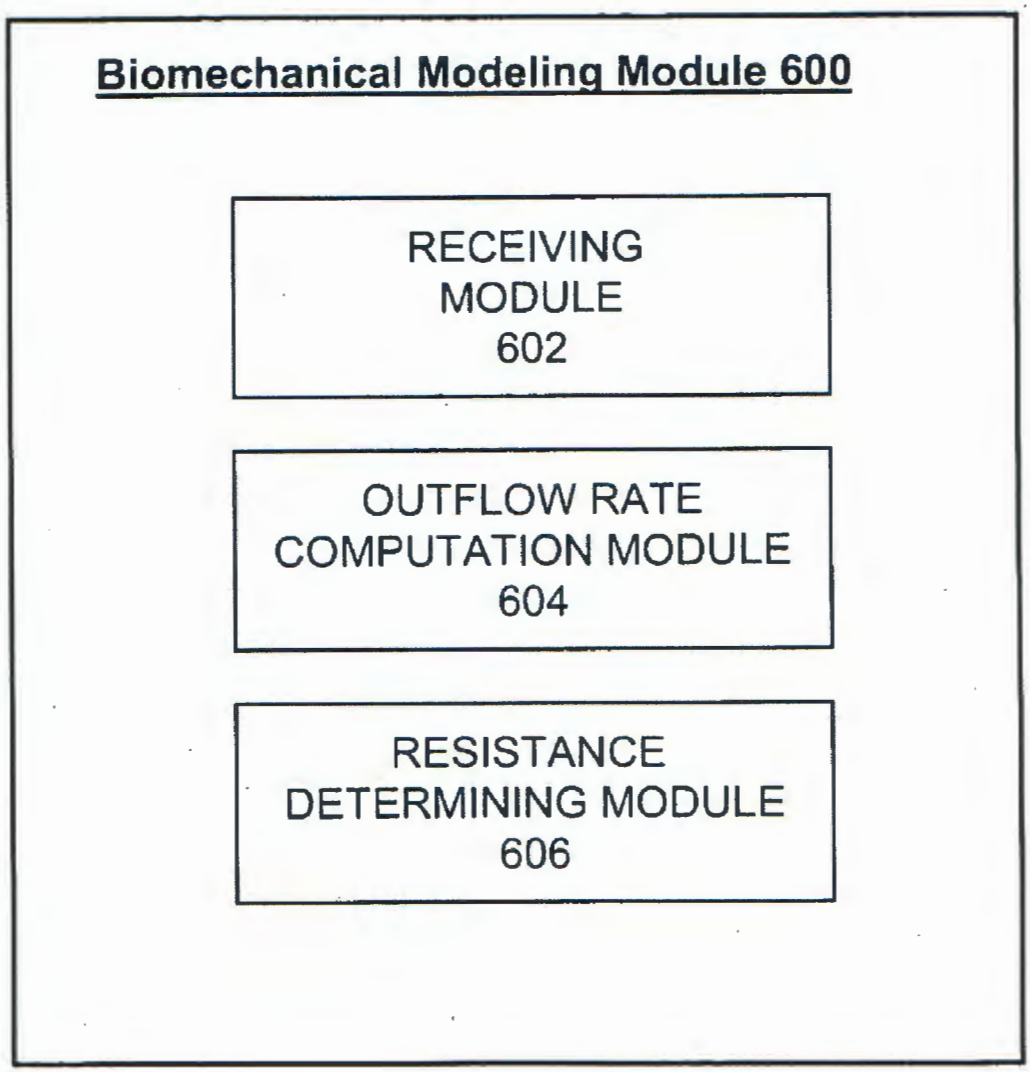

Biomechanical Modeling Module 600
RECEIVING MODULE 602
OUTFLOW RATE COMPUTATION MODULE 604
RESISTANCE DETERMINING MODULE 606

FIGURE 6

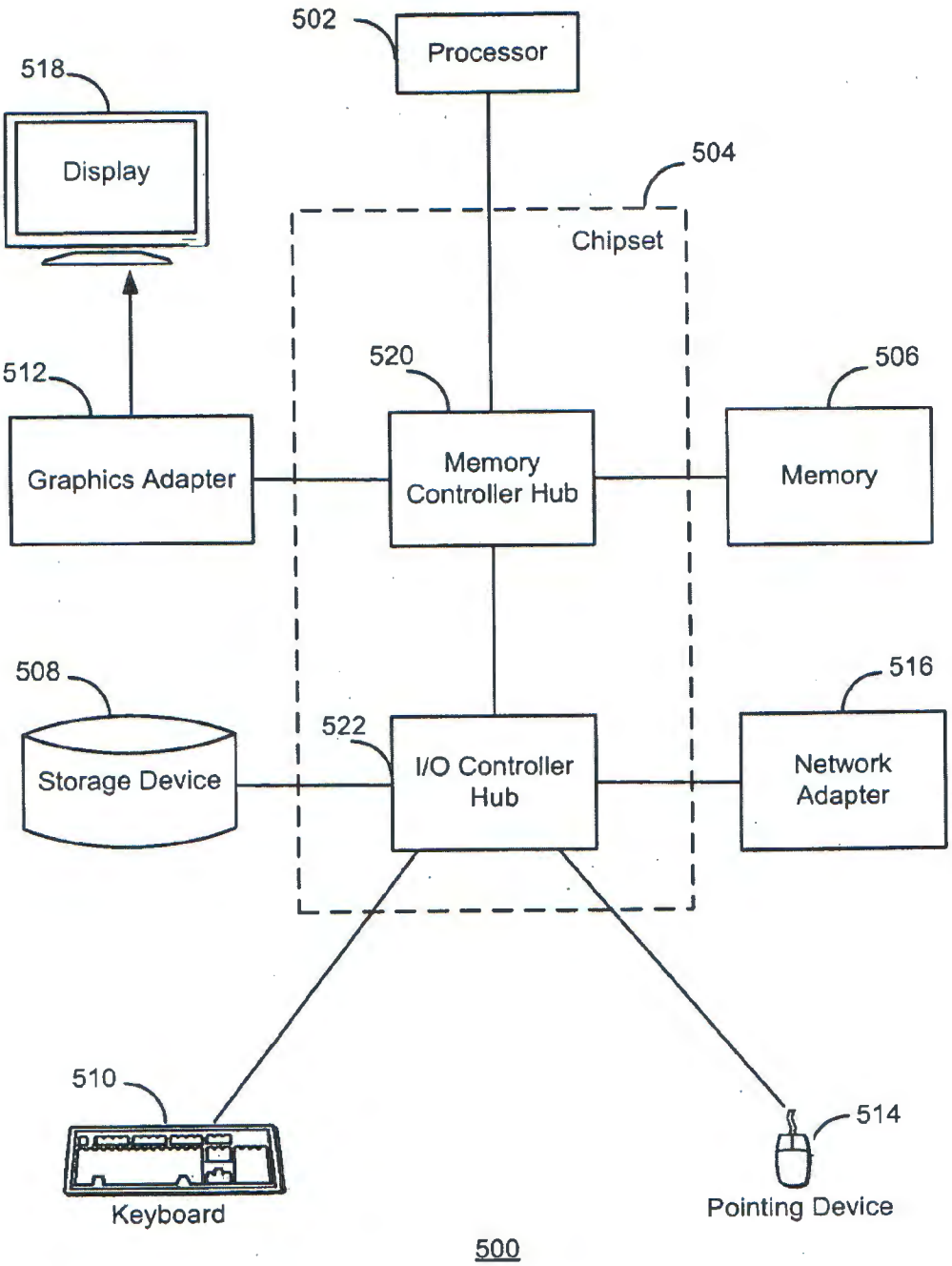

502
Processor
518
Display
504
Chipset
512
520
506
Graphics Adapter
Memory Controller Hub
Memory
508
516
522
Storage Device
I/O Controller Hub
Network Adapter
510
514
Keyboard
Pointing Device
500

FIGURE 5

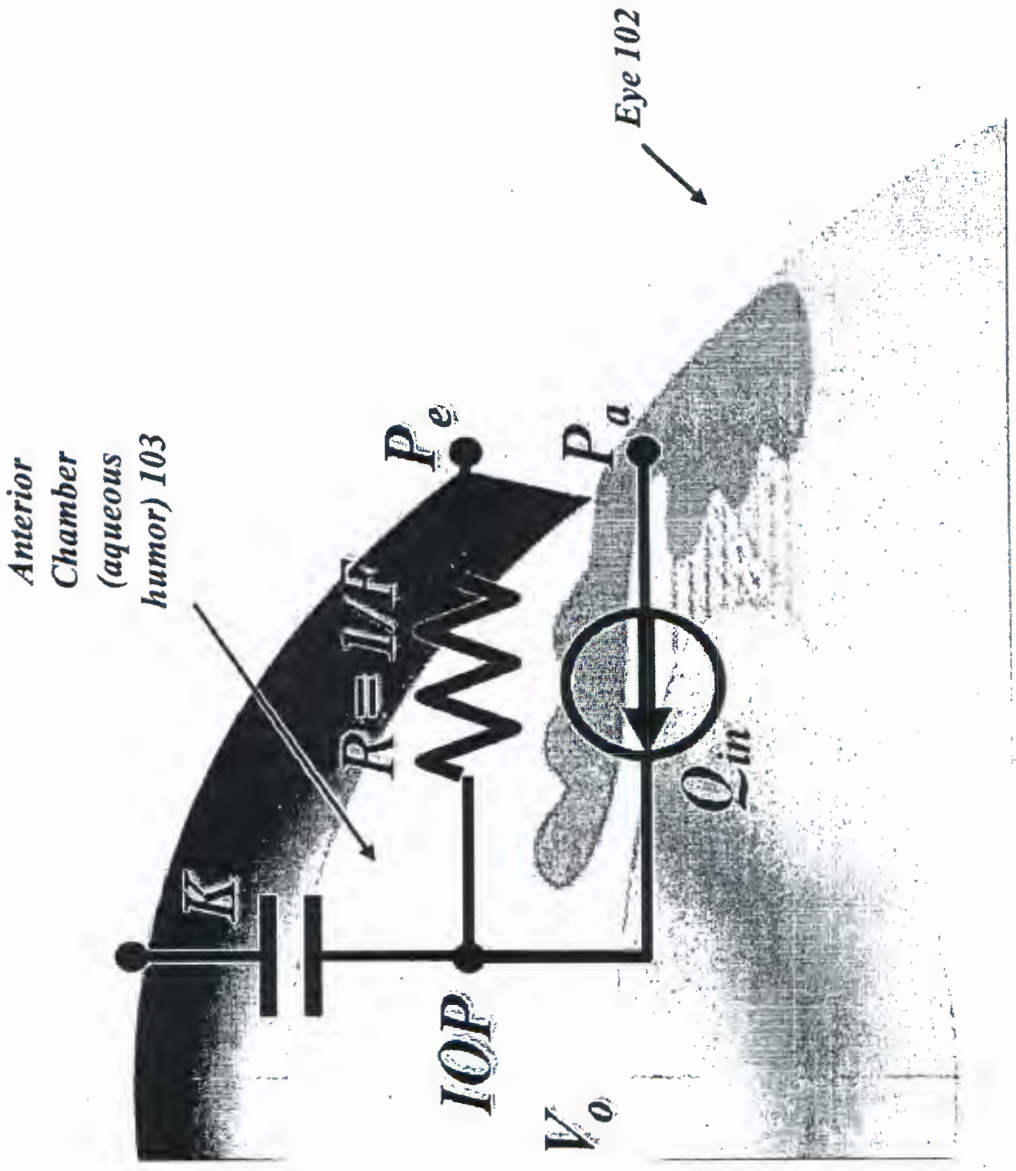
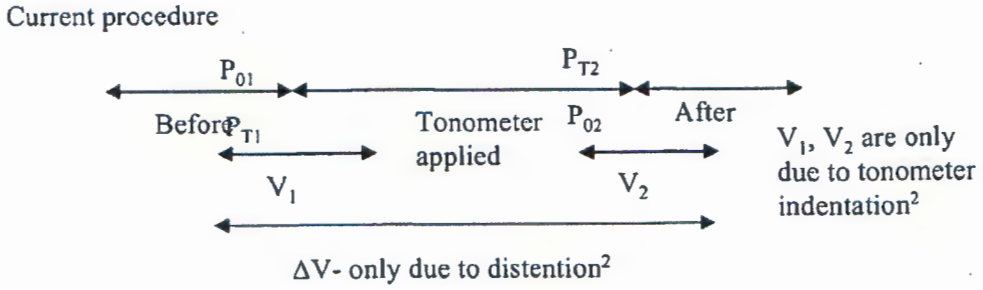

Eye 102
Anterior Chamber (aqueous humor) 103
P_e
P_a
$R = 1/F$
Q_{in}
K
IOP
V_o

Figure 4c



$$\Delta V = 1/K_D * \log(P_{01}/P_{02})$$
$$V_1 = 1/K_T * \log(P_{T1}/P_{01}) \longrightarrow \Delta V = K_T/K_D * (1/K_T * \mathrm{Log}(P_{T1}/P_{T2}) - V_2 + V_1)$$
$$V_2 = 1/K_T * \log(P_{T2}/P_{02})$$

Figure 4a

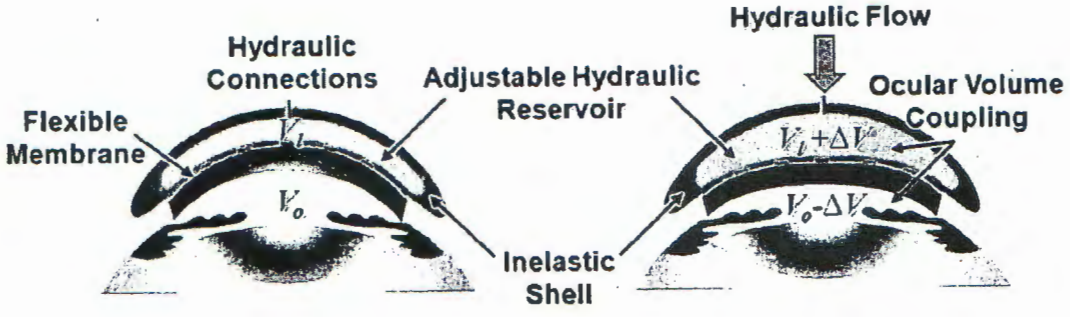


Figure 4b

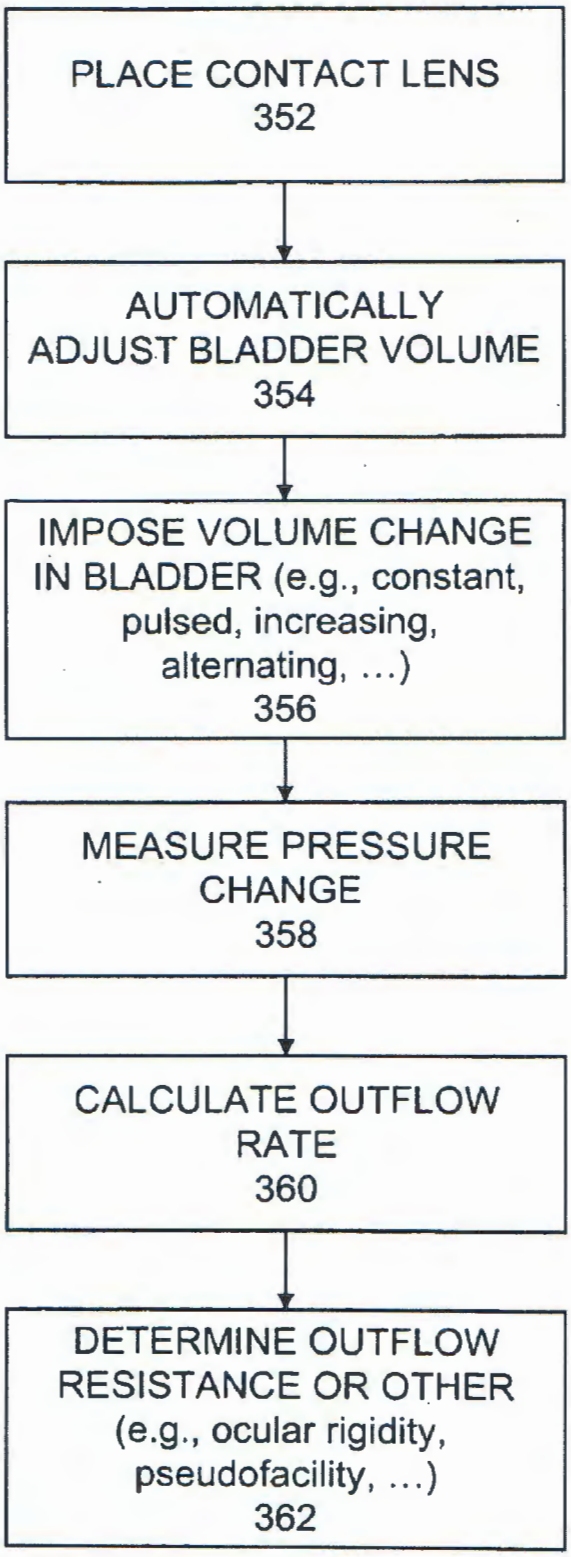

PLACE CONTACT LENS
352
AUTOMATICALLY ADJUST BLADDER VOLUME
354
IMPOSE VOLUME CHANGE IN BLADDER (e.g., constant, pulsed, increasing, alternating, ...)
356
MEASURE PRESSURE CHANGE
358
CALCULATE OUTFLOW RATE
360
DETERMINE OUTFLOW RESISTANCE OR OTHER (e.g., ocular rigidity, pseudofacility, ...)
362

Figure 3b

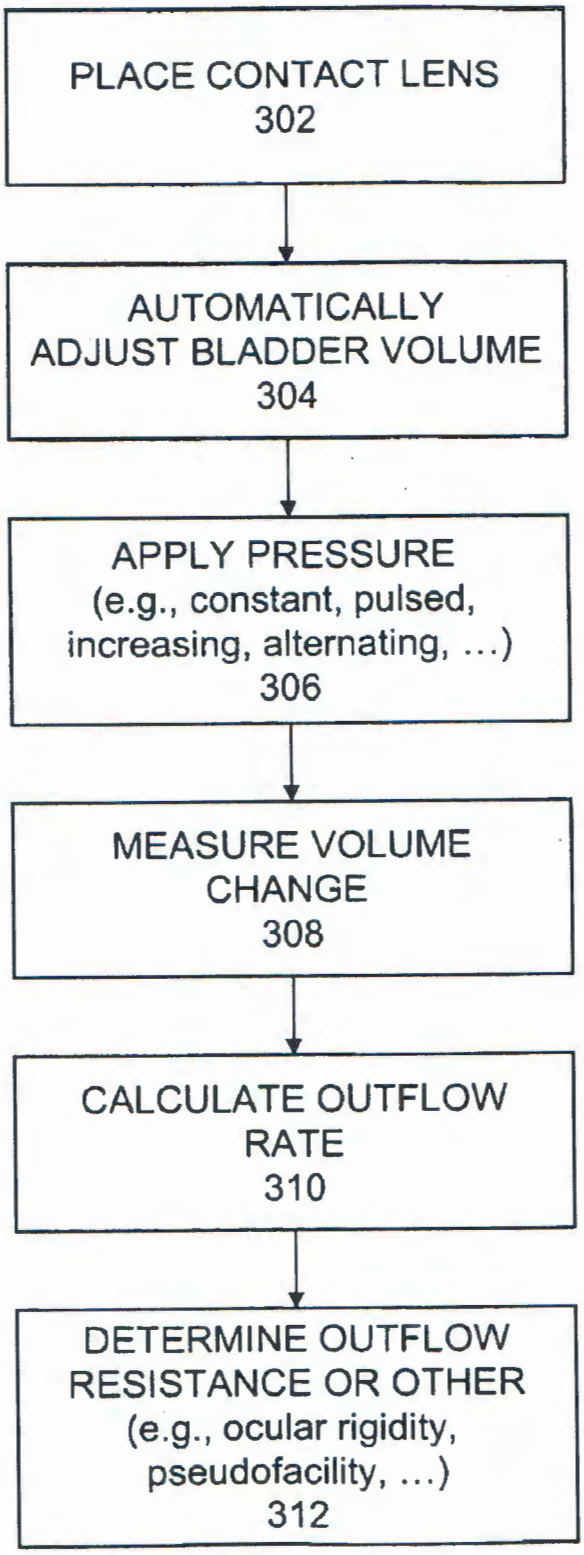

PLACE CONTACT LENS
302
AUTOMATICALLY
ADJUST BLADDER VOLUME
304
APPLY PRESSURE
(e.g., constant, pulsed,
increasing, alternating, ...)
306
MEASURE VOLUME
CHANGE
308
CALCULATE OUTFLOW
RATE
310
DETERMINE OUTFLOW
RESISTANCE OR OTHER
(e.g., ocular rigidity,
pseudofacility, ...)
312

Figure 3a

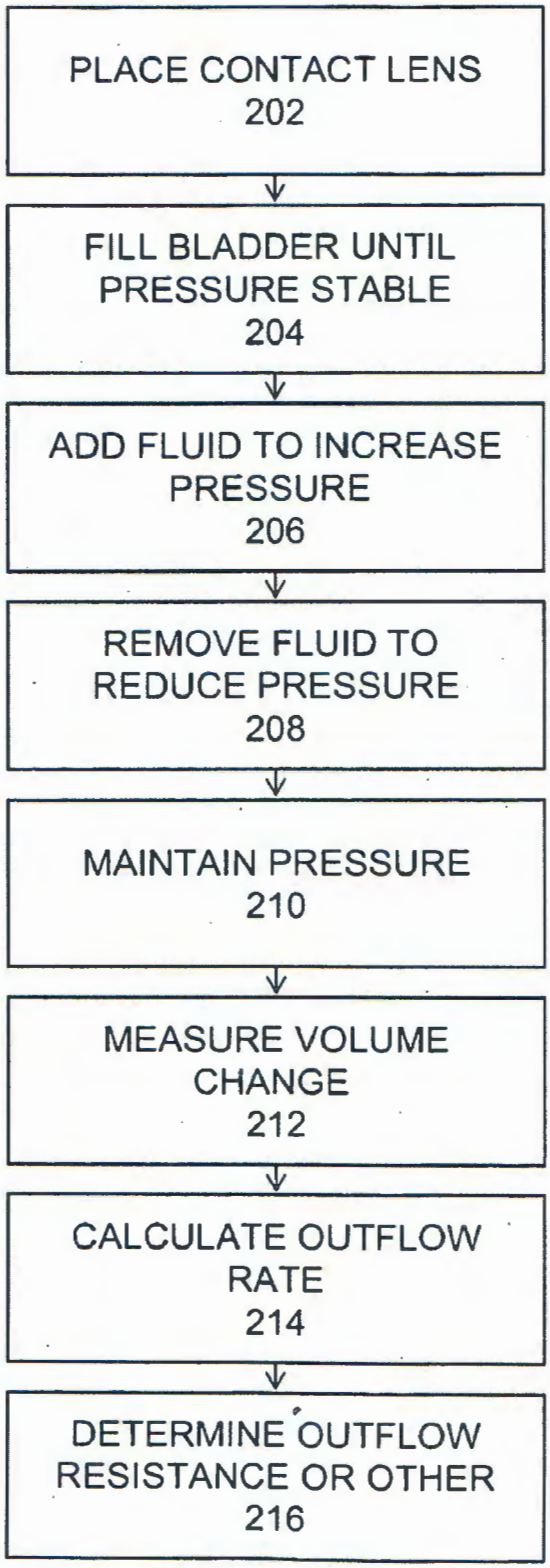

PLACE CONTACT LENS
202
FILL BLADDER UNTIL PRESSURE STABLE
204
ADD FLUID TO INCREASE PRESSURE
206
REMOVE FLUID TO REDUCE PRESSURE
208
MAINTAIN PRESSURE
210
MEASURE VOLUME CHANGE
212
CALCULATE OUTFLOW RATE
214
DETERMINE OUTFLOW RESISTANCE OR OTHER
216

Figure 2

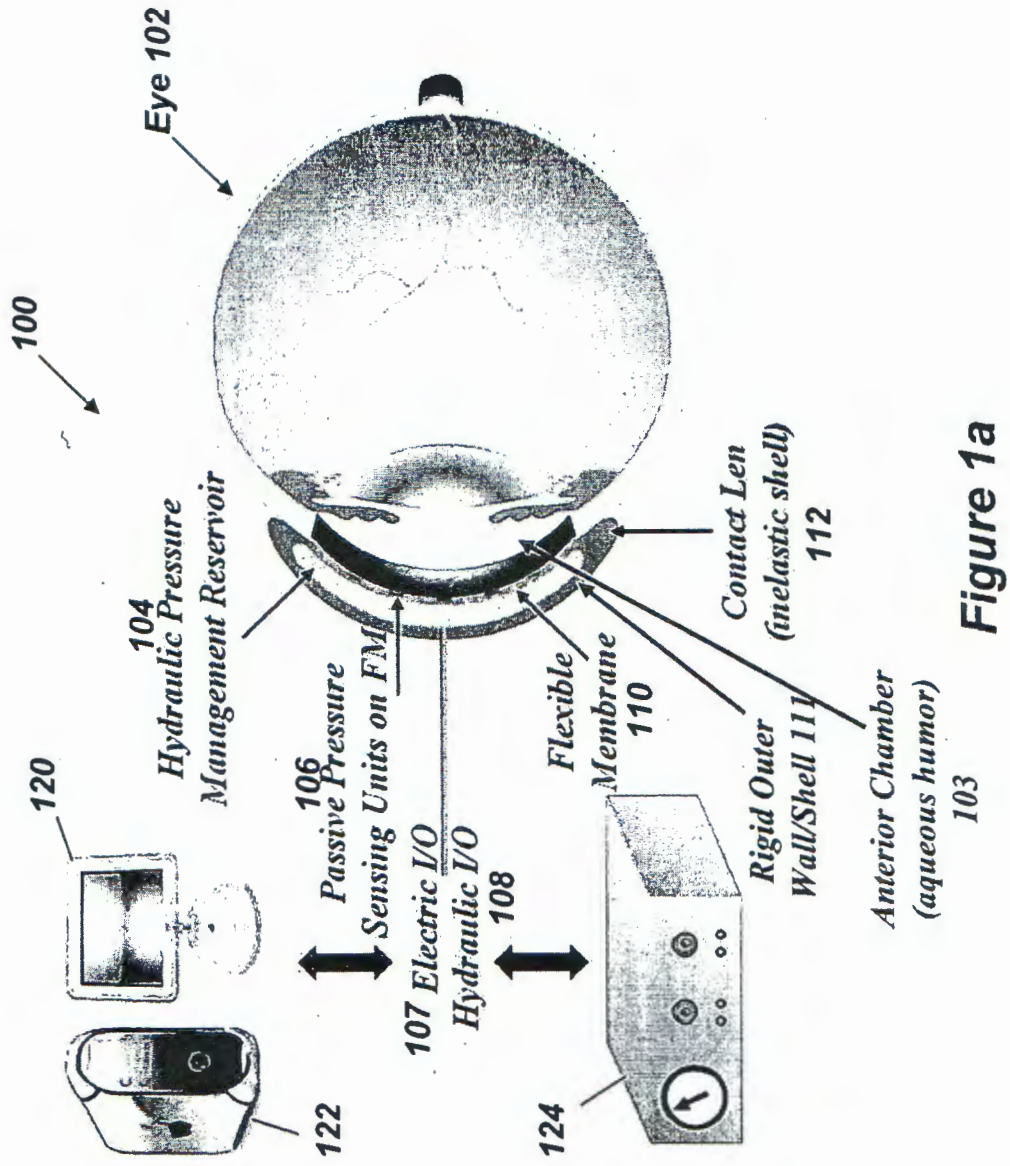

Eye 102
100
104
Hydraulic Pressure
Management Reservoir
106
Passive Pressure
Sensing Units on FM
107 Electric I/O
Hydraulic I/O
108
Flexible
Membrane
110
Contact Len
(inelastic shell)
112
Rigid Outer
Wall/Shell 111
Anterior Chamber
(aqueous humor)
103
120
122
124

Figure 1a

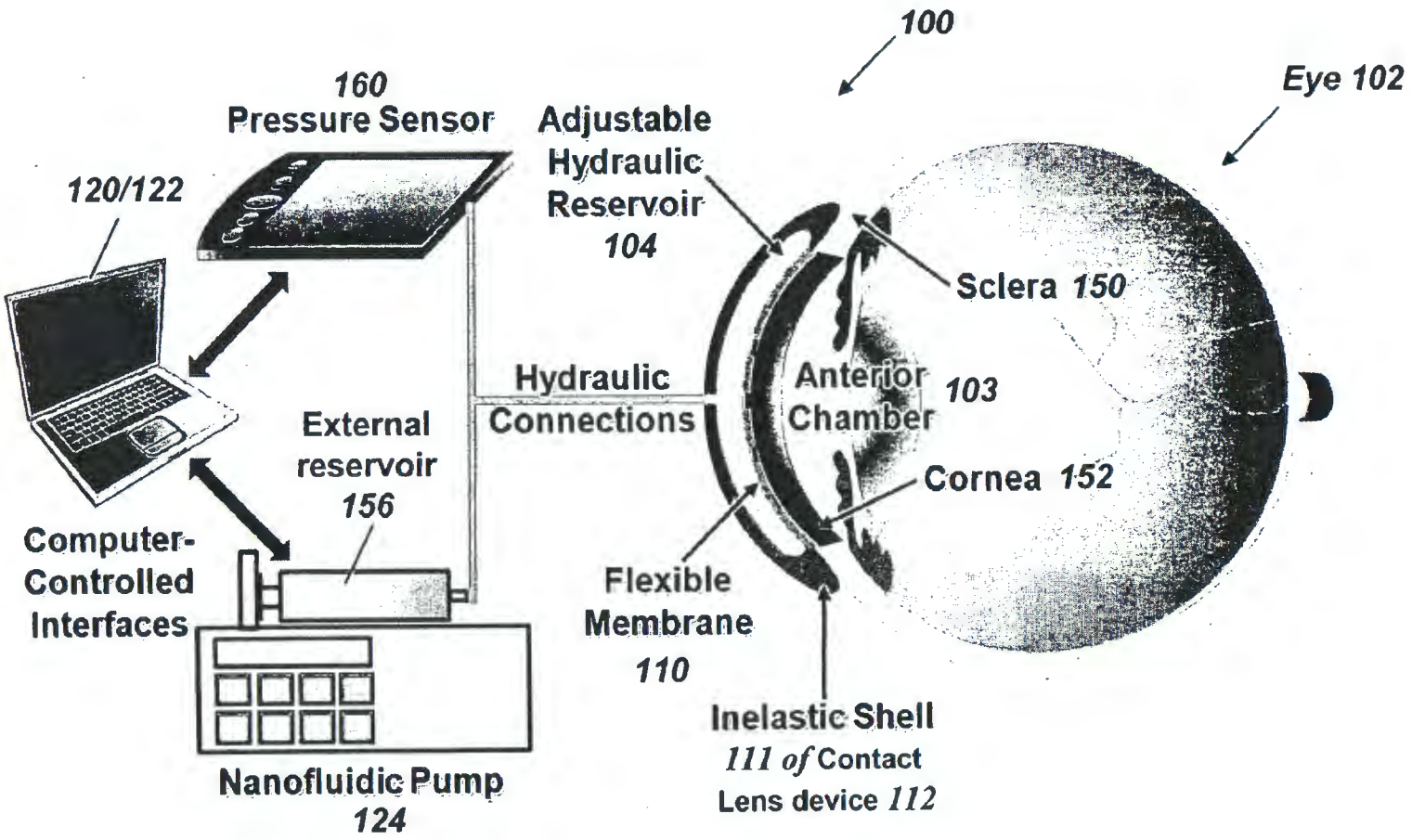

100
160
Pressure Sensor
Adjustable
Hydraulic
Reservoir
104
Eye 102
120/122
Sclera 150
Hydraulic
Connections
Anterior
Chamber
103
External
reservoir
156
Cornea 152
Computer-
Controlled
Interfaces
Flexible
Membrane
110
Inelastic Shell
111 of Contact
Lens device 112
Nanofluidic Pump
124

Figure 1b

15. The system of claim **12**, wherein the hydraulic unit is configured to control filling of the bladder with fluid to increase pressure on the eye and is configured to control removal of fluid from the bladder to decrease pressure on the eye.

16. The system of claim **12**, wherein the hydraulic unit comprises a volume sensor for directly measuring change in the volume of fluid in the bladder as a proxy for fluid outflow from the eye, the hydraulic unit being coupled to the bladder via micro-tubing through which fluid flows to and from the bladder.

17. The system of claim **12**, wherein the logic further comprises logic for using a biomechanical model of the eye to model dynamic effects, the model being used in conjunction with experimental data to determine the outflow resistance and an ocular rigidity of the eye.

18. The system of claim **12**, further comprising a computer interface for monitoring nanoliter volume displacement in the eye, represented by volume change in the bladder over time.

19. A computer program product for measuring an outflow resistance of an eye, the computer program product comprising a computer-readable storage medium containing computer program code that comprises:

receiving a pressure measurement representing an applied pressure to an eye;

receiving a set of volume measurements representing a directly measured volume change of the eye created by the applied pressure to the eye;

computing an outflow rate of fluid from the eye based on the measured volume change of the eye over time; and

determining the outflow resistance of the eye as a function of a ratio of the applied pressure and the outflow rate, and using a biomechanical model of the eye to model dynamic effects.

20. The computer program product of claim **19**, wherein the model uses the set of volume measurements and the pressure measurement to calculate the outflow resistance or facility of outflow and an ocular rigidity of the eye.

21. The computer program product of claim **19**, wherein receiving the pressure measurement further comprises receiving the pressure measurement from a device with an inflatable bladder placed in the eye having a flexible membrane contacting the eye, the device being coupled to a pressure sensor for measuring the applied pressure.

22. The computer program product of claim **19**, wherein the volume measurements received are based on a change in volume of fluid in the inflatable bladder as a proxy for a change in volume of fluid in the eye over time.

* * * * *

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CLINICAL MEASUREMENTS OF AQUEOUS OUTFLOW

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BOSTON

IT IS THE purpose of this paper to report certain observations on facility of outflow and rate of formation of aqueous humor in human beings. Special consideration will be given to those changes which are concerned in the pathogenesis of glaucoma. The basis for this report is provided by measurements made on patients' eyes by means of a tonographic method, already published.[1] Approximately 1,000 of these measurements have been made on 600 clinically examined eyes, a majority of which were glaucomatous.

This study makes available a quantitative method of evaluating glaucoma. Specifically, it enables one to evaluate the respective roles of resistance to outflow and rate of formation of aqueous humor. This possibility has apparently not previously been explored in the manner of the present study. Previous investigations of aqueous outflow have yielded information only in terms which have left it undetermined whether the changes which were detected in outflow resistance represented a major or a minor influence in producing variations in the intraocular pressure in glaucoma. Thus, the literature contains many unresolved conjectures as to whether various sorts of glaucoma might be due to obstruction of outflow or to hyperformation of aqueous humor, or to both.

METHOD

The method by which resolution of this uncertainty has been sought in the present study is as follows: The amount of resistance to, or, inversely, the facility of, escape of aqueous from the eye has been determined by allowing an electronic Schiøtz tonometer to rest for four to five minutes on a patient's topically anesthetized cornea, an initial increase in the intraocular pressure caused by the weight of the tonometer being followed by a slow fall toward the original pressure as the aqueous is expressed from the eye at a greater than original rate. The whole performance of the eye during the four to five minutes under these conditions is recorded automatically from the electronic tonometer on a moving-paper electrocardiograph strip in terms of the amount of indentation of the eye by the tonometer. The data obtained in this manner are then converted into terms of actual intraocular pressure, increment of intraocular pressure due to the weight of the tonometer, and change in ocular volume. The rate of change in these factors with time permits calculation of the rate of expression of aqueous due to the artificially increased pressure. The relation between these last terms, i. e., the relation of pressure to rate of aqueous loss, defines physically and quantitatively one of the factors, the facility of aqueous outflow, which govern the steady-state intraocular pressure. For convenience,

From the Howe Laboratory of Ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary.

Read before the Section on Ophthalmology at the One-Hundredth Annual Session of the American Medical Association, Atlantic City, N. J., June 14, 1951.

1. Grant, W. M.: Tonographic Method for Measuring the Facility and Rate of Aqueous Flow in Human Eyes, Arch. Ophth. **44**:204-214 (Aug.) 1950.

this facility of aqueous outflow is expressed as a coefficient in units of cubic millimeters per minute per millimeter of pressure (Hg). The third factor, the rate of aqueous formation, in the relation of intraocular pressure, facility of aqueous outflow, and rate of aqueous formation is calculated from the first two measured quantities. It is considered that the rate of outflow is a simple function of the pressure and that if C cu. mm. of aqueous is found to escape per minute per millimeter of pressure and the intraocular pressure is P mm. in the steady state, the net rate of flow of aqueous, or the equivalent rate of formation, is $(P - 4)$ times C cu. mm. per minute.[2]

However, it is to be noted that determination of the facility of aqueous outflow and of the net rate of flow by the tonographic method is predicated on the existence of an essentially steady state, i. e., equal rates of formation and outflow and constant intraocular pressure, before the measuring procedure is applied. If the intraocular pressure is changing before the measurement is begun, an error is introduced which is a function of the rate of spontaneous change of intraocular pressure. The error is considerably worse for the value of net rate of flow than for the facility of outflow.

The calibration data which have been employed in the conversion of the recorded data into terms of intraocular pressure are those which in 1950 Dr. Jonas S. Friedenwald regarded as his best and generously made available for the present investigation, although they had not been published. He has referred to this as his "absolute" calibration. The changes in ocular volume, similarly, have been calculated from his data, utilizing his equations and his constant in relating ocular volume and pressure in the presence of distortion by the Schiøtz tonometer.

The limitations of the method employed in this study appear to be determined primarily by the limits of accuracy of tonometric measurement and calibration. The uncertainties arise in some degree from purely instrumental problems of sensitivity and accuracy, but in larger degree from the problems of instrumental calibration in terms of pressure and volume change in a biologically variable structure such as the eye. Although the best available calibration data have been utilized, the physical and mathematical aspects of the application and extension of these data are extremely complex and fraught with a variety of uncertainties: Some reassurance of justification in the manner in which Friedenwald's data have been employed has been obtained from the preliminary results of an independent experimental evaluation, in which measurements on enucleated human eyes have indicated reasonable conformity of calculated and experimentally determined values for pressure and volume. Whether there may be some moderate absolute error affecting equally the values for facility of aqueous outflow and those for rate of aqueous formation is not of serious import in the present clinical investigation, since the interpretations which are made here are based primarily on comparison of values for different types of eyes rather than on absolute values. Unfortunately, both absolute and comparative values from patient to patient may be affected by variations in the coefficient of scleral rigidity among the population. This factor can be measured and corrected for in the calculations, but in the present series of cases it has not always been feasible to evaluate the scleral rigidity adequately. Instead, in order to minimize the error from this source, conclusions have been based on measurements of a sufficiently large number of eyes to permit some

2. A simple proportionality between the intraocular pressure and the rate of escape of aqueous from the eye has been found to hold experimentally in human and rabbit eyes post mortem from a pressure of 50 mm. Hg down to approximately 4 mm. Hg, although the simplest physical relation which one might have expected, envisaging fixed escape channels, would have been a proportionality with the square root of the pressure. This experimentally determined deviation from the physical square-root law suggests, in conformity with Thomassen's observations on aqueous veins (Thomassen, T. L.: On the Exit of Aqueous Humor in Normal Eyes, Acta ophth. **28**:479-487, 1950), that in the eye an increasing number of channels for outflow open up with increasing pressure. It is unfortunate that the low-pressure limit at which aqueous outflow may cease in the living eye has not been directly determinable and that it has been necessary to use the value obtained in eyes post mortem. However, this factor is not a consideration in the determination of the facility of outflow. Only the absolute values for rate of formation would be influenced by a change in the value for the low limit, and, within reasonable margins of error, the principal conclusions of this paper would not be altered.

statistical validity despite the expected individual variations. An additional factor which must be considered in assessing the reliability of the values obtained by the tonographic method, and one which at present is rather difficult to evaluate fully, is the possibility that the measuring procedure itself might alter the very factors which it is intended to measure. From the evidence so far available it seems that this effect must ordinarily be small, although it may conceivably become significant in certain types of eyes. This potential source of error may presumably be minimized by employing the smallest possible weight.

Interference from excessive eye movement may occasionally vitiate a measurement and necessitate its discard. Transient circulatory variations may occasionally influence the intraocular pressure during tonography, but the evidence so far available indicates that tonographic determination of aqueous outflow does not fundamentally involve vascular phenomena. In general, any transient extraneous interference in tonographic measurement is detectable by inspection of the paper-strip recording. An estimate of the reliability can be obtained from the smoothness of the curve. In the event of small irregularities, improvement in reliability has been sought by prolonging the period of measurement.

Considering all the various limitations which have been listed, and the variability of results in individual normal eyes, it appears that only differences of more than 20% in values obtained for the coefficient of facility of aqueous outflow should be regarded as significant. In all cases in the present study, conclusions have been based on measured changes considerably greater than this. Individual differences in values for rate of aqueous formation are considered significant only if greater than approximately 40%. Future improvements in accuracy of calibration, formulation, and instrumentation will undoubtedly alter the present values numerically, but I believe that such changes will not be of a magnitude to affect the validity of conclusions based on the present data.

RESULTS

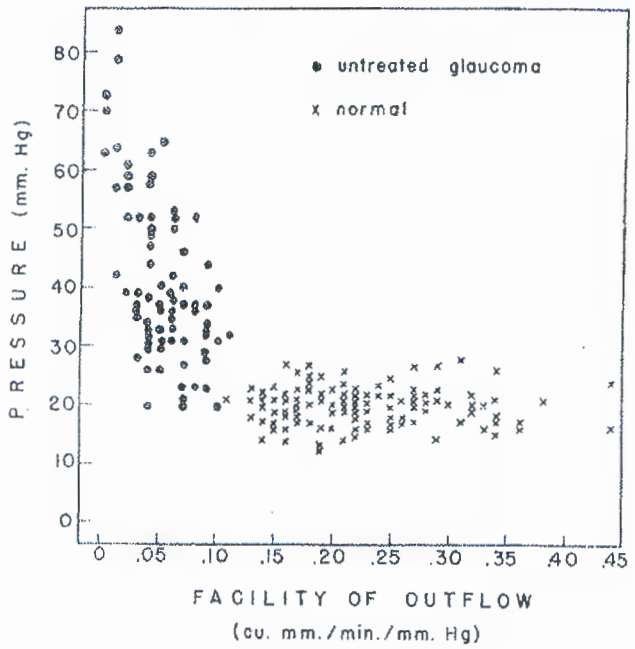
The 600 human eyes on which tonographic measurements were made have been divided into several clinically distinctive groups for characterization. Some of the eyes have been measured only a single time, but many have been measured at several stages of glaucomatous involvement or at different stages in treatment, and this has proved particularly informative.

Normal Eyes.—One hundred and eighteen normal eyes have now been measured, and an average facility of outflow of 0.22 cu. mm. per minute per millimeter of pressure has been found, with individual values ranging from 0.11 to 0.44 cu. mm. The distribution is shown in the accompanying chart. The normal net rate of flow, or rate of formation of aqueous, was estimated by the present method to average 2.4 cu. mm. per minute, with a range of from 1.1 to 5.3 cu. mm. Age has not been found to be a factor in determining either facility of outflow or rate of formation.

Aphakic Eyes.—A relatively slight, and possibly insignificant, difference from the normal is found in eyes which have had uncomplicated cataract extractions. In 10 well-healed aphakic eyes most of which had had intracapsular extractions with iridectomy, the average value for facility of aqueous outflow was 0.19 cu. mm. per minute per millimeter of pressure, as compared with 0.22 cu. mm. for normal eyes, and the average rate of aqueous formation was 2.0 cu. mm. per minute, as compared with a normal of 2.4 cu. mm. The range of variation of the individual values was similar to that of normal eyes.

A general comparison of normal eyes with untreated glaucomatous eyes may be of some interest before the findings in individual types of glaucoma are discussed. A suitable comparison can be made with the random collection of 75 eyes in the present series which had definite clinical diagnoses of glaucoma of all types but which were untreated at the time of measurement, except for a few eyes on which the measurements were made during a remission and which will be discussed subsequently. In

this heterogenous group of glaucomatous eyes the facility of aqueous outflow ranged from 0 to 0.11 cu. mm. per minute per millimeter of pressure, and the rate of formation, from practically 0 to 3.5 cu. mm. per minute, with an average of 1.5 cu. mm. per minute. By comparison of these values with the corresponding values for normal eyes, and by inspection of the chart, in which the relation of the intraocular pressure, expressed according to the standard clinical scale, and the facility of aqueous outflow is shown for both normal and untreated glaucomatous eyes, certain differences between these two groups are apparent. The glaucomatous eyes consistently have a poorer facility of aqueous outflow, i. e., a greater resistance to outflow, than the normal eyes, and the rate of formation of aqueous is not increased in the glaucomatous eyes, but, on the average, appears to be somewhat less than in the normal eye.[3] In all untreated glaucomatous eyes in this group, as well as in approxi-



Comparison of the intraocular pressure and facility of aqueous outflow in 118 normal eyes and 75 untreated glaucomatous eyes.

mately 150 additional glaucomatous eyes of various types, which are to be discussed subsequently, all elevations of the intraocular pressure were adequately accounted for by the degree of increase of resistance to aqueous outflow; and, contrary to popular belief, in no case was the glaucoma attributable to hyperformation of aqueous.

3. It may be further deduced that the increased resistance to outflow is of a frictional sort, and that glaucoma is not ordinarily produced by an antecedent elevation of pressure in the veins receiving the aqueous outflow, for, by the methods of measurement and calculation employed in this study, an elevation of the low-pressure limit for outflow in glaucomatous eyes would have caused the values obtained for rate of formation of aqueous to be higher, rather than somewhat lower, than normal.

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The difference which has been observed between the facility of aqueous outflow of normal eyes and that of glaucomatous eyes suggests that evaluation by tonographic measurement may be of some significance in early diagnosis or in determination of predisposition to glaucoma. Preliminary results indicate this to be the case in primary wide-angle glaucoma, but a considerably longer period of observation will be necessary before a definite assessment of the prognostic value can be made. This is to be the subject of a future communication.

Narrow-Angle Glaucoma.—In the acute form, narrow-angle glaucoma provides a striking correlation of tonographic findings with other clinical observations, particularly the appearance of the angle of the anterior chamber with the gonioscope. In each of 10 eyes with acute narrow-angle glaucoma, with pressures ranging from 79 to 49 mm., marked obstruction to aqueous outflow was indicated by the very small values which were obtained for the facility of outflow—0.01 to 0.06 cu. mm. per minute per millimeter of pressure. This abnormal resistance to outflow was great enough in all instances to account for the whole rise in pressure without necessity of postulating any hyperformation of aqueous. In fact, the calculated rate of formation was uniformly somewhat low, ranging from 0.5 to 2.9 cu. mm. and averaging 1.8 cu. mm. per minute. In all of these eyes which it was possible to examine with the gonioscope the angle of the anterior chamber was seen to be closed by forward displacement of the periphery of the iris. These findings were entirely consistent with the concept that obstruction to aqueous outflow and the associated elevation of tension in acute narrow-angle glaucoma are due to blockage of the channels for aqueous outflow by the iris in the angle. Additional evidence for this mechanism was provided by measurements and observations which were made on 15 eyes during and after treatment for acute narrow-angle glaucoma. When the angle was caused to open up either by iridectomy or by use of miotics, as ascertained by gonioscopy, the facility of aqueous outflow returned to normal and the tension was normalized, except in those cases in which bands of peripheral anterior synechia had formed. In these instances, in which the disease was converted to a chronic form by formation of synechias, obstruction to aqueous outflow was found to persist somewhat in proportion to the synechial involvement of the angle. In a small number of eyes which had suffered an acute attack of narrow-angle glaucoma and had been successfully relieved by miotics, it was observed that the tension thereafter could remain normal for a period without further treatment, but these eyes were, of course, vulnerable to further attacks. During the period of such remission the angles appeared open, though very narrow, and the facility of aqueous outflow was found to be normal.

The companion eyes of those having acute narrow-angle glaucoma were observed in 13 instances to have extremely narrow, but open, angles, and in these eyes the facility of aqueous outflow and the intraocular pressure were normal. However, evidence that these companion eyes were also susceptible to development of acute glaucoma was obtained from observation of a subsequent change to obstructed outflow, with closed angle and high pressure in several instances. In one such instance measurements were made immediately before, during, and after an acute attack. Before the attack the facility of outflow and the tension were normal, but a few minutes later the tension began to rise rapidly and reached 70 mm. within 45 min. At this stage, although the pupil remained constantly at 3.5 to 4 mm. in diameter.

the iris was seen gonioscopically to be bulging forward in the periphery into contact with the back of the cornea, and the facility of aqueous outflow had become reduced markedly to approximately 0.02 cu. mm. per minute per millimeter of pressure. An hour after application of carbachol drops, when the pupil had become miotic, the facility of aqueous outflow returned again to a normal value of approximately 0.22 cu. mm. per minute per millimeter of pressure. The pressure was then essentially constant at 17 mm., and on gonioscopic examination the periphery of the iris was seen to have become separated from the cornea and trabeculum.

It appears that the occurrence of narrow-angle glaucoma is dependent on the physical apposition of the iris against the aqueous-outflow channels and that slight physical dissimilarities in companion eyes may influence their susceptibility to valve-like angle closure. The present study suggests that if an increase in rate of aqueous formation has anything to do with precipitating an attack by bulging the iris forward, it must be of brief duration, since no evidence of hyperformation has so far been obtained in this study from numerous measurements at various stages.

In the subacute and chronic forms of narrow-angle glaucoma the same sort of mechanism appears to exist, in that obstruction to aqueous outflow measured tonographically can be satisfactorily correlated with the tension and with the degree of closure of the angle. In the subacute and chronic forms the degree of obstruction to outflow was found to be moderate in comparison with that in acute narrow-angle glaucoma. Outflow appeared to be obstructed functionally and reversibly in some instances by forward bulging of the periphery of the iris, but in most eyes there was also some degree of permanent obstruction by peripheral synechias. In some eyes only by intensive use of miotics could the facility of aqueous outflow and the tension be improved to normal medically, but relief of the obstruction due to forward bulging of the iris was generally aided by iridectomy. After iridectomy the angle was seen to become wider, as it did in treatment of the acute form, and the outflow of aqueous was found to be facilitated to the extent permitted by residual peripheral anterior synechias.

It is of some interest that of 29 patients whose narrow-angle glaucoma had become chronic, the disease was found to be bilateral in 26, but that in 13 of 19 patients who were having their first attack or two of acute glaucoma the disease at that stage was essentially monolateral. The companion eyes, which were still clinically normal except for very narrow but open angles, consistently had normal facility of aqueous outflow and rate of aqueous formation.

Primary Wide-Angle Glaucoma.—The eye with this form of glaucoma was found to differ in several respects from the eye with narrow-angle glaucoma. In eyes with wide-angle glaucoma the iris was never seen to bulge forward to close the angle; in fact, in most instances the angle was indistinguishable gonioscopically from a normal angle. Nevertheless, all abnormal elevations of intraocular pressure were found to be completely accounted for by decreased facility of aqueous outflow. In general, the amount of resistance to outflow and the associated ocular tension varied in a less labile or erratic fashion in wide-angle than in narrow-angle glaucoma. From examination of eyes with primary wide-angle glaucoma in various stages of the disease, it appeared that an early feature of the disease was an appreciable decrease in the facility of outflow as compared with that of definitely normal eyes. In some of the eyes with subnormal facility of outflow which were examined at a

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stage when the glaucoma was essentially latent, the ocular tension was not significantly elevated most of the time, presumably on account of a low rate of aqueous formation, but under close observation the tension was found on occasion to rise well into the 30's. In another group, it has been suspected that primary wide-angle glaucoma is developing because both the facility of aqueous outflow and the tension have become borderline between the definitely normal and the definitely abnormal. In a few of these eyes additional evidences of glaucoma have appeared to add weight to the suspicion, but longer observation will be necessary before the prognostic significance of borderline findings can be properly evaluated.

In the more overt stages of wide-angle glaucoma, in which the tension is chronically elevated and damage to the optic nerve may occur, the disease has been observed to be almost always bilateral. The bilaterality in occasional instances may not be evident by the ordinary means of clinical examination, but by tonographic measurement there can usually be found a facility of outflow in the companion of the glaucomatous eye which is poorer than that of definitely normal eyes, probably presaging later overt development of glaucoma. Wide-angle glaucoma was found in the present study to be bilateral by the usual clinical standards in 30 of 37 patients with the disease, and by the standards of tonographically measured facility of aqueous outflow in 35 of the 37 patients.

Among untreated eyes with primary wide-angle glaucoma, impairment of facility of outflow has been encountered in all gradations, from the lower limit of normal to a moderately severe degree of obstruction, corresponding in general to the tension level and the clinical severity of the disease, although the degree of damage of the optic nerve is less consistently related. The graded distribution of values for facility of outflow, from the lower limit of normal down, suggests that during the development of primary wide-angle glaucoma the transition from the normal to the abnormally obstructed state may be gradual. In untreated narrow-angle glaucoma, by contrast, values for facility of outflow show greater extremes of distribution and characteristically may vary rapidly from normal, in the phases in which the angle is open and the tension normal, to markedly reduced readings when the angle is closed and the tension elevated.

Glaucoma Capsulare.—In eyes in which the onset of glaucoma has apparently been associated with exfoliation of the lens capsule, particularly in eyes with angles of moderate width and no other evident cause for the glaucoma, it has been assumed that the diagnosis was glaucoma capsulare, although very little exfoliated material could be seen in the angle. Elevation of tension in these eyes, also, was found to be due only to increased resistance to aqueous outflow. This type of glaucoma was found to be monocular, with normal outflow present in the other eye much more commonly than was the case with primary wide-angle glaucoma (in 4 of 9 cases of glaucoma capsulare). Unfortunately, no tonographic observations have yet been made on the effects of lens extraction in eyes with glaucoma capsulare.

Secondary Glaucoma.—When glaucoma has occurred secondary to an intraocular inflammation, such as iridocyclitis, it has been shown by tonographic measurements at various stages in the disease that elevation of tension is associated with diminished facility of aqueous outflow, but that under certain conditions the tension may be found in the normal range despite considerable obstruction to the outflow

of aqueous. It has been observed that with mild signs of inflammation in the aqueous there may be moderately increased resistance to aqueous outflow with the tension elevated, but with the rate of formation still nearly normal. However, in association with an increase in flare and cells in the aqueous, the tension has been noted at times to become normal, or even subnormal, despite persisting obstruction to outflow, presumably by reason of a diminished rate or efficiency of formation of aqueous. It may be postulated that the secretory transport of ions into the posterior chamber decreases in efficiency the leakier the blood-aqueous barrier becomes. In general, in secondary glaucoma, in addition to the common factor of reduction of facility of aqueous outflow, a considerable variation in the rate of formation, but not hyperformation, appears to be characteristic. The reduction of facility of outflow tends to increase the intraocular pressure, while the impairment of formation tends to decrease it, the resultant effect on the pressure being determined by the degree to which one of these influences may outweigh the other. In secondary glaucoma the disturbance appears commonly to be a monocular condition, for of 18 cases, a bilateral abnormality of tonographic measurements was found in only five.

The evolution of secondary glaucoma has been observed to follow several different courses. In eight instances, uveitis with secondary glaucoma has been observed to improve rapidly, with a complete return of all tonographically measureable factors to normal. In more protracted forms of inflammatory disease, peripheral anterior synechias have formed, which subsequently have been associated in some cases with chronic glaucoma, due to persistent obstruction of aqueous outflow after the inflammatory phase of the disease had subsided. In cases of uveitis of marked chronicity extensive peripheral anterior synechias have been observed, correlated with much obstruction to aqueous outflow, but in some instances with the tension in the normal range for long periods, even after the inflammatory disease was quiescent. The depression of aqueous formation in these cases is presumably correlated with damage and atrophy of the ciliary body. However, it is noteworthy that, although severe chronic obstruction to outflow may be compensated by a low rate of formation, a critical situation may be obtained thereby in which small absolute changes in obstruction or formation may cause large changes in tension.

A relatively unusual kind of secondary glaucoma due to leakage from a hypermature lens has been studied in one instance before and after cataract extraction. Prior to operation, there was a considerable flare in the aqueous, and the facility of aqueous outflow was reduced to 0.03 cu. mm. per minute per millimeter of pressure, with the pressure elevated to 71 mm., but several weeks after operation, when the eye was clinically normal and aphakic, the facility of outflow and tension were found to have become normal.

Glaucomatocyclitic Crisis.—Observed at various stages in three cases, this unusual form of acute monocular wide-angle glaucoma was found to be characterized by considerable obstruction to aqueous outflow during an attack, without significant change in rate of formation and without closure or synechias of the angle. During periods of remission the facility of aqueous outflow was found to be normal, or at times even greater than in the companion eye, with some relative hypotony.

Glaucoma Associated with Anterior Synechias.—In this category have been included eyes in which glaucoma appears to be due to peripheral anterior synechias produced by an antecedent ocular disturbance which is no longer active. Among

the eyes which have been measured tonographically, the commonest disturbances productive of anterior synechias and glaucoma have been previous secondary glaucoma, postoperative and post-traumatic inflammatory reactions, protracted postoperative flat anterior chamber, and iris bombé or narrow-angle glaucoma in which pupillary block has not been relieved early enough by iridectomy. Included are most instances of so-called aphakic glaucoma and glaucoma following posterior dislocation of the lens when these conditions have become chronic.

In general, the degree of obstruction of aqueous outflow has been found by tonographic measurement to be roughly proportional to the extent of synechial obstruction of the angle estimated gonioscopically. Both the proportion of the angle involved and the density of the synechias, estimated by transillumination, appear to be correlated with the measured degree of obstruction of outflow. In cases in which the whole circumference has been sealed off by a dense synechial band, the facility of outflow has been measured as essentially zero and the tension has been in the 70's. In one instance, that of companion aphakic eyes, one of which was normal and the other had just half of the circumferential angle closed off by an iridocorneal adhesion, the value for facility of outflow was normal in the first eye, but only half as great in the second.

Elevation of intraocular pressure has been approximately commensurate with the measured degree of obstruction of outflow in some cases, but in a number in which there has previously been considerable intraocular inflammation the elevation of pressure has been disproportionately small. As already mentioned in connection with secondary glaucoma, it is assumed that in these cases the mechanism for formation of aqueous has been impaired.

Low-Tension Glaucoma.—A small number of observations have been made on a puzzling group of elderly patients who, despite normal ocular tensions, have typical glaucomatous cupping and atrophy of both optic nerve heads. The tonographic findings in this condition have been sufficiently diverse as to suggest at least two varieties of this condition. In several patients whose tensions have been reliably known for some years to have been normal, but who have had definitely progressive cupping and optic nerve atrophy, tonographic measurements have indicated the facility of aqueous outflow and rate of formation of aqueous to be entirely within the normal range. These circumstances suggest that in these cases the abnormality lies primarily in the optic nerves or their supporting structures. In several other patients, whose tensions have been known for a relatively short period and whose visual field changes may be more static, tonography has given definitely subnormal values for both the facility of outflow and the rate of formation of aqueous. It seems possible that these persons may have had overt, but unrecognized, glaucoma in the past and that their ciliary body may now have become atrophic. More prolonged observation will help in deciding.

Surgical Treatment of Glaucoma.—The effect of various surgical procedures on aqueous outflow in glaucoma has been studied by comparing the preoperative and the postoperative tonographic measurements. Iridectomy, either peripheral or complete, in the presence of narrow-angle glaucoma has produced improvement of the facility of aqueous outflow in proportion to the amount the angle of the anterior chamber has become opened. The limitation of improvement is approximately in

proportion to the persistence of peripheral anterior synechial obstruction of the so-called filtration area. The effect of iridectomy in primary wide-angle glaucoma has not been observed, but in a small number of normal cataractous eyes iridectomy combined with intracapsular lens extraction appears to have caused little change in the facility of aqueous outflow.

The so-called filtering operations, such as iridencleisis and trephination, have been found to increase the facility of aqueous outflow to normal or greater than normal when they are successful, or to leave the facility of aqueous outflow poor, or even to make it poorer than before operation, when they are unsuccessful. Trephination in general was found to produce the greatest increase in facility of outflow, not infrequently to values greater than normal, with some attendant hypotony. No decrease in rate of formation has been observed in association with marked lowering of the tension by trephination; in fact, when the tension has been lowered to 14 mm. or below there has usually been an increase in rate of formation to 2.5 cu. mm. per minute on the average, approximating the average rate in normal eyes. Effective control of tension by cyclodialysis has been found to be dependent primarily on improvement of the facility of aqueous outflow, but in practically all instances in which the tension has been reduced to 12 mm. or less in the absence of miotics a reduction in the rate of formation has been observed, to an average of 0.9 cu. mm. per minute. This low rate of formation, compared with the normal rate in trephined eyes at comparably low tensions, suggests that cyclodialysis may impair the formation of aqueous humor in some way, as well as improve the facility of outflow. Control of tension by cyclodialysis has been correlated in all instances with the establishment of a cleft between sclera and ciliary body, which is visible with the gonioscope. The effects of goniotomy, goniopuncture, and cyclodiathermy have not yet been examined.

Medical Treatment of Glaucoma.—Comparison of tonographic measurement in the presence and in the absence of the use of drugs permits an evaluation of their mode of action. However, because of the short duration of action of most drugs, the approximation of steady-state conditions may be poor. As previously noted, this circumstance reduces the accuracy of the tonographic method and requires special consideration in the evaluation of results. Accordingly, in the present study only those effects which have been observed with reasonable consistency have been accepted as dependably real. Comparisons have been made of comparable groups of glaucomatous eyes without treatment and other groups with treatment and also of conditions in individual eyes under various forms of treatment. The latter type of comparison seems to be the more informative.

The lowering of tension in glaucoma by locally applied miotics is found commonly to be accomplished by an improvement of the facility of aqueous outflow. In narrow-angle glaucoma the improvement in outflow appears to be correlated with opening of the angle, but in wide-angle glaucoma no significant change in the width of the angle has been observed despite measured improvement in outflow. In narrow-angle glaucoma of acute or subacute type, when the mechanical obstruction of the angle by the iris has not persisted long enough for the formation of synechias, relief of the attack by miotics has been observed to return the facility of outflow, tension, and rate of formation all to the normal range in six of six cases. On the other hand, in chronic narrow-angle glaucoma with peripheral anterior

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synechias, although in six of seven cases an observed lowering of tension by miotics was wholly accounted for by the measured amount of improvement in facility of outflow, it was commonly found that the facility of aqueous outflow did not come up completely to the normal range, even when the tension was essentially normalized (nine out of 15 cases). It is inferred that in these eyes there may be a persistence of the somewhat subnormal rate of formation of aqueous, which was noted previously as a tendency in eyes with untreated glaucoma. In primary wide-angle glaucoma it was also observed that the amount of lowering of tension by miotics was usually adequately accounted for by the degree of improvement of aqueous outflow (11 of 15 eyes), but that even though normal tensions were obtained the facility of outflow commonly persisted somewhat below normal (19 of 31 eyes); again, this would be explainable on the basis of continued subnormal rate of formation. In glaucoma from anterior synechias secondary to an antecedent ocular disturbance, the response to miotics was essentially of the same nature, six out of eight cases having sufficient increase in facility of outflow to account for the amount of decrease in pressure. The amount of improvement in facility of outflow with miotics in some of these eyes has been surprising, in view of the apparent extent of synechial involvement of the angle. A twofold or threefold increase in facility of outflow has not been unusual, but only in two eyes has the outflow attained the normal range. In glaucoma capsulare, on the other hand, in only one case out of five was enough facilitation of outflow found for the observed lowering of pressure. The possibility of a depressant effect on formation is to be considered in this situation, but the total number of cases of glaucoma capsulare is statistically small. Evidence for a depression of aqueous formation by miotics was found in only 8 of the 36 eyes with wide-angle, narrow-angle, or synechial glaucoma which were measured with and without medication. The average value for rate of formation for 67 glaucomatous eyes under treatment with miotics, with the tension below 30 mm., was slightly less than that for 85 eyes with untreated glaucoma—1.34 cu. mm., as compared with 1.45 cu. mm., per minute. It seems that lowering of intraocular pressure by suppression of aqueous formation is a relatively uncommon mode of action for miotics. Further investigation is undoubtedly needed.

The effect of epinephrine in lowering intraocular pressure has been measured so far in only a few heterogeneous cases. Both in secondary glaucoma and in primary glaucoma in conjunction with sufficient miotic medication to keep the pupil small, the facility of outflow was improved commensurate with pressure decrease in five of six eyes.

SUMMARY AND CONCLUSIONS

Measurements have been made in a series of patients of the facility with which the aqueous humor can be expressed from the eye, utilizing a tonographic method employing an electronic tonometer and recording galvanometer. The rate of formation of aqueous in these eyes under steady-state conditions has been calculated from the steady-state pressure and the measured coefficient for facility of outflow. The net rate of outflow has been found experimentally to be a direct function of pressure from approximately 4 to 50 mm. (Hg) pressure.

In glaucomatous eyes elevation of tension above normal has been found in every instance to be due exclusively to abnormal resistance to aqueous outflow, and no case of glaucoma due to hyperformation of aqueous has been observed. In narrow-

angle glaucoma, the amount of obstruction to outflow by measurement and the degree of closure of the angle estimated by gonioscopic examination have been well correlated, as has the elevation of intraocular pressure. In primary wide-angle glaucoma, decreased facility of aqueous outflow was consistently found, although no closure or gonioscopically visible obstruction of the angle was present. In secondary glaucoma, measured obstruction to aqueous outflow was also responsible for the elevation of tension, but this form of glaucoma was peculiar in that spontaneous return to normal or low-pressure levels was the result in some cases of return of facility of outflow to normal, but in other cases it apparently was the result of a decrease in rate of formation of aqueous with abnormal resistance to outflow persisting. Surgical treatment in general was beneficial only when it improved the facility of aqueous outflow. Iridectomy, either peripheral or complete, in eyes with narrow-angle glaucoma improved outflow toward normal in proportion to the degree of opening of the angle obtained. Treatment with miotics was effective principally in improving the facility of aqueous outflow, but in a small proportion of cases there was indication of a depressant effect on aqueous formation.

It is concluded that the increase in intraocular pressure in glaucoma is practically always, possibly exclusively, caused by increased resistance to outflow of aqueous humor from the eye (i. e., subnormal facility of outflow), and not by hyperformation of the aqueous humor. The beneficial effect of current surgical and medical treatment is achieved principally through improving the facility of aqueous outflow.

243 Charles St.

Miss Elizabeth O. Cushing has assisted in all aspects of this investigation, and Dr. Harry E. Braconier has cooperated in examination of some of his patients with cyclodialyses. Stimulation has been furnished by frequent discussion with Dr. Paul A. Chandler.

ABSTRACT OF DISCUSSION

Dr. Jonas S. Friedenwald: It has long been known that when the tonometer is allowed to rest on an eye for a protracted period the intraocular pressure tends to fall. This so-called massage effect has been studied by a number of authors. Thomassen and, especially, Kronfeld have shown that the massage effect is diminished in eyes with uncompensated glaucoma. Moses and Bruno attempted to place this analysis on a quantitative basis by relating the increasing volume of the corneal indentation during prolonged tonometry to the average excess of the intraocular pressure during tonometry over that present in the eye before the measurement was begun.

It has been Dr. Grant's great achievement to bring this type of measurement into the range of clinically significant procedures. He has accomplished this, on the one hand, by greatly refining the tonometric recording system, and, on the other, by taking account in his estimate of the volume of fluid expressed from the eye—not merely the increase in the volume of the tonometric indentation, but also the shrinkage, i. e., the diminished distention of the eyeball as a whole during the period of the falling intraocular pressure.

Dr. Grant has said that the validity of his estimates depends on the reliability of the data which I have made available to him out of the study on calibration of tonometers undertaken for the Committee on Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology. These data have not yet been published in full, but I hope to be able to make them available in print in the near future. In view of the dependence of Dr. Grant's data on my previous measurements, it becomes my responsibility to analyze the sources of error and the

range of error in these data. This analysis implies no criticism of Dr. Grant's work. Most of the sources of error which I shall enumerate are thoroughly familiar to him. It is, in fact, a great satisfaction to me that the data which I have compiled, even in their present crude form, have been shown by Dr. Grant's significant clinical results to be sufficiently accurate for this type of application.

The first step in Dr. Grant's analysis is the estimate of the amount of fluid expressed from the eye during tonometry. The formula which he uses may be expressed in approximate form as

$$(1)\quad \Delta V = \frac{1}{K_T}\log\frac{P_{T1}}{P_{T2}} - V_2 + V_1$$

where ΔV is the volume of fluid expressed, P_{T1} and P_{T2} are the intraocular pressures with the tonometer resting on the eye at the beginning and the end of the measurement, and V_1 and V_2 are the volumes of the corneal indentation at the beginning and the end of the measurement. This formula is based on my finding that, to a reasonable approximation, the relation of pressure to volume in an eye when it is distended by intraocular injection of fluid can be represented by the empirical formula

$$(2)\quad \Delta V = \frac{1}{K_D}\log\frac{P_1}{P_2}$$

and when it is distorted by the tonometer, by

$$(3)\quad V = \frac{1}{K_T}\log\frac{P_T}{P_0}$$

where P_T is the pressure in the eye with the tonometer resting on it, P_0 the pressure before tonometry, and V the volume of the corneal indentation. Now, unfortunately for mathematical simplicity, K_D, the coefficient of rigidity with respect to ocular distention, and K_T, the coefficient of rigidity with respect to ocular distortion, are not necessarily equal. Dr. Grant's application of the tonometric distortion coefficient, K_T, to the situation during prolonged tonometry, when the eye changes in respect both to distention and to distortion, is an extrapolation of the empirical formula into a region where it does not necessarily apply accurately. A formula similar to Grant's, and free from this objection, can be derived as follows:

Considering the eye immediately before and immediately after prolonged tonometry, and representing the initial and final pressures by P_{01} and P_{02}, the fluid lost by ΔV, then, since we are dealing only with changes in distention,

$$(4)\quad \Delta V = \frac{1}{K_D}\log\frac{P_{01}}{P_{02}}.$$

On the other hand, when the tonometer is first placed on the eye, we are dealing only with distortion. Therefore

$$(5)\quad V_1 = \frac{1}{K_T}\log\frac{P_{T1}}{P_{01}}.$$

Similarly, when the tonometer is finally removed from the eye

$$(6)\quad V_2 = \frac{1}{K_T}\log\frac{P_{T2}}{P_{02}}.$$

If we subtract equation 5 from equation 6 and combine with equation 4, we get

$$(7)\quad V = \frac{K_T}{K_D}\left(\frac{1}{K_T}\log\frac{P_{T1}}{P_{T2}} - V_2 + V_1\right)$$

It will be seen that this formula differs from that of Dr. Grant's equation 1 only by the factor $\frac{K_T}{K_D}$. Grant's formula represents the assumption, as a first approximation, that $K_T = K_D$. Now measurements of these two coefficients by the

same investigator on the same eye have not so far been reported. However, Dr. Grant has been making such measurements on enucleated human eyes, and he says that he has been finding no great difference between K_T and D_D, and that the ratio $\frac{K_T}{K_D}$ is therefore not far from unity.

In all probability, this ratio changes little, if at all, from eye to eye. It enters into Dr. Grant's data merely as a scale factor and does not significantly influence the relative values which he gets in comparing different eyes. It will become a matter of crucial importance only if data compiled by Dr. Grant's method are compared with those compiled by other procedures.

If we neglect this scale factor and analyze the items inside the bracket in equation 7, we come to matters of more immediate concern. The values P_{T_1} and P_{T_2} are taken from my tonometric calibration measurements, in which the eye tested was connected with open stopcock to a pressure reservoir. These "open-manometer" measurements show remarkably good reproducibility. My own data are in close agreement with those of Schiøtz of 50 yr. ago. Almost the same values are obtained on rabbit, cat, pig, and human eyes. Variations in corneal curvature and in corneal thickness, therefore, have no significant influence on the readings. The accuracy of the values P_{T_1} and P_{T_2} depends, consequently, almost exclusively on the accuracy of the tonometer-scale reading. Assuming that Dr. Grant can read his graphic record to 0.2 scale unit, the value of log $\frac{P_{T_1}}{P_{T_2}}$ may be assumed to be correct within ± 5%.

For K_T, Dr. Grant has used the estimated average value on normal eyes. In 1936 I published estimates of the value of K_T for 500 normal human eyes. The frequency distribution of these values follows an essentially normal frequency curve, and the standard deviation can be readily estimated. Allowing for the fact that this standard deviation is partly the result of reading errors in tonometry, it can be concluded that in the normal population the use of the average normal value of K_T, instead of the particular value appropriate for each eye, yields an uncertainty in the item $\frac{1}{K_T} \log \frac{P_{T_1}}{P_{T_2}}$ of about ± 25%. Exact estimates of K_T for any single eye are difficult and require many measurements. Dr. Grant is not to be criticized for having used the average normal value as a first approximation.

The tables of values for V_1 and V_2 were obtained by direct experimental measurements on 10 human eyes and on 60 cat and rabbit eyes. The mean values for the measurements on human eyes at various fixed pressures fell on a reasonably smooth curve, and resulting tables which were used by Dr. Grant appear to be solidly based. The experimental scatter in these measurements was, however, much larger than in determining the P_T values, and it became clear from an analysis of the data that the volume of the corneal indentation corresponding to a particular tonometer reading is very considerably influenced by variations in corneal curvature and thickness, even within the normal range. In taking the difference $V_2 - V_1$ between two readings on the same eye, the variability is somewhat reduced, but I should not feel that the value of $V_2 - V_1$ (uncorrected for corneal curvature and thickness) could be estimated closer than ± 15%. This would hold for eyes with clear corneas of the normal range of curvature. For edematous or scarred corneas, for buphthalmos or microphthalmos, no estimate whatever can be given at the present time.

If we include the reading errors of the measurement but still disregard the scale factor $\frac{K_T}{K_D}$, the estimated uncertainty in ΔV, due largely to normal variations in K_T and in corneal curvature and thickness, is, under favorable conditions, of the order of ± 20%.

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Now we come to Dr. Grant's second equation. He estimates the "facility of outflow," designated by the coefficient C in the equation

$$(8) \quad C = \frac{\Delta V}{T(P_{T_{av}} - P_{o_1})}$$

The numerator on the right of this equation has an uncertainty of the order of $\pm$ 20%. In the denominator, T (the time in minutes) and $P_{T_{av}}$ can be determined accurately. P_{o_1}, however, involves all the uncertainties of tonometer calibration. The Schiøtz chart currently approved by the Committee on Standardization of Tonometers is based on a compromise between my own experimental findings and those of the half-dozen others who have attempted to calibrate this instrument during the last 50 yr. Dr. Grant has used my data. It is most gratifying that by the use of these data he gets generally consistent results, and this fortifies my own opinion that my calibration is a good deal closer to the truth than those of previous investigators. The strongest evidence is Grant's finding that on very prolonged tonometry, P_{T_2} approaches P_{o_1}, as it should when the intraocular pressure finally regains its initial equilibrium value. Incidentally, this affords a new and valuable method for tonometer calibration. The P_{o_1} values, however, are based on assumed average normal ocular rigidity. In case an eye deviates in its K_T value by the standard deviation from the average normal, the P_{o_1} values will be erroneous by approximately $\pm$ 15% and the $(P_{T_{av}} - P_{o_1})$ by at least $\pm$ 30%.

Since both the numerator and the denominator in the estimate for C (equation 8) are affected largely by uncertainties in the value of K_T for the particular eye measured, one might hope that these errors would tend to cancel themselves out. Unfortunately, this is not the case. If an eye has a rigidity greater than the average normal, then the numerator will be overestimated and the denominator underestimated. The two errors are, therefore, substantially additive, and the uncertainties in estimation of the coefficient of facility of outflow (C) correspondingly large.

Up to the present I have been considering uncertainties in the estimates in terms of the statistical measure: standard deviation. In a series such as that presented by Dr. Grant for normal eyes, the range of variation would be approximately double the standard deviation. On the basis of the factors so far enumerated, i. e., reading errors and normal variations in ocular rigidity and in corneal curvature and thickness, and if the facility of outflow were identical in all normal eyes, one would expect a range in the estimates of facility of outflow from about one-half the average value to about twice the average value. Dr. Grant finds his estimates for C in normal eyes to vary from 0.11 to 0.44, with an average of 0.22. The extremely close agreement of these figures with the estimate of expected range on the basis of the above analysis is largely fortuitous, but one is, nevertheless, justified in concluding that the true range of variation in the facility of outflow in normal eyes is probably very much narrower than that obtained by Dr. Grant. This is indeed an encouraging circumstance, for it indicates that as methods of estimating the facility of flow become more precise, it will be possible to give clinical significance to much smaller deviations than those found by Dr. Grant between normal eyes and eyes with uncompensated glaucoma. The early diagnosis of deep-chamber-angle glaucoma looms as a significant possibility. Furthermore, the conclusion that the normal range of variation in facility of outflow is relatively narrow greatly fortifies the clinical significance of the difference which Dr. Grant finds between the average reading on normal eyes and the average reading on eyes with uncontrolled glaucoma. It should be pointed out that in repeated measurements on the same eye most of the sources of error enumerated will be constant, and hence that quite small changes in facility of outflow may be detectable.

The third step in Dr. Grant's calculations is to use the facility of outflow and the intraocular pressure before tonometry to estimate the rate of flow of the intraocular fluid. In his first paper, he estimated the rate of flow, F, by

$$(9) \quad F = C\,P_{o_1}.$$

In his present paper, on the basis of experiments on enucleated eyes, he has made a slight modification:

$$(9A) \quad F = C\,(P_{oi} - 4)\,.$$

These equations assume that if the formation of intraocular fluid were stopped the intraocular pressure would drop to zero (equation 9) or to 4 mm. Hg (equation 9A). If one neglects the possible contribution of the osmotic pressure of plasma proteins, the intraocular pressure, if aqueous formation were stopped, should not drop lower than the episcleral venous pressure, which I shall designate P_v. Thus, the first approximation for the estimate of the rate of flow should be

$$(10) \quad F = C\,(P_{oi} - P_v)\,.$$

Admittedly, the pressure in the episcleral veins is hard to estimate. By methods which are not wholly satisfying, Goldmann estimates this pressure at about 10 mm. Hg. Löhlein gives similar figures, and both these authors believe that the P_v may differ substantially in glaucomatous, as compared with normal, eyes. Until measurements of P_v can be included in the clinical technique, I believe that estimations of F are hazardous.

It should be pointed out that if the P_v of normal eyes is the same as or higher than that of glaucomatous eyes, then Dr. Grant's method of estimating F would give relatively lower values in glaucomatous eyes than in the normal eye. Whether this would account for the whole of the differences that he finds remains uncertain, but on the basis of the present data the conclusion that the rate of flow is diminished in glaucoma seems to me extremely uncertain. Dr. Grant has suggested this conclusion with due reserve. I emphasize this point merely to warn careless readers of Dr. Grant's paper from disregarding his judicious reservations.

In connection with the significance of episcleral venous pressure, it should be pointed out that this pressure may well be raised during tonometry. The weight of the tonometer rests on the eyeball and must raise the intraorbital pressure. Assuming that the supporting orbital pressure operates over the area enclosed by the insertion, the anterior orbital fascia on the eye, a circular area of 15 to 20 mm. in diameter, then the rise in intraorbital pressure during tonometry will be between 5 and 10 mm. Hg. To what extent this will be reflected by a rise in episcleral venous pressure is uncertain. So far as this is a significant factor, it will enter as a correction for P_{o_1} in equation 8 and for P_{T_1} and P_{T_2} in equation 7. In view of Dr. Grant's finding that on very prolonged tonometric determination, P_{T_2} approaches the estimated value of P_{o_1}, the disregard of changes in orbital pressure during tonometry will not, in general, amount to a large error. It should be pointed out, however, that in some glaucomatous eyes with very small facility of outflow the pressure reading, P_T is found to rise during the first minute or two of tonometry. Such a paradoxical rise can most readily be accounted for by the gradual adjustment of the intraocular pressure to the change in episcleral venous pressure. At any rate, I should regard this as a more tenable hypothesis at present than the alternative that the application of the tonometer is some mysterious way may stimulate active secretion of intraocular fluid.

I should like to emphasize again that the analysis of sources of error in the measurements that I have made implies no criticism of Dr. Grant's very significant contribution. He has developed this method to the point at which it has already made a useful contribution to our clinical evaluation of the individual problems in cases of glaucoma and has very largely fortified the conclusion that the essential defect in all varieties of glaucoma is an obstruction of aqueous outflow. I believe that the estimate of the facility of outflow is, in the present state of development of this method, much more reliable than the estimate of flow in the undisturbed eye. Dr. Grant has been fully aware of the sources of error in measurements that I have enumerated and has stated his conclusions with due reserve. He deserves very great credit for having brought this method to the level of clinical serviceability and for having thereby opened a new and very important field in the analysis of the pathologic physiology of glaucoma.

DR. PAUL CHANDLER: Dr. Grant's clinical measurement of aqueous outflow has furnished us with one of the most valuable tools for the study of glaucoma which has been evolved in the last several decades. Perimetry, tonometry, and, to a less degree, measurements of visual acuity have long been the principal tools for the diagnosis and management of glaucoma, and doubtless they will continue to play the most important role. In the past two decades gonioscopy has made possible valuable contributions to knowledge of glaucoma, principally in the classification of the glaucomas. Gonioscopic studies have indicated that the mechanism of obstruction to outflow in glaucoma is of an entirely different nature in narrow-angle than in wide-angle glaucoma, that in the former the obstruction to outflow is due to block of the angle by forward displacement of the root of the iris, whereas in the latter the obstruction is evidently in the angle structures themselves. Dr. Grant's work has beautifully confirmed this conception. He has invariably found in narrow-angle glaucoma that when the iris periphery does not overlie the filtration area the facility of aqueous outflow is normal. In other words, if aqueous can gain access to the pectinate ligament, there is no obstruction to its escape, whereas in wide-angle glaucoma at all stages obstruction to outflow is present.

Thus, the classification of primary glaucoma into the narrow-angle and the wide-angle groups, as first suggested by Raeder (*von Graefes Arch. Ophth.* 112:29, 1923), and further elaborated by Barkan (*Am. J. Ophth.* 24:768, 1941), Sugar (*Am. J. Ophth.* 32:425, 1949), and others, is proved to be valid. Once one accepts the essential difference in the mechanism in the two types of glaucoma, one can go on to a more intelligent selection of a particular type of treatment for a particular type of glaucoma.

In the glaucoma secondary to inflammation of the anterior segment of the eye, Dr. Grant has always found obstruction to outflow. When the tension falls while the inflammation is still active, though there is still obstruction to outflow, the lowered tension is found to be due to decreased formation of aqueous, presumably as a result of the opening of the blood-aqueous barrier.

It is good to have the ghost of hypersecretion as a factor in glaucoma finally interred. Dr. Grant has furnished conclusive proof that obstruction to outflow is the sole factor in the increased tension in glaucoma, and the whole problem is thereby that much simplified.

Tonography bids fair to supersede the various provocative tests for wide-angle glaucoma. Dr. Grant has consistently found a rate of outflow below normal, not only in early wide-angle glaucoma, when the diagnosis has been established by the presence of cupping, increased tension, or loss of field, but also in most instances in the fellow eye, in which the diagnosis of glaucoma has not been made by the usual clinical methods.

In the patients with progressive cupping and atrophy with tension always in the normal range, he has found some cases in which aqueous outflow is normal, indicating that the mechanism of the damage is to be sought in the optic disk or nerve. In other cases clinically similar, obstruction to outflow suggests that the condition is a true glaucoma, with the normal tension due to a low rate of aqueous formation.

Tonography should be a useful method for the evaluation of new drugs for the treatment of glaucoma. Drugs may one day be discovered which will lower the tension in glaucoma by reducing the rate of aqueous formation.

It is a great personal satisfaction to me to have this opportunity publicly to congratulate Dr. Grant on developing and applying this new method, which promises to add so much to our understanding of the problem of glaucoma.

DR. PETER C. KRONFELD, Chicago: The method of clinical investigation which Dr. Grant has so aptly named tonography has been a special concern of mine for over 20 yr. Reading Dr. Grant's paper and listening to his masterful presentation have made me so excited that I find it hard to keep my feet on the ground. I find it difficult to distinguish between what has been established already and what we hope to establish in the next five years.

The observations of Dr. Grant, as well as those of Drs. Moses and Bruno, and those of Dr. Philip Shane, of St. Louis, which were reported to us at a meeting of the Chicago Ophthalmological Society a month ago, as well as my own observations in this field, are so similar that I think we have the right to speak of established facts.

The principal established fact is the greater resistance to outflow characteristic of the chronic wide-angle glaucoma. From the data available at this time, it is highly probable that the course of glaucoma correlates better with this coefficient of outflow than with the tension levels determined by single or repeated, or even frequently repeated, tonometric measurements. In other words, it seems to me that tonography is at the moment the most reliable tool in the follow-up study of glaucoma. Because of the slow evolution of many forms of glaucoma, it will take years before the tonographic characteristic of all types and phases of glaucoma will be established, but Dr. Grant has laid a sturdy foundation.

By a mathematical analysis, which entails certain simplifying assumptions, Dr. Grant has shown that tonographic data permit one to make estimates of the second factor in fluid exchange of the eye, namely, the rate of formation of the most minute volume of the aqueous. Variations in this factor have always played an important part in the clinician's attempt to explain the mechanism of certain glaucomatous situations. Now, for the first time, I believe, in the history of ophthalmology, we have a simple way of estimating that rate of formation or cessation of secretion, and I should like to cite a striking instance of an anomaly of that rate of formation. It concerns a postoperative state, namely, a state of a very low ocular tension after cyclodialysis—and before I introduce the case of cyclodialysis, I shall note the case of the tension after a trephination. A patient has been operated on for chronic wide-angle glaucoma by the trephining method and has what is generally considered a good result, with a beautifully filtering bleb, tension between 13 and 15 mm. Schiøtz, and good maintenance of visual function. Such a patient, if tested by Dr. Grant's method, proves to have a coefficient of outflow that by far exceeds the coefficient of outflow of the normal eye. In other words, fluid runs out of that eye with much greater ease than it runs out of one's own eye. The rate of formation of aqueous in that eye is slightly, perhaps at times moderately, diminished, but one can, by Morton Grant's method, arrive at a figure for the rate of formation which is just a little below normal.

Now, I shall consider an eye which, also for glaucoma, has had a cyclodialysis, and in which tensions vary from 4 to 8 mm. (Schiøtz); in other words, on one day the tension is 8 mm., and two days later it may be 4 mm. That patient, if tested tonographically, has a coefficient of outflow of either normal or slightly below normal, magnitude. In other words, the superciliary cleft is functioning, and one has a right to assume that, with a standard of outflow, this superciliary cleft functions almost as well as, or in a manner similar to, the normal Schlemm system. However, if that patient is examined on a day when his tension is only 4 mm. and the tonometer is left on the cornea for five minutes, no coefficient of outflow is obtained. In other words, the eye seems suddenly to maintain its low tension. I believe that since on the preceding day it was demonstrated that this eye had a mechanism of outflow and since the cleft is open—wide open—on both days, there is only one conclusion, namely, a greatly reduced rate of formation of aqueous.

There is another method by which estimates of the rate of formation have been tried, and that is the fluorescence method of Goldman. Goldman, with this method, has arrived at the same conclusion, namely, that in cyclodialysis, especially, very low levels of tension are accomplished, and that a reduction in rate, not a cessation of fluid formation, is an important factor.

Dr. Andrew deRoetth Jr., New York: At the Institute of Ophthalmology in New York, Dr. Neissen and I have also been working on the aqueous flow. We made about 250 tests on approximately 200 eyes. Half of the eyes were normal; half were glaucomatous. Of the 100 normal eyes, about nine, or 9%, had the

coefficient of aqueous outflow in the abnormal, that is, the low, range, meaning that the coefficient was below 0.15. Of the 100 glaucomatous eyes, about 30 were without treatment—with no medication at all. Of these 30 glaucomatous eyes, the chronic noncongestive type, as Dr. Grant has also shown, fell in the group with low, abnormal aqueous outflow. However, most of the glaucomatous eyes of the congestive type, when they were examined between the congestive attacks, that is, in a quiescent phase, showed a normal coefficient of aqueous outflow.

In more than half the 70 glaucomatous eyes receiving mild medication, although the tension in most of them was well controlled, the aqueous outflow fell in the low, or abnormal, range. Therefore, if this aqueous outflow is any criterion of the success of our treatment of glaucoma as we know it at present, we are in a sorry state.

I should like to thank Dr. Grant for showing us this extremely interesting and, I believe, very useful diagnostic test.

Dr. K. W. Ascher, Cincinnati: I wish to express my admiration for Dr. Grant's method, as well as for his presentation. I can only ask a question, which I do not expect to be answered by any of the discussers today, but which I hope will be answered in the future, perhaps years, perhaps decades, from now.

You, Dr. Grant, and everyone working in your field, has stated what we have accepted or assumed for years, that the main factor in glaucoma, in its etiology, is retention of aqueous, impediment of aqueous outflow. My question is this: Where does this impediment take place? There are three main possibilities: (1) where the fluid enters the canal of Schlemm, the trabecular region; (2) where the fluid leaves the canal of Schlemm, the outlets, unfortunately called collectors—they are not collectors, but distributors, of the aqueous humor from the canal into the ciliary veins—and (3) these superficial veins, which finally take the intraocular fluid away.

Dr. Thomas M. D'Angelo, Flushing, N. Y.: I should like to ask Dr. Grant how he arrived at a measurement of the intraocular pressure in terms of millimeters of mercury.

Dr. W. Morton Grant, Boston: I wish to thank all the discussers for their contributions and the information that observations of this nature by others are in accordance with those which I reported.

The question about millimeters of mercury of intraocular pressure I can nicely pass to Dr. Friedenwald.

TONOGRAPHIC METHOD FOR MEASURING THE FACILITY AND RATE OF AQUEOUS FLOW IN HUMAN EYES

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BOSTON

THE PURPOSE of this preliminary report is to describe a manner of utilizing the Schiøtz tonometer to obtain a measure of the patency of the channels of aqueous humor outflow and of the steady state net rate of aqueous humor flow. It is believed that the method described here provides a means of discerning in what measure changes in intraocular pressure are due to change in facility of outflow or to change in net rate of aqueous humor formation. A subsequent report will describe the alterations in these factors which are effected in normal and in glaucomatous eyes by various medical and surgical influences.

The electronic Schiøtz tonometer is electrically connected to an amplifier and recording galvanometer in such a manner that all measurements made by the tonometer are continuously and automatically recorded on a moving paper strip, such as is employed in electrocardiography. The apparatus is pictured in figure 1. The tonometer foot plate assembly is placed on the patient's cornea in the manner customarily employed for simple measurement of ocular tension but is allowed to remain there for five to six minutes. During this period there is a gradual decrease in ocular tension, which is permanently recorded on the paper strip, as shown in figure 2. The pulse wave and any incidental effects of respiration or eye movement on the ocular tension are also clearly reproduced.

From the recording are determined, by means to be described shortly, the steady state intraocular pressure before application of the tonometer, the intraocular pressure during the period the tonometer is resting on the eye and the decrease in volume of the eye during this period. From these figures are calculated, first, the average increment in intraocular pressure during the measurement (due to the weight of the tonometer) and the constant of proportionality between the pressure and the rate of volume loss. This constant represents primarily a measure of the facility with which fluid in the eye can leak or be forced out, expressed in terms of cubic millimeters of fluid per minute per millimeter

From the Howe Laboratory of Ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary.

(mercury) of intraocular pressure, assuming the small pressure increment involved in the measurement to have an insignificant effect on the rate of formation of aqueous humor. An approximation of the total steady state rate of outflow, in cubic millimeters per minute, which in

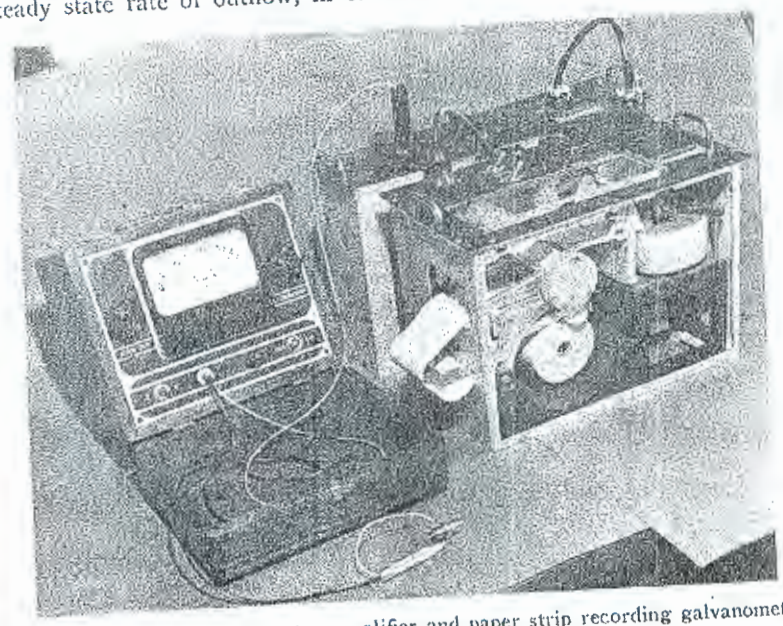

Fig. 1.—Electronic tonometer, amplifier and paper strip recording galvanometer employed for tonography.

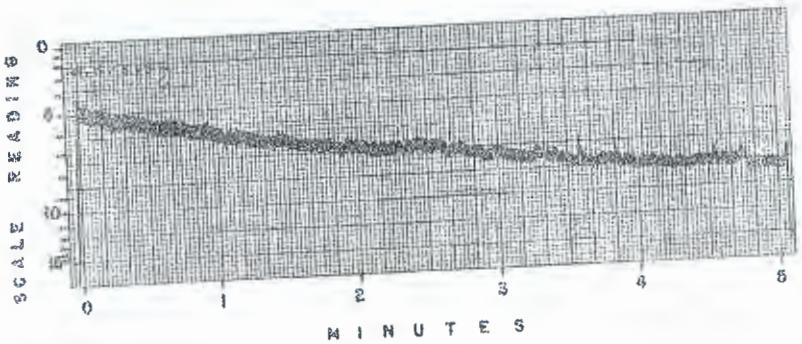

Fig. 2.—Typical tonogram of a normal human eye obtained during five minutes of recording.

a steady state also equals the net rate of aqueous humor formation, is then provided by the product of the steady state intraocular pressure and the pressure coefficient of outflow. The basis for these calculations will now be considered in more detail.

RELATION OF TONOMETRIC READING, INTRAOCULAR PRESSURE AND OCULAR VOLUME

When the Schiøtz tonometer is allowed to rest on a human eye in the usual manner, the intraocular pressure is raised because the cornea is indented and a small volume of fluid is displaced which can be accommodated elsewhere in the eye essentially only by a distention of the coats of the eye. The artificial pressure levels obtaining in eyes with the Schiøtz tonometer resting on them have been measured numerous times by other investigators, employing enucleated eyes which were connected by means of a cannula to a simple open manometer, and data have been obtained relating the tonometer scale readings with various weights on the plunger to the coexisting intraocular pressures. The most accurate of such data are those of Friedenwald.[1] These data are used in the present work to convert the tonometer scale readings which are graphically recorded on the moving paper strip into terms of the corresponding actual ("open manometer") intraocular pressure obtained during the recording. This intraocular pressure with the tonometer resting on the eye is, of course, greater than that existing in the absence of the tonometer. Ordinarily, and also for the purposes of the present work, it is desirable to know what the intraocular pressure was when the tonometer was not on the eye, and this information is obtainable from the standard calibration charts which accompany Schiøtz tonometers. Again, undoubtedly the most accurate data are those calculated by Friedenwald.[1]

For application of the method described here, the eye is assumed to exist in a steady state before application of the tonometer, with the intraocular pressure determined by the net rate of aqueous humor formation and the amount of resistance to escape of aqueous humor from the eye. Application of the tonometer is considered to disturb this steady state by increasing the intraocular pressure and increasing the rate of escape of fluid, presumably aqueous humor, from the eye. The pressure increment by which the conditions of equilibrium are disturbed is represented by the difference between the undisturbed original pressure, Po, and the artificially elevated pressure, P_T.

With increase in rate of escape of aqueous humor from the eye, the total ocular volume decreases at a rate corresponding to the difference between the rate of loss and the rate of formation of aqueous humor, that is,

Aqueous humor formation — aqueous humor loss = change in ocular volume

So far as the rate of formation remains unchanged, the rate of decrease

1. For use in the present work, Dr. Jonas Friedenwald made available detailed data obtained in 1949, and as yet unpublished. Previous data were published by Dr. Friedenwald in the *American Journal of Ophthalmology* (20:985-1024, 1937; 22:375-383, 1939; 31:935-944, 1948).

in ocular volume will equal the increase in rate of loss of aqueous humor. Experimental evidence, to be presented subsequently, indicates that the rate of formation is altered little by the small increase in pressure produced by application of the tonometer. Accordingly, pending the development of means for actual correction of any small change in rate of formation, in the present method the rate of decrease of ocular volume is taken as an adequate approximation of the increase in rate of loss of aqueous humor. Now ocular volume has been shown by Friedenwald to be a function of the logarithm of the intraocular pressure, and if adequate data for conversion were available the change in intraocular pressure found during the recording period could be converted into terms of change in ocular volume and rate of fluid outflow. Such data have been derived in the following manner:

With the tonometer resting on the eye at a given intraocular pressure, the cornea is somewhat indented by the foot plate and plunger, and the coats of the eye are in a certain state of distention. When there is a loss of fluid from the eye, the pressure decreases, the eye is less distended and indentation by the tonometer increases. Actually, the volume of the increase in indentation plus the volume of the decrease in distention must equal the volume of fluid lost from the eye, since dilute watery solutions are essentially incompressible. Fortunately, Friedenwald has calculated the volume of tonometric indentation for the whole range of conditions encountered in ordinary measurements.[1] Also, in the course of his measurements and calculations he has obtained for human eyes under tonometric distortion a reasonable approximation of the coefficient of rigidity and an expression relating intraocular pressure to distention volume. From his data have been calculated the combined change in corneal indentation and scleral distention volumes related to change in tonometer scale readings while the tonometer is on the eye.[2]

2. It is of some incidental interest to note that at the very outset of the recording procedure, when the tonometer is placed on the eye, the volume of the eye is momentarily the same at Po as at P_T, since the fluid contents are essentially incompressible, and that, similarly, after a period during which there has been loss of volume from expression of fluid, if the tonometer is removed from the eye there is momentarily an identical ocular volume with and without the tonometer, although the eye is of different shape under these two conditions. From the usual type of calibration curves for determining undisturbed ("closed manometer") intraocular pressure, one knows reasonably well what the pressure is immediately before and immediately after the tonometric or tonographic determination. At the same time, one has information on the total volume loss during the application of the tonometer from the data of table 1. Now the change in volume from just before to just after the period of application of the tonometer is essentially one of change in distention, which is, as has been seen, necessarily equal to the combined change of indentation and distention volumes under tonometric distortion. One has, therefore, information on both the change in pressure and the change in volume of the eye undistorted by

(Footnote continued on next page)

In table 1 the resultant data are presented for eyes with normal scleral rigidity. The volume value is arbitrarily set at zero in each column of the table to correspond to the zero scale reading. Change in volume during change in scale reading is equal to the difference between the corresponding values for volume read from the appropriate column for whatever tonometer weight is used throughout the recording. The quantitative accuracy of this value, and therefore of all the estimations of volume in this work, depends, of course, on the accuracy of Friedenwald's data.[1]

TABLE 1.—*Relation of Scale Readings to Change in Ocular Volume*

Schiøtz Scale Reading	Volume Change (Cu. Mm.) for Individual Tonometer Weights			
	5.5 Gm.	7.5 Gm.	10 Gm.	15 Gm.
0	0	0	0	0
1	3.1	2.6	2.4	2.0
2	6.3	5.4	4.8	4.1
3	9.5	8.2	7.2	6.1
4	12.7	11.0	9.6	8.3
5	16.0	13.8	12.1	10.4
6	19.5	16.7	14.6	12.5
7	22.8	19.7	17.3	14.8
8	26.3	22.9	20.1	17.2
9	29.9	26.1	22.8	19.6
10	33.7	29.3	25.7	22.3
11	37.3	32.6	28.7	24.8
12	41.2	36.0	31.7	27.6
13	45.3	39.6	34.7	30.5
14	49.4	43.4	38.2	33.5
15	53.7	47.3	41.5	36.7

One now has the means for deriving from the recorded information on the paper strip the following information: the steady state pressure, *Po*, before application of the tonometer, the amount of elevation or increment of pressure, ΔP, above the steady state pressure during the recording, and the resultant loss of fluid volume, ΔV, from the eye during the same period. As will be shown subsequently, the rate of loss of ocular volume, $\frac{\Delta V}{T}$, or increased escape of fluid during recording, is found to be directly proportional to the amount of increase in pressure, i. e.,

$$\frac{\Delta V}{T} = C \cdot \Delta P$$

or, in a more convenient expression, volume loss is proportional to the product of the pressure increment and the time of application, i. e.

$$\Delta V = C\,\Delta P \cdot T$$

the tonometer, and from this one can calculate the coefficient of rigidity for the normal, undisturbed eye. Determined in this manner, the coefficient of rigidity is essentially identical with that which is held to represent the condition of the eye when under compression by the tonometer, suggesting that distortion or oblation of the globe by the Schiøtz tonometer has little influence on the rigidity of the sclera.

The total change in ocular volume or loss of fluid which occurs from beginning to end of the recording becomes equal to the product of the changing pressure increment from beginning to end times the time, but this is found to be adequately represented by an arithmetical average of the pressure increment for successive half-minute intervals times the total time, i. e.,

$$\Delta V = C\,(Av.\,P_T - Po)\,T$$

The coefficient in which we are interested, C, which represents the rate at which fluid can be expressed from the eye by pressure, in terms of cubic millimeters per minute per millimeter (mercury) pressure, is obtained arithmetically from the expression

$$C = \frac{\Delta V}{(Av.\,P_T - Po)\,T}$$

Information on the net rate of flow of aqueous humor through the eye under steady state conditions can be obtained by utilizing the pressure coefficient, C, in conjunction with the estimated steady state pressure. Thus, at the steady state pressure, Po, when the net rate of aqueous humor formation and the rate of outflow, K, are equal, Po presumably represents the pressure required for the escape of aqueous humor at the rate K, owing to the resistance to outflow expressed by the pressure coefficient of outflow, C, i. e.,

$$K = Po \cdot C$$

It will be seen from experimental data to be presented that the net rate of flow of aqueous humor, K, for normal eyes arrived at in this manner from determinations of Po and C corresponds reasonably well with the generally accepted values which have been obtained by other methods.

APPARATUS

The Müller electronic tonometer has been adapted to recording by taking the alternating current voltage between the cathode of the 6J5 tube and ground, on the advice of the manufacturer, and rectifying this voltage to filtered direct current by means of a full wave selenium instrument rectifier (Conant type M) with a 10 microfarad (25 volt) electrolytic condenser across its output. This direct current voltage is connected to a direct current amplifier (Sanborn, model 124), operated at full amplification. The output of the amplifier drives a recording galvanometer (Sanborn, model 123) with special slow speed drive to give a paper movement of 30 mm. per minute. This arrangement gives essentially edge to edge recording on the paper for full scale swing of the tonometer needle. To obtain smooth movement of the tonometer plunger, as evidenced by a good pulse wave in the recording, it was found helpful to buff the sliding metal parts of the tonometer to a higher luster than that furnished by the manufacturer. At each recording run, a calibration scale is recorded on the paper strip by manually positioning the tonometer plunger to bring the tonometer needle successively to each full unit of the tonometer scale for a few seconds. Any point on the recording from the eye is evaluated by reference to this recorded calibration scale.

RESULTS

A typical recording of five minutes duration from a normal human eye is reproduced in figure 2. Recordings of this nature are feasible over considerably longer periods and have been made for as long as twenty-three minutes, limited only by the tonometer's eventually going off scale.

The relation of pressure increment, time and volume loss during a single recording on a typical normal eye is presented in figure 3, in which the progressive loss of volume, ΔV, is plotted against the product of pressure increment, ΔP, and time. From the approximately linear relation which is apparent, it can be deduced that the loss of volume

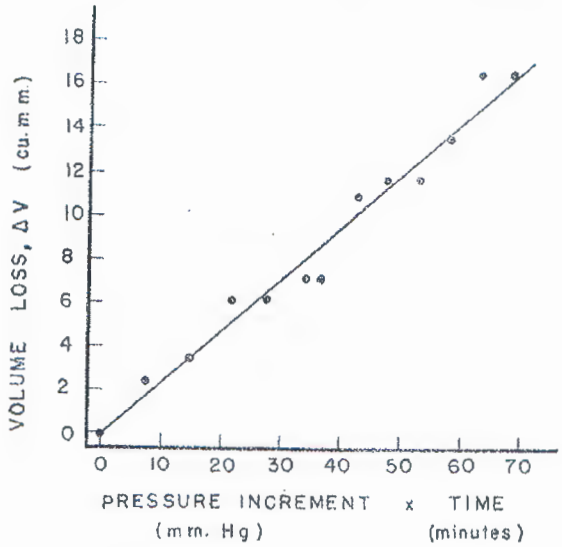

Fig. 3.—Relation of progressive loss of volume from a normal eye to the product of the intraocular pressure increment induced by the weight of the Schiøtz tonometer (with 5.5 Gm. weight) and its duration of application.

is proportional to the product of the pressure increment and its duration.

A representation of the relation of rate of loss of volume, $\Delta V/T$, to the pressure increment, Av. $P_t - Po$, which is induced by the weight of the tonometer, is given in figure 4. The data in this figure were obtained by several runs on the same normal eye, using four different plunger weights (5.5, 7.5, 10 and 15 Gm.) to extend the range of pressures employed. It appears that for the pressure range which was studied the rate of loss of volume was proportional to the increase in intraocular pressure to which the eye was subjected. It is of considerable interest to observe also that the experimental points in this figure

which represent progressive loss of volume and decrease in pressure extrapolate toward zero rate of volume loss at zero pressure increment, indicating a tendency to return during tonographic recording to the pressure, *Po*, which obtained in the original normal steady state. It may be deduced that the equivalence of flow in and flow out, which is disturbed by application of the tonometer, tends to reestablish itself as the pressure drops toward *Po* while the tonometer continues on the eye. If the tonometer was removed from the eye after a period of recording, the intraocular pressure was then lower than normal; and if periodic brief measurements were made during the period of spontaneous recovery in a normal eye, a similar approach to *Po* was observed with diminishing

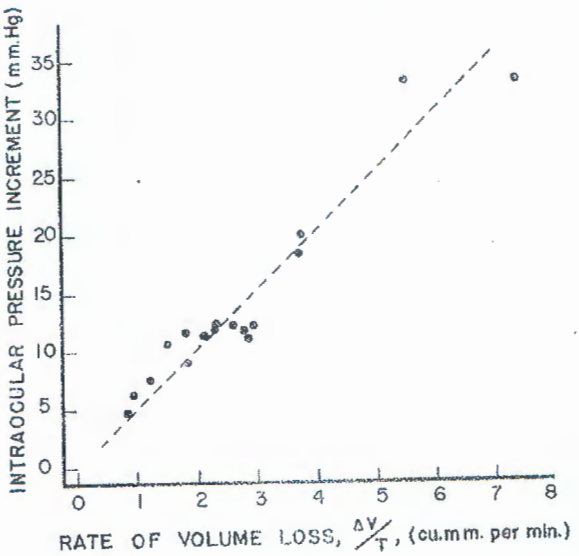

Fig. 4.—Relation of the rate of loss of volume from a normal eye to the increment in intraocular pressure produced by the weight of the Schiøtz tonometer.

rate of regain of volume to zero, again reestablishing the steady state pressure, *Po*. The latter observations have not been included in the figure, both in the interest of simplicity and because they are not entirely germane to the methods of measurement primarily under consideration.

The results of measurements on a series of normal eyes of *C*, the rate of expression of fluid per millimeter of pressure, and of *K*, the inferred approximate net rate of aqueous flow, at the steady state are presented in table 2.

Tonographic measurements were also made on enucleated normal human eyes which had been immersed in saline solution long enough to have established a fairly constant intraocular pressure. In these eyes the intraocular pressure which obtains during bathing in sodium chloride

solution is a function of the osmotic pressure of the bathing solution. When the rate of osmotic gain of water and the rate of leakage of aqueous humor are nearly equilibrated, as indicated by a very small rate of spontaneous change of intraocular pressure, an approximation of steady state conditions exists. Values for C which are obtained under these conditions average close to the values obtained for normal living human eyes.

CORRELATIVE EXPERIMENTS

Additional experiments, intended to aid in determining the validity of the present methods of measurement and calculation, were carried out thus: Recordings were made on rabbit eyes in the same manner as for human eyes; but, because adequate conversion data are not yet available for the pressure and volume relations of this species, only qualitative, or at best semiquantitative, measurements have been possible. However, by comparison of relative rates of change in the tonometer

TABLE 2.—*Measurements of Pressure Coefficients and Net Rates of Flow*

	Pressure Coefficient of Outflow, C (Cu. Mm./ Minute/Mm. Pressure)	Steady State Net Rate of Aqueous Flow, K (Cu. Mm./Min.)
31 normal human eyes	Range, 0.15 to 0.34; average, 0.243	Range, 2.3 to 5.4; average, 3.66
14 measurements on a single eye	Range, 0.15 to 0.24; average, 0.196	Range, 2.4 to 4.5; average, 3.25
8 measurements on another single eye	Range, 0.17 to 0.26; average, 0.215	Range, 2.0 to 3.1; average, 2.73

reading on individual eyes under various experimental conditions, useful information has been derived. In normal rabbit eyes the nature of the decline in pressure during application of the tonometer resembles that in human eyes. When a rabbit is dead, and therefore its aqueous humor formation is diminished, the rate of decline of ocular volume during tonographic measurement, as would be expected, is distinctly greater than that during life. On the other hand, if the aqueous humor of a dead rabbit eye is replaced by a viscous aqueous solution of methyl cellulose, the decline in pressure is very much slowed. Similarly, if aqueous humor outflow in the living eye is impeded by injection of methyl cellulose into the anterior chamber, persistent glaucoma is produced, and the tonographic rate of decline is much reduced.

The rate of fluid outflow from eyes of dead rabbits at various intraocular pressures was determined by means of a simple open manometer and capillary flow meter connected with a needle in the anterior chamber. It was found that the rate of outflow from these eyes was directly proportional to pressure over the range measured of 20 to 60 mm. of mercury.

COMMENT

It has long been known that pressure on the eye would cause a temporary fall in intraocular pressure, and it has been noted several times that in glaucomatous eyes the decrease in intraocular pressure on repeated or sustained tonometry is generally not so great as in normal eyes. In such previous observations no attempt was made to utilize the knowledge of the decrease in intraocular pressure to provide quantitative information on rates of aqueous humor flow. However, after the present method had been developed, I learned from Dr. Friedenwald that Moses and Bruno had previously obtained information on progressive changes in volume in the eye in response to sustained compression with the Schiøtz tonometer. Dr. Moses furnished a prepublication description of their work, which is now in print.[3] According to this description, Moses and Bruno employed the electronic tonometer with periods of application of only one to two minutes, and read or obtained a photographic record of the movement of the tonometer needle during this time. They made estimates of the rate of volume loss from the eye and related this to total intraocular pressure during measurement. However, in their estimate of change of volume they considered only the change in corneal indentation by the tonometer and neglected the change in scleral distention, which is of similar magnitude. They did not utilize their data to calculate pressure coefficients of outflow or steady state net aqueous humor flow. The short period which they employed for measurement would seem to be disadvantageous in the light of experience with the longer electronic tonographic recordings, for not infrequently during the initial one-half to one minute of recording the ocular tension may behave somewhat erratically as compared with the relatively consistent rate of change which is recorded in subsequent minutes.

The principal questions which require discussion in connection with the validity of the method of measurement described in the present report concern the interpretations of the data rather than the instrumental technic. It is important to establish whether the fluid expressed from the eye by artificially increased pressure is in fact the aqueous humor, and whether the decrease in ocular volume which is observed is attributable in significant degree to expression of blood from the intraocular vascular bed or to suppression of formation of aqueous humor. That the change in ocular volume under compression is primarily a function of facility of escape of aqueous humor is indicated by the observations which were made on living and on dead normal rabbit eyes, as well as on eyes with artificially viscous aqueous humor. Thus the rate of tonographic decline was even greater in dead eyes in which

3. Moses, R. A., and Bruno, M.: The Rate of Outflow of Fluid from the Eye Under Increased Pressure, Am. J. Ophth. **33**:389-397, 1950.

the formation of aqueous humor had previously been arrested and the vascular bed had collapsed than in living eyes. Furthermore, by repletion of the aqueous humor in dead eyes by injecting saline solution, the curves could be repeated, and by substitution of methyl cellulose solution they could be strikingly altered, as they could in life by the same procedure. Further evidence that expression of blood or suppression of formation of aqueous humor contributes little to the changes in ocular volume which are measured in normal human eyes is furnished by the observation that the pressure coefficients of outflow are of the same magnitude for normal eyes as for eyes which are dead and enucleated, and therefore devoid of a blood circulation and a vital mechanism of aqueous humor formation. It is concluded for the present, until better evidence can be adduced, that in the method of measurement described in this report it is principally the increased outflow of aqueous humor that is measured and that the inaccuracy introduced by expression of blood or depression of inflow is probably small.

SUMMARY

A continuous automatic recording of the ocular tension is obtained for periods usually of five to six minutes from an electronic paper strip recorder connected to a commercial electronic Schiøtz tonometer while the foot plate and plunger assembly rests on the cornea. From these data are determined the steady state pressure, the pressure during the measurement procedure and the volume of fluid expressed from the eye. The rate of volume loss is proportional to the increment of pressure above the steady state pressure. A coefficient for the facility of aqueous humor outflow is calculated in terms of cubic millimeters per minute per millimeter (mercury) of pressure, yielding values of 0.15 to 0.34, with an average of 0.243, for normal human eyes, assuming on the basis of evidence presented that factors other than increased outflow of aqueous humor contribute little to the measured volume loss. From this coefficient and the steady state intraocular pressure is calculated the rate of outflow under steady state conditions, this rate being considered equal to the net rate of aqueous humor formation under those conditions. Values for normal eyes varied from 2.3 to 5.4 cu. mm. for 34 eyes, with an average of 3.66 cu. mm. per minute. This method is believed to present a means for discerning in what measure alterations of steady state intraocular pressure are due to changes in resistance to outflow or in what measure to changes in net rate of aqueous humor formation. Applications which are being made of the method include investigations of the mechanisms of glaucoma and of the effects of various medical and surgical influences in normal and in glaucomatous eyes.

243 Charles Street (14).

Miss Elizabeth O. Cushing has assisted in all aspects of this investigation, and Dr. Robert R. Trotter gave assistance in carrying out preliminary studies.

Re-evaluation of the Schiotz tonometer calibration

Douglas R. Anderson and W. Morton Grant*

The calibration scale for the Schiøtz tonometers was tested by comparing Goldmann applanation and Schiøtz measurements on the eyes of 906 patients. The study differed from several previous studies in that both the applanation and Schiøtz measurements were made with the subjects lying on their backs, thus eliminating errors due to change in intraocular pressure as the subject changed from one position to another. This direct calibration approach is quite different from the approach used for the currently accepted 1955 scale, which was an indirect calibration based on calculations from theoretical considerations and measurements on enucleated eyes. In this study, the average intraocular pressure (measured by applanation) for any given Schiøtz scale reading was higher than predicted by the 1955 scale and is closer to the 1948 calibration scale. Analysis of the data also points out that calibration scales give only an average value for intraocular pressure, and that because of varying ocular rigidities, the Schiøtz reading indicates only that the intraocular pressure is within a certain range. The table giving the results of this study indicates a range of values with 95 per cent confidence in addition to an average value.

Key words: Schiøtz tonometry, Schiøtz tonometer calibration, applanation-Schiøtz comparison.

As the Goldmann applanation tonometer is used more and more, there would seem to be less need for an accurate calibration scale for the Schiøtz tonometer. This is particularly true since extreme accuracy is not required to make clinical judgments concerning the treatment of glaucoma. However, when the Schiøtz tonometer is used for tonography, the value obtained for facility of outflow depends heavily upon the accuracy of the Schiøtz calibration scale.

It was decided to test the accuracy of the current calibration scale by making a series of paired applanation and Schiøtz readings. This kind of direct comparison has been done before, but in previous attempts to derive calibration scales from data,[1, 2] the applanation readings were not made with the subject in the same position as for Schiøtz tonometry, namely, lying on his back.

In contrast to calibrations by direct comparison of Schiøtz readings with independently obtained pressure determinations, the currently accepted calibration, the 1955 scale, was obtained by indirect methods involving laboratory measurements on enucleated eyes, comparisons of paired Schiøtz readings on patients, and theoretical calculations.[3, 4] McBain[5-7] also derived a calibration scale by an indirect method that was slightly different. The indirect calibrations suffer from several faults, including possible measurement errors in the data and a number of important assumptions. For example, it is assumed that the effective volume change during tonometry is the volume occupied by corneal inden-

From the Howe Laboratory of Ophthalmology, Boston, Mass.

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tation, the assumption being that there is no other effect—for example, flattening of the posterior part of the globe, due to its being displaced backward into the orbit by the weight of the tonometer. Another problem is the unsettled questions about ocular rigidity,[6, 8-11] how it is best represented mathematically and whether the same mathematical formulation applies equally to living and to enucleated eyes.

Despite these deficiencies, the calibration scale derived by indirect methods was considered to be the best, because the direct calibration by Schiøtz[12] ("closed stopcock" cannulation experiments) were done on enucleated eyes under suboptimal conditions. Only a few data are available from direct cannulation of living eyes.[1, 13] Before the development of the Goldmann tonometer, cannulation was the only method for directly determining intraocular pressure accurately for comparison with the Schiøtz tonometer readings.

Materials and methods

With the subject lying on his back, the pressure of each eye was measured with a Goldmann applanation tonometer, modified for use in the supine-recumbent position. Immediately thereafter, with the patient remaining in the same spot, a reading was made with one of 8 certified electronic Schiøtz tonometers. Usually both eyes were included in the study, but occasionally measurements were made on only one eye. Many, but not all, patients also had their intraocular pressures measured in the sitting position with a Goldmann applanation tonometer, immediately preceding the measurements in the recumbent position; these measurements in the sitting position were for comparison with the applanation measurements in the recumbent position, and these form the data of a separate report.

The applanation measurements were made in the manner prescribed by Goldmann. Repeated measurements were made, alternating from one eye to the other, until successive readings on each eye did not differ by more than 1 mm. Hg. This usually required 3 to 4 measurements on each eye. The final steady value was used in the calculations. For Schiøtz tonometry, two successive applications of 5 to 10 seconds' duration (usually about 7) were made on each eye, separated by a 20 to 30 second interval. The average of the scale readings read from the tonographic chart was used in the calculations. For both the applanation and Schiøtz measurements, the values were taken from the middle of the swing of the ocular pulse.

The applanation tonometers, one for use in the sitting position and another for use in the recumbent position, were standardized by means of the standard calibration bar supplied with the Haag-Streit instrument. The accuracy of the Goldmann tonometer readings has on occasion been tested by use of cannulation manometry on enucleated eyes. The Mueller-Schiøtz electronic tonometers were certified by the approved testing stations. An independent confirmation of conformity to specification No. 5 of the Committee on Standardization of Tonometers was obtained for plunger excursion and plunger tip profile. The plunger excursion was found to agree within the required limits by micrometer measurement, and the radius of curvature of the tip of the plungers was established as being within the required dimensions by measurements on highly magnified photographs of the plunger tips.

Almost all of the subjects were patients who had been referred for consultation regarding the diagnosis or treatment of glaucoma. The majority were adults of middle age or older. As far as we know, there was nothing unusual about the distribution of types of refractive error. None of the subjects had previous surgery on the cornea or scarring of the cornea from any other cause.

All tonometries were done by Dr. Grant, and the analysis and interpretation were done by Dr. Anderson.

Results and data analysis

Mathematical notations. Italicized capital letters *A* and *S* will be used to denote applanation pressures (in mm. Hg) and Schiøtz readings (in scale units), respectively. Subscripts will be used to denote the plunger load used on the Schiøtz tonometers; thus, $S_{5.5}$ indicates a Schiøtz scale reading with a 5.5 Gm. plunger load.

Italicized lower case letters *a* and *b* will be used for the coefficients of equations, with *a* being the intercept on the *y* axis and *b* being the slope or regresison coefficient. Logarithms are natural logarithms to the base *e*, not common logarithms.

Other notations include standard statistical symbols, such as *N* for number of observations or data points, *P* for probability of the null hypothesis, and *r* for correlation coefficient.

Population and data characteristics. Data were collected from 906 patients. Paired applanation and Schiøtz readings were obtained for 700 right eyes and 686 left eyes with a 5.5 Gm. weight, for 173 right and 178 left eyes with a 7.5 Gm. weight, and for 55 right and 75 left eyes with a 10.0 Gm. weight. Twenty-one per cent of these eyes either had had previous antiglaucoma surgery or were currently receiving antiglaucoma medications. Seventy-five per cent of the eyes were not receiving medical therapy and had not been subjected to surgical treatment in the past. For 3 per cent of the eyes, the treatment status was not recorded.

The applanation readings ranged from 8 to 66 mm. Hg, with 92% of the readings between 14 and 31 mm. (mean = 22.3, median = 21, standard deviation = 6.13).

With the 5.5 Gm. weight, Schiøtz readings ranged from 1.7 to 11.0, with more than 90 per cent of the readings between 3.5 and 7.1 (mean 5.14). With the 7.5 Gm. weight, Schiøtz readings ranged from 2.5 to 8.2, with more than 90 per cent of the readings between 4.0 and 7.0 (mean 5.5). With the 10.0 Gm. weight, Schiøtz readings ranged from 2.2 to 11.3, with 85 per cent of the readings between 4.5 and 10.0 (mean 6.8). It is clear that most of the readings are below the scale reading of 8.0, and there were only a few as high as 10.0. Therefore, the results of this study, if used as a calibration scale, can be used with greatest confidence in the range between scale readings 3 and 8. There is less confidence for use beyond scale readings of 10.0, where the scale becomes an extrapolation beyond the limits of the data. Fortunately, there is rarely a need to know the pressure corresponding to higher scale readings.

There was a very highly significant correlation between the right and left eyes, as shown in Table I. In all cases, P is less than 0.001. This high degree of correlation reflects a tendency for the two eyes to have the same pressure.

Plan of data analysis. The basic assumption of this study is that readings made with a Goldmann applanation tonometer are accurate measurements of intraocular pressure (P_o). The goal of the data analysis is to derive a table that will give the applanation reading, $A = P_o$, that corresponds to any given Schiøtz scale reading, S. This is done most easily by deriving an equation that expresses P_o or A as some mathematical function of the Schiøtz readings: $P_o = A = f(S)$.

Table I. Correlation between readings on right and left eyes

Measurement	*N*	*Correlation coefficient (r)*
Applanation pressure	815	0.671
Schiøtz reading, 5.5 Gm.	649	0.690
Schiøtz reading, 7.5 Gm.	147	0.329
Schiøtz reading, 10.0 Gm.	39	0.666

The first step is to choose the appropriate form for the equation. Next it must be determined whether each of the 8 different tonometers gives the same result. Then it is to be determined whether the tonometers give equivalent results on treated and untreated eyes. Finally, the desired mathematical equation is derived; from this a calibration scale is to be tabulated and its characteristics examined.

Choice of the form of the mathematical equation. When any of the historical or current calibration scales[1-4, 12, 17] for the Schiøtz tonometer is plotted on a graph, the result is a curved line. Inspection of the curves suggested that a logarithmic function might describe the line. Indeed, when semilogarithmic plots of the previous calibrations are made, most of them form a nearly straight line, and especially the 1955 calibration scale (Fig. 1).

Therefore, in a trial run, the data were fitted to a linear function with log A as the independent variable and S as the dependent variable. Only the right eyes were used, since methods that test statistical significance would be invalidated if data points were duplicated due to a high de-

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N	Correlation coefficient (r)
815	0.671
649	0.690
147	0.329
39	0.666

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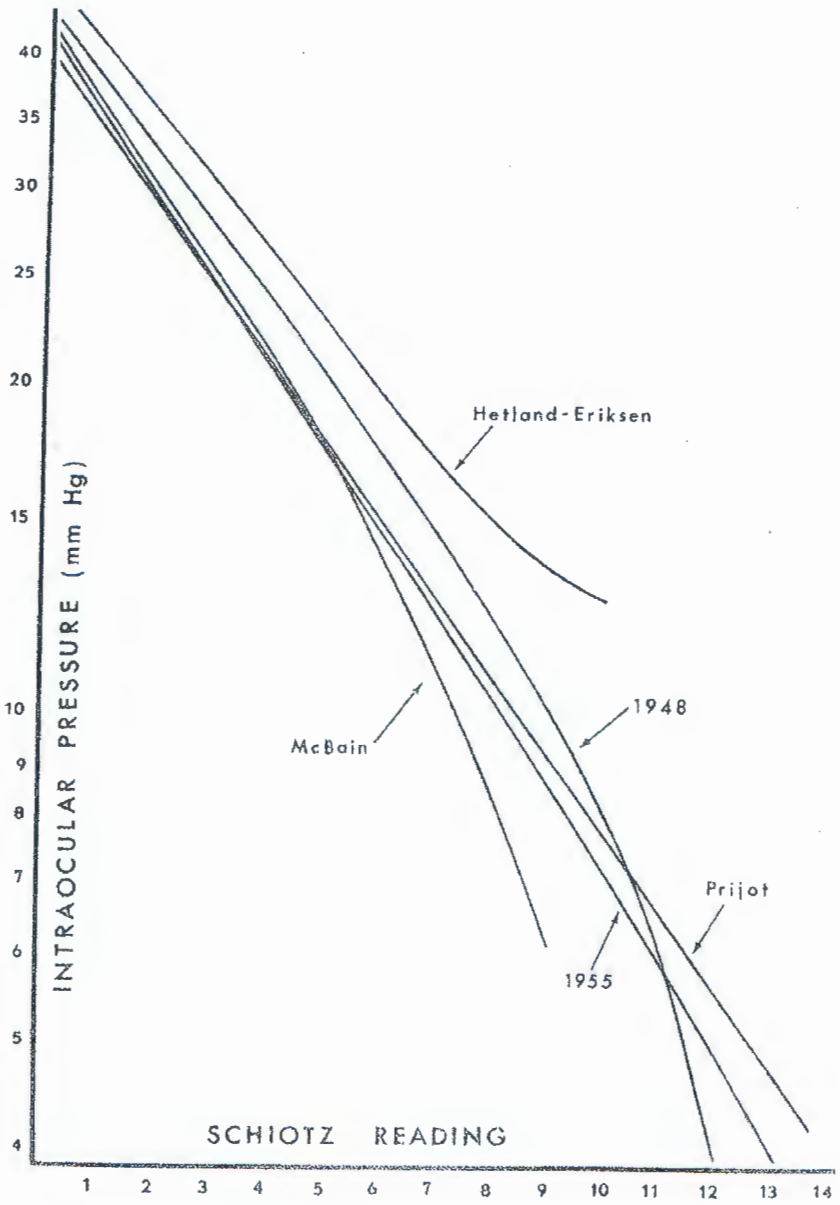

Fig. 1. Calibrations of the Schiøtz tonometer for a 5.5 Gm. plunger load on a semilogarithmic plot. The 1955 calibration scale and that devised by Prijot (1960) are nearly linear. The other calibration scales are linear for the low Schiøtz readings, but become curved for higher readings. Omitted are the calibration by Schiøtz in 1909, which is close to the 1955 scale, and the calibration by Schiøtz in 1924, which is close to the calibration of Hetland-Erikson (1966).

gree of correlation between the behavior of the right and left eyes of the individual patients.*

There were 667 right eyes that had readings made with a 5.5 Gm. plunger load paired with an applanation reading. The mean Schiøtz reading ($S_{5.5}$) was 5.18 and the mean log A was 2.99 ($A = 19.9$). The regression coefficient (b) determined by the least squares method was –4.203 (S.E. = 0.11475). This gives the equation $S_{5.5} = 17.76051 - 4.10200 \log A$. The correlation coefficient (r) between the variables log A and S was –0.81767 ($P << 0.01$). In an analysis of variance comparing variation due to the regression line with deviation about the regression line, an F value of 1341.53 ($t = \sqrt{F} = 36.62691$) was obtained ($P << 0.01$, since an F value of 6.6 is significant at 0.01 level). This statistic indicates that the data points are closely grouped about the regression line, and that the semilogarithmic equation describes very well the relationship between A and $S_{5.5}$ as determined by the data points. The mean square deviation of the points to the regression line is 0.33353 units on the Schiøtz scale.

The goodness of fit to a logarithmic equation was confirmed for the 7.5 Gm. plunger load. There were 167 right eyes with Schiøtz readings, with a 7.5 Gm. weight. The least squares method yielded the equation $S_{7.5} = 22.20514 - 5.06126 \log A$ ($r = 0.7708$). The mean square deviation from the regression line was 0.31277 Schiøtz scale unit, and the F value was 241.5318.

Other equations were tested, with the data for the 7.5 Gm. plunger load. The data were fitted to a linear equation, yielding $S_{7.5} = 7.2122 - 0.06292\ A$ ($r = -0.44999$). The mean square deviation about the regression line was 0.597, and an analysis of variance yielded an F value of 43.418 ($P < 0.01$).

The data were also fitted to a binomial equation of the form $S = f(A)$, yielding $S_{7.5} = 5.70565 + 0.14068\ A - 0.0053\ A^2$. The mean square deviation from the regression line was 0.34975, with an F value of 98.09244 ($P < 0.01$).

It can be seen that of the equations tested, the data coincide best (lowest mean square deviation, highest F value) with the semilogarithmic equation. This was also evident visually when the three regression lines were plotted along with the data points. The linear and binomial equations for $S = f(A)$ had the further unsatisfactory feature that they predict that no matter how low the intraocular pressure ($P_o = A$), the Schiøtz reading (S) never becomes larger than 7 scale units, which is not in accord with reality.

We did not test the reverse binomial equation, $A = f(S)$. This is the form of the equation that was used by Hetland-Eriksen, whose data fit the regression $A = P_o = 46.028 - 6.0755\ S_{5.5} + 0.2738\ S^2_{5.5}$. It is interesting to note that, when his regression line is plotted on semilogarithmic paper (Fig. 1), it gives a nearly straight line for scale readings under 9. This suggests that within the range of 3 to 8 scale units, wherein nearly all of the data lie, the semilogarithmic equation and binomial equation ($A = f(S)$) would give identical results, and either could be used. The binomial equation of the form $A = f(S)$, however, has an unsatisfactory feature—above scale unit 11 or 12, the P_o becomes higher again, and there are no Schiøtz readings corresponding to pressures under 10 mm. Hg (for scale reading 12, $P_o = 13$;

*As already mentioned, there is a highly significant correlation between the pressure of the right and left eyes measured by either applanation or by Schiøtz tonometry (Table 1). This in itself would not invalidate the statistical tests, but if a Schiøtz reading of the right eye were lower than average for its applanation pressure reading, statistical trouble might arise if the left eye would tend also to have a lower than average Schiøtz reading for its applanation tension. This would occur, for instance, if the two eyes of a given individual tend to have similar ocular rigidities.

After the calibration scale had been produced, it was possible to actually test this possibility. The equation $\log A = 3.80735 - 0.16023\ S_{5.5}$ was used to predict the applanation pressure of each eye from its Schiøtz reading. The difference between the actual applanation pressure of an eye and the predicted applanation pressure (the difference is called the "residual") was determined. The correlation of the residual of the right eye with the residual of the left eye was tested, yielding a correlation coefficient, $r = 0.7014$ ($N = 539$, $P << 0.001$). This shows that there is a very significant correlation between the ocular rigidities of the two eyes of an individual, and that the decision was well founded to use only the data from right eyes for the initial stages of the data analysis.

Table II. Regression lines for 8 Schiøtz tonometers* ($S_{5.5} = a + b \log A$)

Tonometer	N	Coefficients: Intercept (a) scale units	Coefficients: Slope (b) scale units per mm. Hg	Mean $S_{5.5}$ scale units	Mean log A	Antilog of mean log A (mm. Hg)	Correlation coefficient $S_{5.5}$ vs. log A
1	57	16.64746	-3.66542	5.58594	3.01780	20.45	-0.83566
2	43	18.17987	-4.33078	5.19999	2.99713	20.05	-0.90398
3	25	16.11223	-3.72530	4.83200	3.02800	20.67	-0.85844
4	138	17.30283	-4.05451	5.30573	2.95895	19.3	-0.79918
5	55	15.99232	-3.64834	5.02362	3.00649	20.2	-0.81960
6	103	19.71834	-4.86743	4.95237	3.03363	20.8	-0.86484
7	70	16.33148	-3.81817	5.04853	2.95507	19.2	-0.81484
8	8	18.07509	-4.35004	4.82500	3.04597	21.0	-0.90019

*Based on untreated right eyes only.

for scale reading 15, $P_o = 17$; and for scale reading 20, $P_o = 34$). Thus binomial regressions, no matter which is the dependent variable ($A = f(S)$ or $S = f(A)$), give non-sensical results for higher scale readings or lower pressures.

We therefore chose the semilogarithmic equation for the subsequent analysis for three reasons: (1) Of the equation forms tested, it gave the best fit, and when plotted along with the data points, it did not seem that a better line could be chosen. (2) The equation gave sensible results when extended beyond scale readings of 10. This does not mean that it is accurate in this region, but at least it did not give values that are obviously erroneous, as is true of the linear and binomial equations. (3) The semilogarithmic equation is easier to handle statistically, because it can be treated as a linear equation, interchanging S and log A as dependent and independent variables at will, while retaining a linear equation form. This cannot be done with the binomial equation and still retain the same equation form.

Comparison of the 8 Schiøtz tonometers. For this comparison, the function $S = a + b \log A$ was used rather than the relationship $\log A = a + bS$. The reason is that it is hoped to detect discrepancies in the Schiøtz reading (not in the applanation readings), and the basis for the statistical analysis will be a comparison of the actual Schiøtz reading with the Schiøtz reading predicted by the equation from the applanation reading.

Since the effect of treatment had not yet been determined, it was elected to use only untreated eyes in this part of the analysis, and as before, only data from right eyes were used. A regression line for the 5.5 Gm. plunger load was computed for each tonometer separately. The results are shown in Table II, and the regression lines are illustrated in Fig. 2. It can be seen from the graph (Fig. 2) that the regression line for tonometer No. 1 is separated from the others, being shifted upwards by about ½ Schiøtz scale unit.

The apparent difference in tonometers can be expressed numerically in terms of calculated residuals. For each pair of readings (i.e., each data point), the applanation pressure was used to predict the Schiøtz reading based on the equation $S_{5.5} = 17.76051 - 4.2 \log A$ obtained from the previous section.* The discrepancy (which is called the "residual") between this predicted value and the actual Schiøtz reading was determined for each point. The mean of the residuals and the standard deviation of the residuals about the mean are shown in Table III. It can be seen that the mean residual for tonometer No. 1 is +0.5, which corresponds to the graph in Fig. 2, where tonometer No. 1 seemed to be ½ scale unit higher than the others.

To test the statistical significance of these differences, the data were subjected

*Since both treated and untreated eyes had been used to derive the coefficients for the equation, it was elected to use all right eyes, both treated and untreated, to calculate the mean of the residuals shown in Table III, as well as for the subsequent analysis of variance.

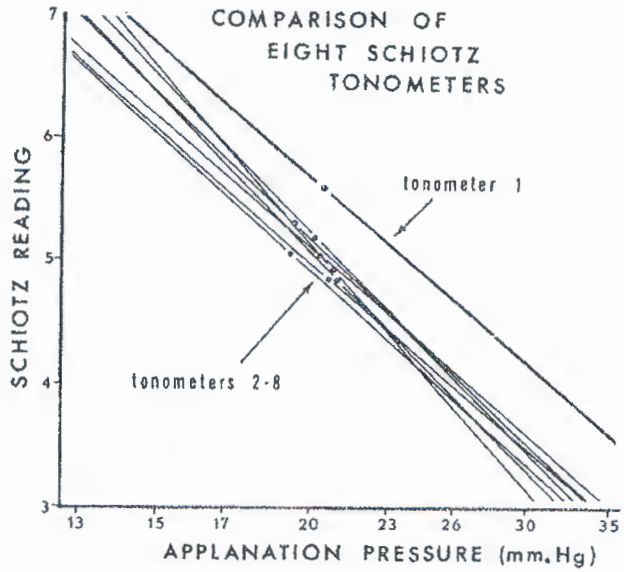

Fig. 2. Comparison of regression lines determined for each tonometer separately. For this comparison, only data from untreated right eyes examined with a 5.5 Gm. plunger load were used. The dot at the center of each regression line indicates the mean Schiøtz and applanation readings for that tonometer.

Table III. Residuals from equation $S = 17.76051 - 4.2 \log A$ (right eyes, treated and untreated, 5.5 gram weight)

Tonometer	*N*	*Mean residual*	*S.d. of residual*
1	81	+0.499	0.568
2	55	+0.014	0.391
3	34	−0.193	0.502
4	186	−0.017	0.573
5	71	−0.088	0.445
6	137	−0.035	0.624
7	92	−0.284	0.480
8	11	−0.029	0.358

Table IV. Regression coefficients (b) for $\log A = a + bS_{a.s}$ (right eyes only)

	Treated		*Untreated*	
Tonometer	*N*	*b*	*N*	*b*
1	14	−0.15466	57	−0.19052
2	11	−0.18258	43	−0.18869
3	9	−0.20350	25	−0.19782
4	46	−0.13579	138	−0.15752
5	15	−0.18004	55	−0.18412
6	19	−0.11588	103	−0.15366
7	20	−0.16540	70	−0.17390
8	3	−0.13467	8	−0.18628

to an analysis of variance. This test, which compared the variance within tonometer groups to variance between tonometer groups, yielded an F value of 14.527 ($P < 0.001$). This indicates that the difference between the tonometers is statistically very highly significant (that the apparent difference is not just a random occurrence). To test how much of this difference was due to tonometer No. 1, the analysis of variance was performed again, this time including only tonometers 2 through 8 in the calculations. This yielded an F value of 3.376 ($P = 0.003$). Thus the F value was considerably reduced by eliminating tonometer No. 1 from the analysis, but there was still a statistically significant difference between the tonometers. This indicates that each of the tonometers has its own characteristic behavior (as expressed by the regression line), presumably due to slight mechanical differences between the tonometers. It is clear, however, that, except for tonometer No. 1, the differences, although consistent, are small.

Table V. Comparison of the regression lines for treated and untreated right eyes for $\log A = a + bS_{5.5}$ (tonometers 2 through 8)

Group	N	Mean S	Mean log A	r	a	b
Treated	123	5.1219	2.99819	−0.83009	3.75817	−0.14838
Untreated	442	5.1017	2.99076	−0.83149	3.83521	−0.16552

To confirm visually the consistency indicated by the statistics, regression lines were determined for each tonometer separately, this time using data from untreated left eyes. When all the right and left eye regression lines were plotted together on the same graph, each left eye regression line was strikingly close to the regression line for the right eye with the same tonometer. As further confirmation, regression lines were determined for all treated right eyes. When all regression lines for untreated right eyes and for treated right eyes were plotted on the same graph, the consistency was again evident, and in particular the regression line for tonometer No. 1 stood apart from the others.

It was concluded from these computations that tonometer No. 1 was in some way aberrant, and for this reason the data derived with tonometer No. 1 were eliminated when the final equation and tables were derived.[9] Even though consistent and statistically significant, the differences between the other 7 tonometers were small, and there was no reason to eliminate any of them from the subsequent calculations.

Treated vs. untreated eyes. It was decided to test the possibility that the regression lines are different for treated and untreated eyes (or possibly different for normal and glaucomatous eyes). Regression lines for the equation form $\log A = a + bS_{5.5}$ were determined separately for treated and untreated eyes, for each tonometer separately. It was recognized

[9] It is interesting to note that several years ago, this tonometer was thought to give readings that were about ½ scale unit too high, and for this reason it was sent away to the tonometer testing station. The tonometer was found to conform to the specifications for electronic tonometers, and no explanation was found for its aberrant behavior.

Table VI. Regression coefficients *(b)* for $\log A = a + bS_{5.5}$ (left eyes only)

Tonometer	Treated		Untreated	
	N	b	N	b
1	14	−0.13501	59	−0.18161
2	10	−0.20037	44	−0.17163
3	7	−0.24158	29	−0.17658
4	41	−0.14797	128	−0.15233
5	18	−0.14017	58	−0.17733
6	18	−0.11620	96	−0.15139
7	21	−0.20648	68	−0.17778
8	2	−1.33531	9	−0.16225

that for each tonometer (except No. 3), the slope *(b)* was less for the treated eyes than for the untreated eyes (Table IV).

To test the significance of this finding, regression lines were determined separately for treated and for untreated eyes, combining the data from tonometers 2 through 8 (thus excluding tonometer No. 1), and using data only from right eyes. The results are in Table V. Student's t test was used to detect a difference between the two slopes, yielding a t value of −0.90 ($P > 0.1$). Thus, there appeared not to be a difference between the regression lines of the two groups.

As a check, regression lines were determined for each tonometer separately, using only left eyes, separated into treated and untreated groups. In contrast to the findings for right eyes (Table IV), the results for left eyes (Table VI) do not show the slope b to be consistently lower in the untreated group. This confirms the belief that the apparently consistent finding in right eyes probably happened by chance.

Final regression lines (calibration scales). On the basis of the preceding analyses, it was decided to eliminate data obtained with tonometer No. 1, but to

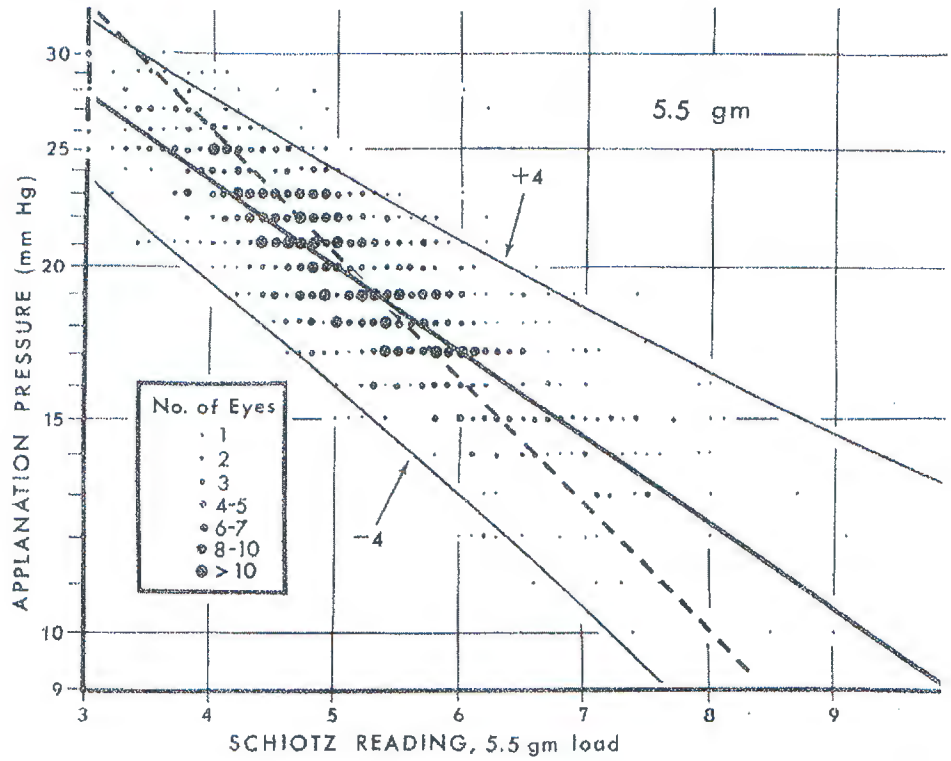

Fig. 3. Regression lines and the 1,157 paired measurements which determine them. The data include all measurements with a 5.5 Gm. plunger load which had a Schiøtz reading greater than 3, excluding all data obtained with tonometer No. 1. The heavy solid line is the regression line with the Schiøtz scale reading as the independent variable. The dotted regression line is the one obtained using applanation pressure as the independent variable. Also indicated is the range defined by 4 mm. Hg above and below the solid regression line.

Table VII. Final regression lines (determined with data from both eyes, treated and untreated, tonometers 2 through 8 eliminating tonometer No. 1 and eliminating data points with Schiøtz readings less than 3)

Plunger load (Gm.)	*N*	*Mean log A*	*Mean S*	*Correlation coefficient*	*Log A = a + bS*		*S = a + b log A*	
					a	*b*	*a*	*b*
5.5	1130	2.98399	5.13858	−0.82382	3.80735	−0.16023	17.77757	−4.23560
7.5	335	3.29060	5.55813	−0.73848	3.95450	−0.11945	20.58171	−4.56561
10.0	98	3.52574	6.41423	−0.87694	4.34501	−0.12773	27.64236	−6.02089

use data from all eyes, both treated and untreated, that had been examined with the other 7 tonometers. It was also elected to eliminate all data points with a Schiøtz scale reading below 3.0—which were very few—because of inaccuracies in the Schiøtz readings below this level.

For each plunger load, regression lines were determined to fit the equations log $A = a + bS$ and $S = a + b \log A$. The results are illustrated in Table VII and in Figs. 3 to 5.

In the table are given coefficients for two equations, one in the form log $A =$

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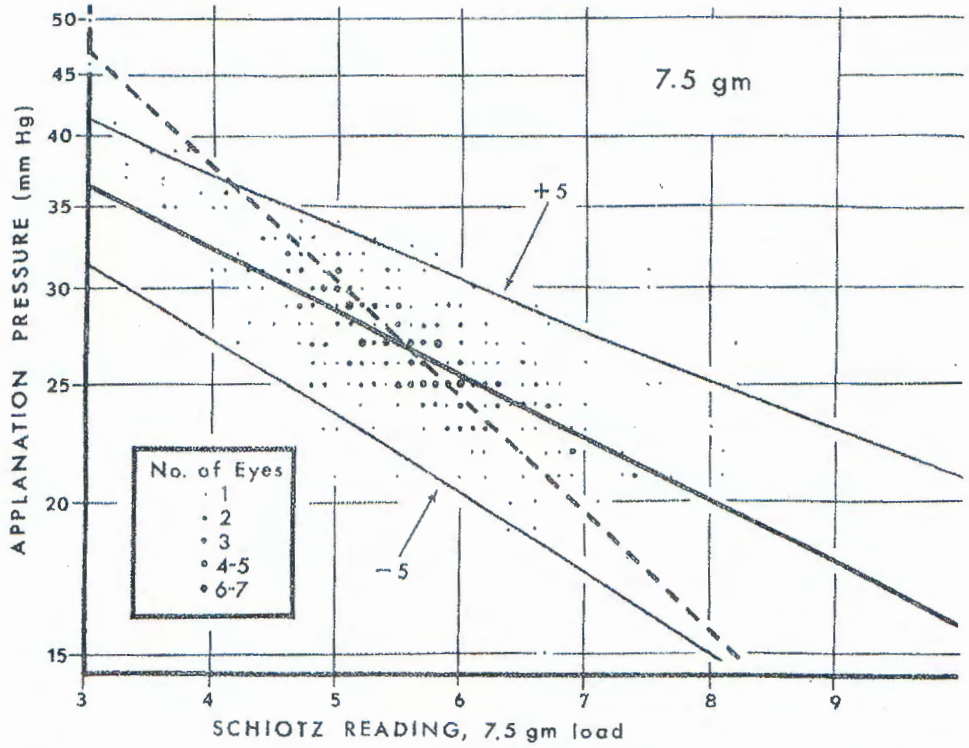

Fig. 4. Regression lines and the 338 paired measurements which determine them. The data include all measurements with a 7.5 Gm. plunger load which had a Schiøtz reading greater than 3, excluding all data obtained with tonometer No. 1. The heavy solid line is the regression line with the Schiøtz scale reading as the independent variable. The dotted regression line is the one obtained using applanation pressure as the independent variable. Also indicated is the range defined by a 5 mm. Hg above and below the solid regression line.

$a + bS$ and the other in the form $S = a + b \log A$. Each equation is determined by the least squares method. The first gives, with the greatest accuracy, the applanation reading that corresponds to a given Schiøtz reading; this is shown by the heavy solid lines in Figs. 3 to 5. The second equation gives, with the greatest accuracy, the Schiøtz reading that corresponds to a given intraocular pressure (determined by applanation); this is shown by the dotted line in Figs. 3 to 5. As seen in Figs. 3 to 5, these two lines do not coincide. The reason for this is not an easy concept to grasp, but it is well known to statisticians that a different regression line is obtained if the dependent and independent variables are interchanged.

To understand the meaning of the two lines, look at Fig. 3, and consider all eyes that have a Schiøtz reading of 4.4 for a 5.5 Gm. plunger load. It can be seen that the applanation pressures of eyes with that Schiøtz reading are distributed equally above and below the solid regression line, which predicts an average applanation pressure of 22 mm. Hg. Most of the points, however, fall below the dotted regression line. On the other hand, if all the eyes with an applanation pressure of 22 mm. Hg are considered, it is clear that more of them are to the right of the heavy line (have higher Schiøtz readings) than to the left, and that the mean scale reading for all eyes with a pressure of 22 mm. Hg is about 4.7 as predicted by the dotted re-

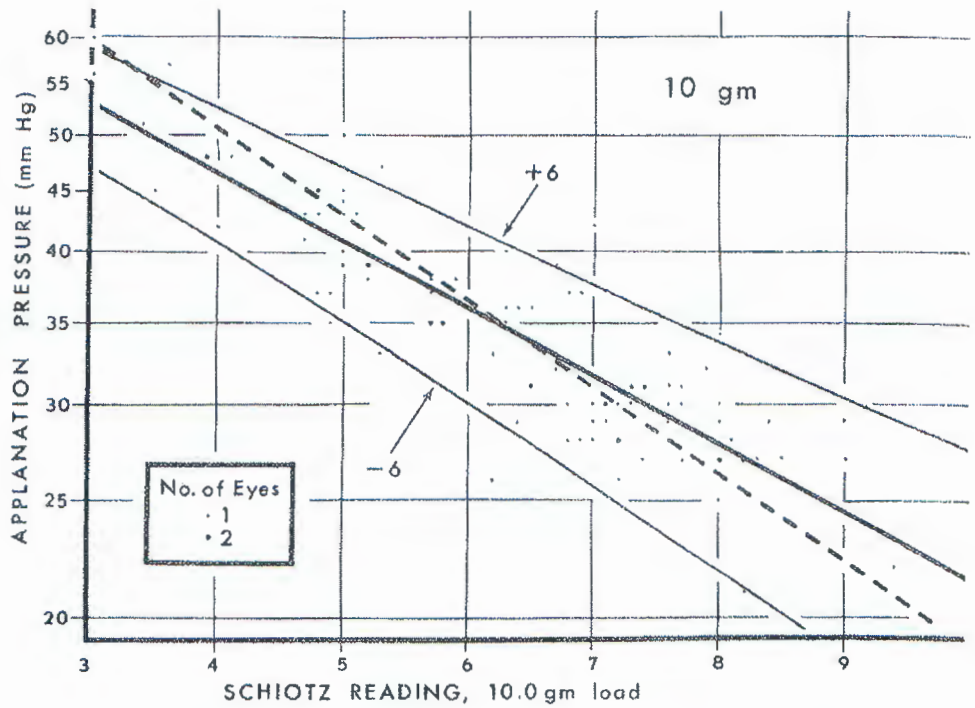

Fig. 5. Regression lines and the 100 paired measurements which determine them. The data include all measurements with a 10.0 Gm. plunger load which had a Schiøtz reading greater than 3, excluding all data obtained with tonometer No. 1. The heavy solid line is the regression line with the Schiøtz scale reading as the independent variable. The dotted regression line is the one obtained using applanation pressure as the independent variable. Also indicated is the range defined by 6 mm. Hg above and below the solid regression line.

gression line. Thus, the regression lines seem to do what the statistical methods promise.

Statistical theory indicates that the amount of discrepancy between the two regression lines is related to the correlation coefficient between the two variables: The higher the correlation coefficient, the closer are the two lines. If the Schiøtz reading had a perfect correlation with the intraocular pressure (i.e., if $r = -1.0$), the two regression lines would coincide and all the data points would fall exactly on the line. However, the Schiøtz reading is determined by other factors (e.g., ocular rigidity and corneal curvature) in addition to intraocular pressure, and the correlation between intraocular pressure and Schiøtz scale reading is not perfect. Thus the two regression lines do not coincide, but because the correlation coefficient is fairly high (near −0.8), the two lines are not really very far apart.

Which of the two regression lines should be used? In biophysical considerations, the dotted regression line would seem more appropriate, since the tonometer reading depends heavily upon intraocular pressure, as well as other factors, and biologically the scale reading is thus properly the dependent variable. Because of this, in previous sections in which we wanted to compare tonometers, we chose to use the mathematical function $S = a + b \log A$.

However, when the tonometer is used in clinical circumstances, one has the Schiøtz reading and wants to know with the greatest accuracy what the patient's

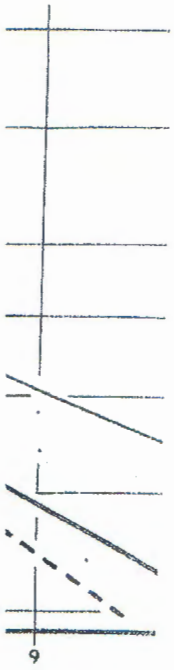

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Table VIII. Applanation pressures for each Schiøtz Reading ($A = P_o$ in mm. Hg)

	Plunger load					
	5.5 Gm.		*7.5 Gm.*		*10.0 Gm.*	
Scale reading	*Mean°*	*Range†*	*Mean°*	*Range†*	*Mean°*	*Range†*
3.0	27.7	24-32	36.5-	31-41	52.6	47-59
3.5	25.5+	22-30	34.3	29-39	49.3	43-55
4.0	23.5+	20-28	32.4	27-37	46.3	40-52
4.5	21.7	18-26	30.5-	25-35	43.4	37-49
5.0	20.0	16-24	28.7	24-34	40.7	35-47
5.5	18.4	14-22	27.0	22-32	38.2	32-44
6.0	17.0	13-21	25.5-	20-30	35.8	30-42
6.5	15.7	12-20	24.0	19-29	33.6	28-40
7.0	14.5-	10-18	22.6	18-28	31.5+	26-38
7.5	13.3	9-17	21.3	16-26	29.6	24-36
8.0	12.3	8-16	20.1	15-25	27.8	22-34
8.5	11.3	7-15	18.9	14-24	26.0	20-32
9.0	10.4	6-14	17.8	13-23	24.4	18-30
9.5	9.6	6-14	16.8	12-22	23.4	17-29
10.0	8.9	5-13	15.8	11-21	21.5-	15-27

°The values given are mean values, given to the nearest tenth of a millimeter for ease in plotting a smooth curve. When a mean value ends in 0.5, it is followed by a plus or minus symbol. A minus symbol indicates that it was rounded off from a value between 0.45 and 0.49, and if the number is to be rounded off again it should be rounded off to a lower value (e.g., 14.5- becomes 14). Conversely, a plus symbol indicates that a number was rounded off from a value between 0.50 and 0.54, and if it is to be rounded off again, it should be rounded off to the next highest integer (e.g., 31.5+ becomes 32).

†The range includes the intraocular pressure of 95 per cent of the eyes that have the given Schiøtz reading.

intraocular pressure is. Obviously, it is the heavy regression line ($\log A = a + bS$), that would give the best estimate of intraocular pressure from any given Schiøtz reading. It is this regression line that was used to give the values in Table VIII.

It was decided to make a final check to see to see if the logarithmic equation form had given good values over the entire range of the data. For this purpose, the mean applanation pressure was determined for eyes that had various Schiøtz readings (Table IX). It can be seen that (taking into consideration the standard error of the mean) the mean values correspond closely to the values given by the regression line (see Table VIII over the whole range of the data.°

It is clear from the scattergrams (Figs. 3 to 5) that the regression line gives only the mean value of applanation pressure for any given Schiøtz reading, but that many individuals are some distance away from the line. For a 5.5 Gm. plunger load, the standard deviation of the applanation pressure was found to be about 2 mm. Hg for various Schiøtz readings along the whole

°In fact, the mean applanation pressures tend to be very slightly higher than that predicted by the equation. This is due to the fact that the equation gives the mean of the logarithm of the applanation pressure, rather than the mean of the applanation pressure itself, and obtaining the mean of the logarithm gives slightly greater weight to values below the mean than to values above the mean. The difference between the two results is fortunately very small.

Table IX. Mean applanation pressure of eyes with various Schiøtz readings (5.5 Gm. plunger load)

Schiøtz reading	*N*	*Mean applanation pressure of all eyes with given Schiøtz reading*	*S. E. M.°*
3.0	11	28.1	0.6
3.5	12	26.1	0.577
4.0	30	24.3	0.365
4.5	44	21.9	0.302
5.0	52	20.0	0.277
5.5	39	18.5	0.320
6.0	35	17.5	0.338
6.5	14	16.1	0.53
7.0	10	15.0	0.633
7.5	4	13.3	1.000
8.0	5	14.0	0.894

°Based on an average standard deviation of 2 mm. Hg.

range of Schiøtz readings.* Since 95 per cent of the individuals are expected to be within 2 S.D. of the mean, lines were placed on the scattergram (Fig. 3) that correspond to the regression line plus 4 mm. Hg and the regression line minus 4 mm. Hg. The range defined by these two lines contained 96 per cent of the points, and 4 per cent of the eyes were outside the interval.

In a similar manner, a range was defined for the 7.5 Gm. plunger load by the regression line plus or minus 5 mm. Hg, and this range was found to include all but 6 per cent of the data points. For the 10.0 Gm. plunger load, a range was defined by the regression line plus or minus 6 mm. Hg and included 94 per cent of the data points. The wider range for the heavier plunger loads is undoubtedly a reflection of the fact that with increasing weight on the plunger, ocular rigidity has a greater influence on the resulting scale reading.

These ranges are given in Table VIII and are intended to include about 95 per cent of the individual eyes. Despite seemingly wide ranges, 1 out of 20 eyes with a given Schiøtz reading will be outside the given range for that reading; 1 out of 40 will have pressures higher than the upper limit of the range indicated for that Schiøtz reading. (Actually, it would be slightly more than 1 out of 40 that would be higher, since, as can be seen from the scattergrams [Figs. 3 to 5], there is a tendency for more individuals to be above the range than below the range.)

Discussion

The approach used in this study, if considered to be an attempted calibration of the Schiøtz tonometer, has two advantages over the methods used to derive the 1948 and 1955 calibration scales. All measurements for the 1948 and 1955 calibrations were done on enucleated eyes,* which might respond differently to the Schiøtz tonometer, owing to influence of blood flow in the living eye or to postmortem changes in cornea and ocular rigidity. Also, this study is a direct comparison of Schiøtz readings with an independent determination of intraocular pressure, rather than indirect calculations involving many assumptions used for the 1948 and 1955 calibrations.

In Figs. 6 to 8, the regression lines derived in this study are compared with the 1948 and 1955 scales, both of which were derived by the indirect calibration method described in the introduction. It can be seen that the results of this study indicate a higher P_o than the currently accepted 1955 calibration scale.

This is certainly not the first time that a series of applanation and Schiøtz readings have been made on the same eyes. In only three of the previous studies,[14-16] however, were the applanation readings made with the subjects lying on their backs, in the same position as for Schiøtz readings. The findings of this study and of the three previous ones are in agreement; the applanation pressures were higher than indicated by the Schiøtz readings converted by the 1955 calibration scale.

In two other studies,[3, 17] Schiøtz readings were compared with applanation pressures taken when the subject was lying on his side. Again, the applanation pressures were higher than would be predicted by the 1955 calibration scale. In one of these studies,[3] a calibration table was constructed, and it gave even higher values

*As indicated, the standard deviation of the applanation pressure was the same over the whole range of Schiøtz readings. This implies that the standard deviation of the logarithm of the applanation pressure would vary along the range of Schiøtz readings. This was found to be true, with the standard deviation of the logarithm being smaller for the lower Schiøtz readings than for the higher Schiøtz readings. This fact violates some of the assumptions in the statistical methods for determining regression lines, etc., but probably there is little error introduced by this violation of statistical method.

*Dr. Elmer J. Ballentine pointed out to us that this is not strictly true. The measurements on enucleated eyes were made first to determine the P_t vs. R readings, the volume of corneal indentation directly using excised corneas, and the general mathematical form of the relationship of ΔP to ΔV. The ocular rigidity coefficient was then determined by calculation from several thousand paired Schiøtz tonometer readings using the 5½ and 10 Gm. weights obtained by Drs. Grant, Kronfield, and Ballentine. The constants were further adjusted to make the average reading with the 5½ Gm. weight approximately 17 mm. Hg upon the advice of Dr. Goldmann following his preliminary experiments with the applanation tonometer.

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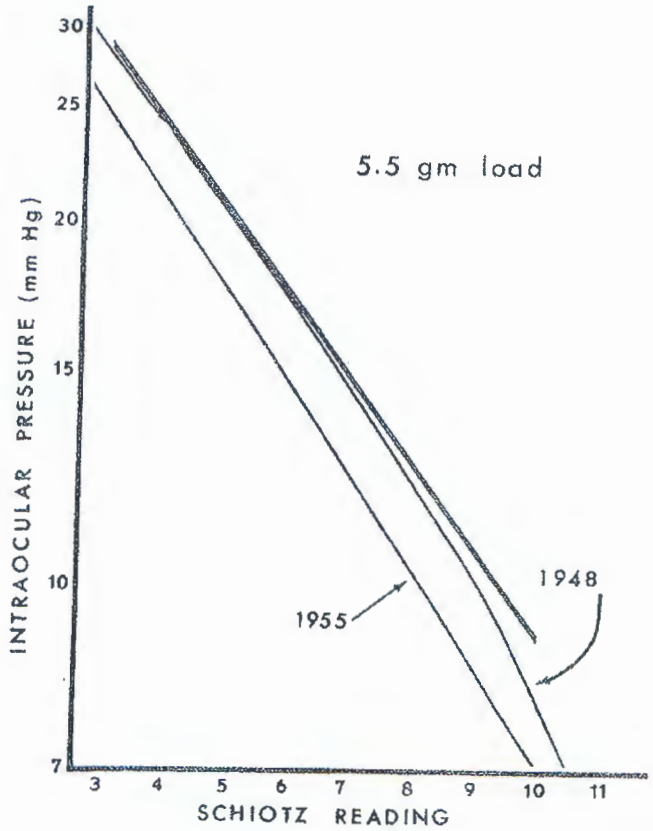

Fig. 6. Comparison of the regression line (heavy line), obtained with Schiøtz scale reading as the independent variable, with the 1948 and 1955 calibration scales (5.5 Gm. plunger load).

for P_0 than Table VIII of this study. Probably this is related to the fact that there is often a higher intraocular pressure when a subject is lying on his side than when he is lying on his back (observation to be published), although this was postulated not to be the case when the studies were done.

In all the remaining comparisons, the applanation pressures were taken with the subject sitting at a slit lamp. There were three categories of results. In some, the 1955 scale gave a value for P_0 that was higher than the applanation pressure.[18-23] These findings, which are the opposite of the findings in this study, were usually interpreted to mean that the intraocular pressure had risen when the subject lay down, and that the findings confirmed the accuracy of the 1955 calibration scale.

In other studies the average sitting applanation pressure was the same as the P_0 from the 1955 calibration scale.[24-27] This would again tend to confirm the 1955 calibration, unless it is assumed that the intraocular pressure is higher when recumbent than when sitting. If that is the case, it would have to be concluded that the P_0 given by the 1955 scale is too low.

Finally, in some series, the P_0 given by the 1955 scale was lower than the sitting applanation pressure,[28-31] which implies that 1955 scale gives too low a value of P_0 no matter whether the intraocular pressure rises or not upon lying down.

How can these different studies be

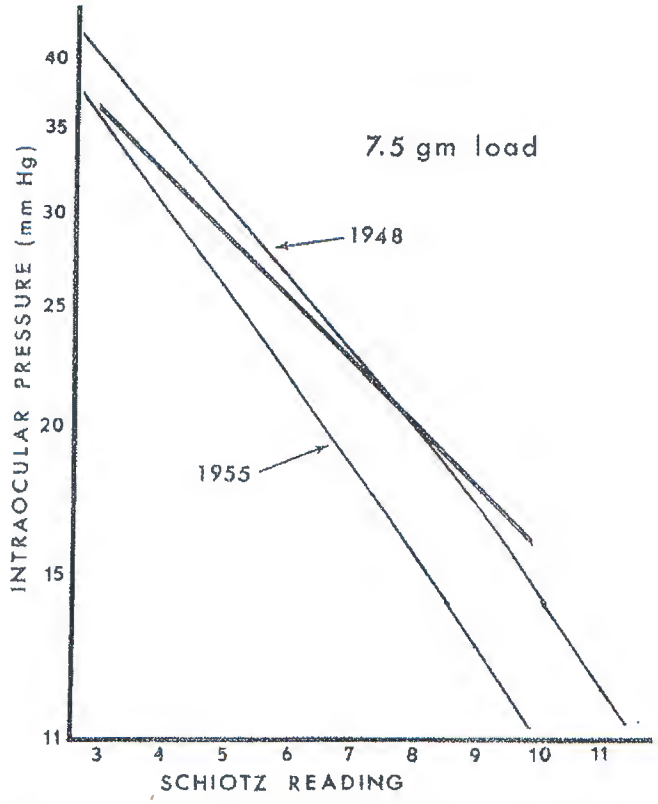

Fig. 7. Comparison of the regression line (heavy line), with Schiøtz scale reading as the independent variable, obtained with the 1948 and 1955 calibration scales (7.5 Gm. plunger load).

reconciled? Goldmann[29] suggested that glaucoma is associated with a lower than normal ocular rigidity. Thus, the Schiøtz readings (converted with the 1955 scale) would correspond to the applanation pressure in normal eyes, but in glaucoma the 1955 scale would give too low a value. This consideration does not bring all the studies into agreement, however, since most of them were done during surveys of normal populations.

Probably there are additional factors that are different in the various studies. In some studies, for instance, the two pressure determinations were done in different rooms and sometimes by different examiners. Other conditions varied undoubtedly, such as the length of time between measurements (and coincident evaporation from anesthetized corneas), the degree of patient relaxation and comfort in different positions, etc.

Since the differences are small (around 2 to 3 mm. Hg), it seems likely that the paired determinations would be most accurate if extraneous factors were eliminated by making both measurements in the same supine recumbent position, with a minimal time interval between measurements, without requiring the subject to move from one place to another between measurements. The results of this study are in agreement with the two other studies where these conditions were fulfilled.

Finally, it should be noted that electronic Schiøtz tonometers were used for this study, since the primary interest in

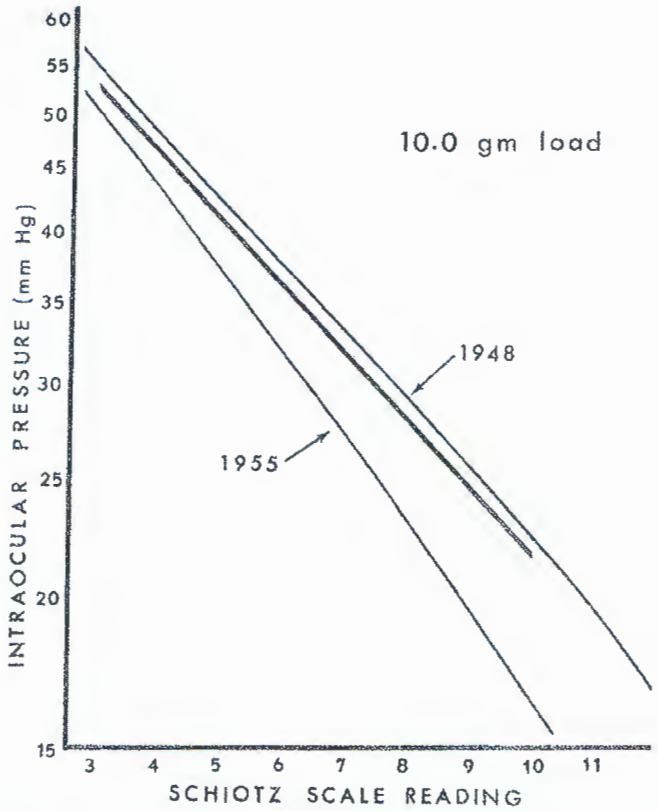

Fig. 8. Comparison of the regression line (heavy line), obtained with Schiøtz scale reading as the independent variable, with the 1948 and 1955 calibration scales (10.0 Gm. plunger load).

deriving a more accurate Schiøtz calibration scale is so that it would be useful for tonography. Probably the conclusion apply equally to the mechanical Schiøtz tonometer, since the two are designed to be equivalent. If there is a difference between the two, it would be expected to be quite small.

Dr. John P. Gilbert of the Research Computing Group, Harvard Computing Center, rendered statistical advice. Computer programming was done by Mrs. Judy Hushon and Miss Jacqueline Siegel of the Research Computing Group.

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A Computer Evaluation on Tonography

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The purpose of this study has been to develop a reliable routine method using an electronic digital computer to evaluate the magnitude of the errors associated with tonography as, well as calculating the outflow parameter. The results are discussed as well as some of the methods of reducing errors.

1. Introduction

Since Grant (1950, 1951) described a method of tonography for evaluating the coefficient of facility of outflow, *C*, this method has, with refinements, remained the basis of tonography used as a clinical procedure for distinguishing glaucomatous from normal eyes. The use of tables (such as Becker and Shaffer 1965) avoids time consuming calculation, but depends on the clinician's ability to draw a straight line through the curves of the tonogram so that the result is given without a measure of its accuracy. The calculation of the corrected coefficient of facility of outflow from the tonographic nomogram (Friedenwald, 1955) reduces only the errors due to variations in ocular rigidity and these may not be clinically significant (Gloster, 1966). The use of a computer allows a far more detailed analysis of the tonographic curve as well as transferring all calculating effort to the computer once the program has been compiled.

The sources of the errors occurring in tonography have been described (Becker and Friedenwald, 1953; Kronfield, Ballantine, Moses, Grant, Becker and Roberts, 1961). These errors can be divided into three types:

(1) *Technical errors*, which can be reduced through the training of the tonography technician, improved co-operation by the patient, and by refinements in the design and construction of the electronic tonometers.

(2) *Systematic errors* are produced by assumptions implicit in the method and are not easily reduced. They include errors derived from the use of Friedenwald's formulas for converting Schiotz readings into their equivalent pressure and volume values, the use in the calculation of a fixed value for the tonographic increase in episcleral venous pressure (Linner, 1954), and the representation of the non-linear tonogram by a straight line.

(3) *Random errors* affect the tonographic readings upwards and downwards, and include the variations due to the cardiac and respiratory rhythms. The magnitude of transient fluctuations can be reduced by incorporating an integrating circuit in the tonometer, but these errors still produce irregularities in the tonographic curve which can complicate the calculation of the overall trend.

The computer program has been developed initially to calculate the random errors, for which the statistical methods are designed. In practice it has been found that the technical errors produce significant increases in the statistical measurements of error, and these measurements have been used to improve technique. In the first

programs the mean outflow value and its variation were calculated from successive or overlapping segments of the tonogram, as this allowed a direct comparison with the values obtained using either the tables or Grant's formula. The final program, however, is based on a curve-fitting technique known as the method of least squares (Crow, Davis and Maxfield, 1960; Scale, 1966); this is a more accurate method and this is the program included in the Appendix B. I have used this program for 2 years and have found it both simple and reliable.

This paper will first outline the mathematical methods used in the computation of the tonogram before showing how the computer program has been developed. There have been two hypotheses regarding tonography; the one represents it as a linear decay and the other as an exponential decay of intraocular pressure. Integral calculus has been used to show that while the first hypothesis fits in well with Grant's formula for calculating C, the second demands a modification in the formula, as would any other type of curve. Finally the results of the analysis will be discussed including the magnitude of the errors and ways of reducing them.

The Calculus of Tonography

Coefficient of facility of outflow (C)

This was the estimate derived from the tonogram by Grant (1950) and is usually calculated (for explanation to symbols see Appendix A):

$$C = \frac{\Delta V}{\Delta T \times (\bar{P}_t - P_{ap} - \Delta P_v)}. \qquad (1)$$

where $\Delta P_v = 1{\cdot}25$ mmHg (Linner, 1954)
and $\bar{P}_t = (P_{to} - P_{tn}) \div 2$.

This method of deriving the mean intraocular pressure during the time (ΔT) of the tonography implies that the tonogram is, in terms of pressure and time, a straight line, since $\bar{P}_t$ must lie on a straight line joining P_{to} and P_{tn}, (see Fig. 1).

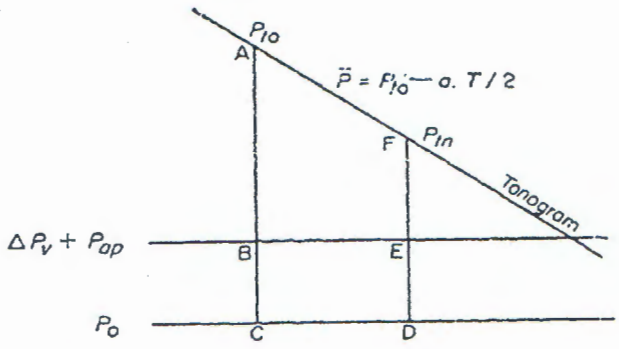

FIG. 1

Further consideration of Fig. 1 will show that, so long as the equation expressing P as a function of T is known, the denominator of equation (1) can always be calculated in terms of the area of the tetragon, A B E F, which is bounded by the tonogram above and by the base-line ($P_{app} + \Delta P_v$) below and by the vertical time-limits each side. This area, A, is the definite integral:

$$\text{Area} = \int_{T_1}^{T_2} f(T).\, d\,T \qquad (2)$$

where $f(T)$ is P as a function of time, T. The equation for a straight line tonogram can be expressed:

$$P_{tn} - P_{ap} - \Delta P_v = (P_{t0} - P_{ap} - \Delta P_v) - a.\Delta T \tag{3}$$

where a is the gradient of the tonogram ($a = \Delta P/\Delta T$). Substituting equation (3) into equation (2):

$$\begin{aligned} \text{area} &= \int_{T_1}^{T_2} [P_{t0} - P_{ap} - \Delta P_v - a.\Delta T]\mathrm{d}T \\ &= \Delta T. \left[P_{t0} - P_{ap} - \Delta P_v - \frac{a.\Delta T}{2}\right] \\ &= \Delta T. [\bar{P}_t - P_{ap} - \Delta P_v], \end{aligned}$$

since $\bar{P} = P_{t0} - a.\Delta T/2$.

For a straight-line tonogram integration may appear trivial, but it demonstrates that the denominator of the outflow equation depends on the type of curve and this method is extended to an exponential outflow in the third section.

Although short segments of the tonogram may approximate to a straight line, it is almost always impossible to fit a tonogram of long duration, even of over 1 min (Armaly, 1964). This may lead to two errors:

(a) a straight line in descending intersects the base line, BE, which has a value $(P_{ap} + \Delta P_v)$, so that the denominator in equation (1) becomes zero or negative and C then becomes excessively large or negative;

(b) The gradient, a, changes its value so that there can be considerable increase in C calculated from the later parts of the tonogram. This trend has been confirmed by the present author (1965) when using Grant's formula, and may be the basis for the diagnostic use of C_{3-7} by Leydhecker (1958), since this increase in C occurs most consistently with eyes which already have a normal or high value of C_{0-4}, rather than a low value.

Coefficient of exponential decay of presure (α)

The concept of the exponential decay of intraocular pressure during tonography has been discussed by Goldmann in his Proctor Lecture (1959) and by Goldmann and Schmidt (1965). The coefficient, α, is defined in the expression:

$$P_{tn} - P_{ap} - \Delta P_v = (P_{t0} - P_{ap} - \Delta P_v).e^{-\alpha T} \tag{4}$$

where e is the exponential constant (2·7183 . . .), so that

$$\alpha = \frac{\log_e (P_{t0} - P_{ap} - \Delta P_v) - \log_e (P_{tn} - P_{ap} - \Delta P_v)}{\Delta T}. \tag{5}$$

As defined, α is a measure of the rate at which the intraocular pressure, increased by tonography, returns towards the pretonography pressure, P_0, and requires no estimation of volume change in its calculation. It should be mentioned, however, that Stepanik (1961) has suggested that many tonograms fall towards a level, P_x, which may be significantly higher than P_0. Although this is probably only a factor when outflow is greatly reduced it does emphasize the importance of an accurate estimation of P_0, preferably by applanation.

Apart from long duration tonograms, the exponential decay curve has been considered a satisfactory description of the pressure changes for the perilimbal suction

cup analysis (Galin, Baras, McLean, 1963) in which decay is followed over a period of 15 min. The results are expressed as the percentage pressure decay (P.P.D.), from which α can be calculated for comparison with tonography:

$$\alpha = \frac{\log_e\left(1 - \frac{(\text{P.P.D.})}{100}\right)}{\Delta T} \tag{6}$$

where $\Delta T = 15$ min.

Exponential coefficient of facility of outflow (C_e)

It is necessary to have a method of calculating the outflow facility for an exponential curve in order to compare accurately the two above methods and their measurements. In this paper C_e is calculated as follows: equation (4) is substituted into equation (2), thereby determining the area A B E F in Fig. 2:

$$\begin{aligned}\text{area} &= \int_{T_1}^{T_2} (P_{tn} - P_{ap} - \Delta P_e).\ e^{\alpha t}.\ dT, \\ &= \frac{(P_{tn} - P_{ap} - \Delta P_e)}{\alpha} \int_{T_1}^{T_2} e^{\alpha t}.\ d(T.\alpha), \\ &= \frac{(P_{tn} - P_{ap} - \Delta P_e)}{\alpha} (e^{\alpha T_1} - e^{\alpha T_2}),\end{aligned}$$

and if $T_1 = 0$, this simplifies to:

$$\text{area} = \frac{(P_{tn} - P_{ap} - \Delta P_e)}{\alpha} (1 - e^{\alpha T})$$

and

$$C_e = \frac{\Delta V}{\text{Area}} = \frac{\alpha.\Delta V.}{(P_{tn} - P_{ap} - \Delta P_e).\ (1 - e^{\alpha t})}. \tag{7}$$

This expression is not difficult to calculate if a slide rule with negative log-log scales is used. In programming a digital computer the greater complexity of equation (7)

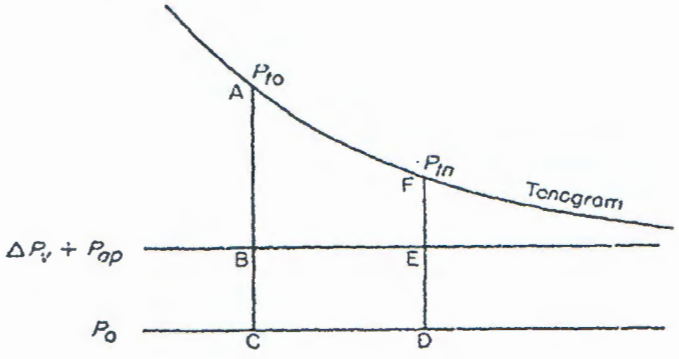

FIG. 2

is more than offset by its use for calculating the outflow in the same program as that which is calculating α and the correlation coefficient, whereas a separate program had to be used to calculate Grant's C over the length of the tonogram. In general C and C_e are the same for short intervals on the tonogram, but for large changes of

pressure or time, C_e becomes greater than C; this is illustrated in Table I, which is calculated on the first four groups of data given by Galan et al. (1963) for the 15-min decay curves following perilimbal suction.

TABLE I*

Patients / Results	Normal	Glaucoma 1	Glaucoma 2 (before Diamox)	Glaucoma 2 (after Diamox)
Steady-state pressure (P_0)	15	22	20	15
Pressure after suction	25	36	32	20
Pressure 15 min later	15	24	21	17
P.P.D.	100%	86%	92%	60%
α	—	0·131	0·168	0·001
Grant's C	0·138	0·008	0·087	0·063
C_e	—	0·089	0·130	0·067

* See Galin et al. (1963).

3. The Procedure for Data Analysis used with the Computer

The computer was presented with data produced by tonography using a Schwarzer electronic tonometer with recorder; all applanation tonometry was performed with a Goldmann tonometer on a Haag–Streit 900 Slit Lamp; and calculations were performed on an ICT 1500 Computer. The coefficient of rigidity was estimated using the applanation and the 4 Schiotz readings on the Friedenwald nomogram.

The data is fed into the computer on the standard IBM FORTRAM punch card (Fig. 3), which can be read photo-electrically at a rate of about 400 cards per min. The top card illustrated gives the following information from left to right:

(i) Five groups of alpho-numerical figures: name of patient, laterality of eye, hospital number, age and diagnostic index.
(ii) Two integers: the number (N) of Schiotz readings on the tonogram followed by a number to summate the subscript and thereby pair the readings along the tonogram for calculation (e.g. P_n and P_{n+c}).
(iii) Five floating-point (decimal) numerals: the time in minutes between each point on the curve, the weight (W) on the tonometer plunger, the applanation pressure (P_{ap}), the coefficient of rigidity (K) and the increase (ΔP_e) of episcleral venous pressure during tonography.

The remaining cards are punched to give the Schiotz readings ($N<40$) at the equal time intervals specified by the top card. The tonogram corresponding to the cards illustrated is shown in Fig. 4 and the print out in Fig. 5. The final program for α and

C_e is given as Appendix B and a few points are noteworthy in the construction of such a program:

(1) The programs have been written in FORTRAN, which is a modified algebra available for use with most larger digital computers. It is explained in many texts such as Moon (1966) and McCracken (1961).

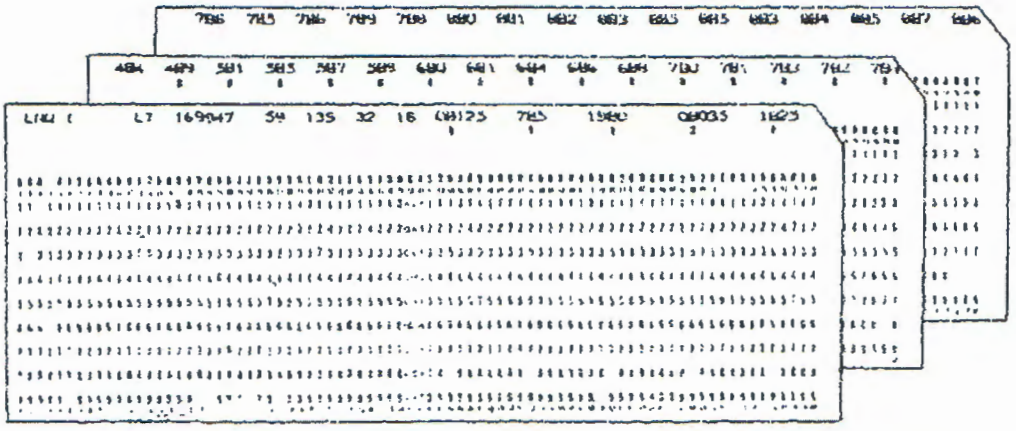

FIG. 3. *Top card*—LAW 1 (name), 169947 (hospital no.), 59 (age) 135 (diagnostic code), 32 (no. of points on curve), 16 (summation of subscript), 0·125 (time in minutes between points), 7·5 (W) 19·0 (P_{mp}), 0·035 (K), 1·25 (ΔP_0).
Other cards—4·5, 4·9, 5·5, etc. (successive Schiotz values for points on curve).

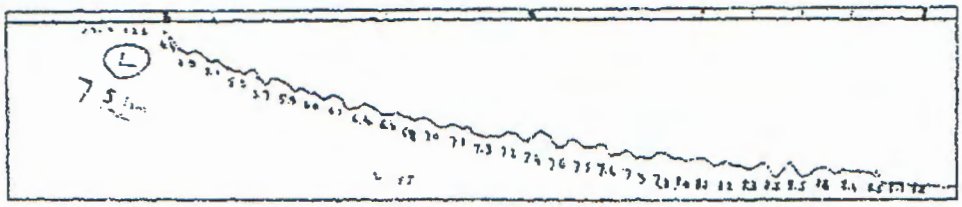

FIG. 4

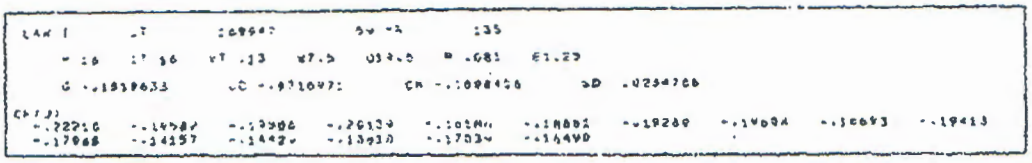

FIG. 5

(2) Most computers use natural logarithms and so there is an instruction to change the value of K accordingly. Also the constants used in the calculation of V_e have been altered for the same reason (statements 7, 8 and 9).

(3) Since the constants used in the calculation of V_e change with the plunger weight (W), an IF—instruction is used to select the correct constants according to the value of W (5·5, 7·5 or 10·0 g) automatically.

(4) The program has been made as general and flexible as possible so that fixed values of K and ΔP_0 have not been assumed and written into the program. There is indeed some reason to believe the ΔP_0 becomes smaller on prolonged tonography (Leith, 1965; Gloster, 1966).

(5) The continuous curve of a tonogram is analogue and requires conversion into a digital form in order to be suitable for calculation on a digital computer. A straight line drawn through the curve is artificial and suppresses all irregularities, so that the more objective compromise has been employed of measuring the Schiotz-values of the curve at equally spaced time intervals. The first program calculated Grants C, using equation (1) and took paired values successively along the curve (e.g. P_1 and P_{17}, P_2 and P_{18}, P_3 and P_{19} . . . etc.; in effect giving results equivalent to a series of overlapping straight-line tonograms, so that the print out includes a mean value for C and its standard error based on a series of values of C, which are printed last and show whether these values are random or tend to increase along the curve. This program was also used to calculate outflow results for non-overlapping adjacent segments of the tonogram (Armaly, 1964) but this reduced the effect of the overall trend so that the variation in outflow values became too large to be acceptable (see Table II).

TABLE II

Effect of time on accuracy of outflow facility

Time interval between points paired for calculation (min)	Number of pairs	S.D.	Standard error of the mean (= S.D./N)	Mean (C)
1/4	31	0·960	0·175	0·357
1/2	30	0·557	0·104	0·407
1	28	0·291	0·055	0·413
4	16	0·052	0·013	0·404

Tonogram used has correlation coefficient = 0·982 and all calculations used identical data.

(6) The final program used calculates the coefficient of exponential decay (α), using equation (5) and the method of least squares. The correlation coefficient for the fit of Schiotz pressure-equivalents to an exponential curve is also calculated. Finally the exponential outflow facility (C_e) is calculated using equation (7) as Grant's (C) cannot be directly calculated from α. The same volume values are used as in the first program and the input format was kept identical in order to facilitate comparison. I advocate this final program, which is based on a least-square fit to the tonogram, as it prints out values for both α and C_e and can therefore be used by those who wish to use either parameter. It also prints out the correlation coefficient in addition to a standard deviation for the mean outflow value.

(7) The representation of the continuous tonographic curve by a series of Schiotz-values provides a vector, the elements of which show a trend of values in time. The iterative DO-loops of the computer program are used, as these repeat the required computation on each element, and successive vectors are produced for intraocular pressure, and intraocular volume changes, and finally outflow facility. With a smooth curve and an adequate method of computation, one should expect the values of the elements for outflow facility to be nearly equal; the standard deviation is used as a measure of their inequality.

(8) Many errors can enter into the measurement of outflow, both instrumental and technical and also through the methods of computation. These tend to be magnified by the smallness of the ratio $(P_{t0}-P_{t4}/P_{t0}-P_0)$, as Langham (1966) has pointed out, although this ratio can be increased by prolonging the duration of tonography (when the curve is flat), or by increasing the weight on the tonometer plunger. It is therefore essential to include an estimate of error in a tonographic program for computer, and the two included here are:

(a) The correlation coefficient, which varies from 1 for a perfect positive correlation through 0 to -1 for a perfect negative correlation. Its value depends almost entirely on the least-square fit of the tonogram to the exponential curve and it proves to be a useful measure of the quality of the tonogram (Fig. 6).

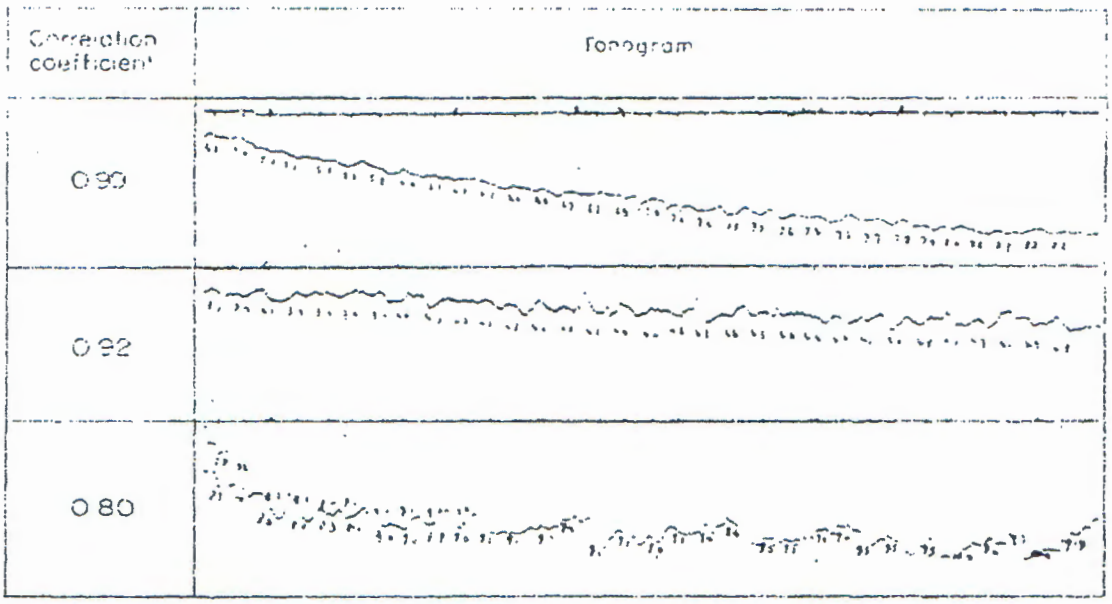

FIG. 6

(b) The standard deviation which measures the scatter of the values of C around the mean C, and 95% of these values will fall within a range of twice the standard deviation on each side of the mean. A large standard deviation with a good correlation coefficient suggests an inadequate computational method.

4. Some Results Obtained by Computation from the Tonogram

Comparison of Grant's C with the exponential C_e

Figure 7 is a graph plotting C against C_e for identical tonographic data. The diagonal line represents equality and each dot the computed mean outflows ($\overline{C}$ and $\overline{C}_e$) from each tonogram. Below a value of 0·20 mm³/mmHg/per min there is virtual equality, but above this level the exponential coefficient tends increasingly to exceed Grant's coefficient.

The standard deviation, S.D., gives an indication of the accuracy of the mean value (since the standard error of the mean $= \text{S.D.}/\sqrt{N}$). Table II shows the ratio of the standard deviation divided by the mean α, C and C_e; for this table the mean

TABLE III

Outflow parameter	Ratio of S.D./mean (42 eyes)
$\bar{\alpha}$	0·34
$\bar{C}$	0·273
$\bar{C}_e$	0·219

TABLE IV

Effect of prolonged tonography on outflow facility, C_e

	Tonogram 1	Tonogram 2	Tonogram 3		Tonogram 4	
Time (min) preceding 4-min segment	Low outflow	High outflow	$\Delta P_p = 1{\cdot}25$	No ΔP_p	C_e	Grant's C
	P_{op} 23	P_{op} 32	P_{op} 22		P_{op} 16 (mmHg)	
0·00	0·092	0·362	0·691	0·603	0·288	0·308
0·25	0·124	0·379	0·668	0·585	0·294	0·309
0·50	0·128	0·423	0·792	0·645	0·297	0·312
0·75	0·121	0·366	0·897	0·686	0·287	0·293
1·00	0·098	0·435	1·038	0·733	0·307	0·318
1·25	0·126	0·434	0·958	0·694	0·286	0·285
1·50	0·127	0·477	0·951	0·678	0·240	0·229
1·75	0·135	0·443	0·931	0·645	0·254	0·244
2·00	0·105	0·454	1·249	0·782	0·247	0·236
2·25	0·119	0·452	1·404	0·810	0·270	0·263
2·50	0·157	0·406	1·618	0·842	0·231	0·221
2·75	0·114	0·433	1·656	0·838	0·220	0·202
3·00	0·199	0·417	2·408	0·929	0·227	0·209
3·25	0·118		2·611	0·907	0·189	0·166
3·50	0·123				0·221	0·202
3·75	0·128				0·265	0·252
4·00	0·171					
4·25	0·144					
4·50	0·151					
4·75	0·134					
5·00	0·150					

α and its deviation have been calculated, not by the least-square method, but by a program using the same paired Schiotz values as for the other ratios. The ratio using the exponential outflow computation is constantly less than the other two and this increase in accuracy may be due to the use of the least-square method in the calculation of the pressure component of the outflow coefficient (see also Table IV, tonogram 4).

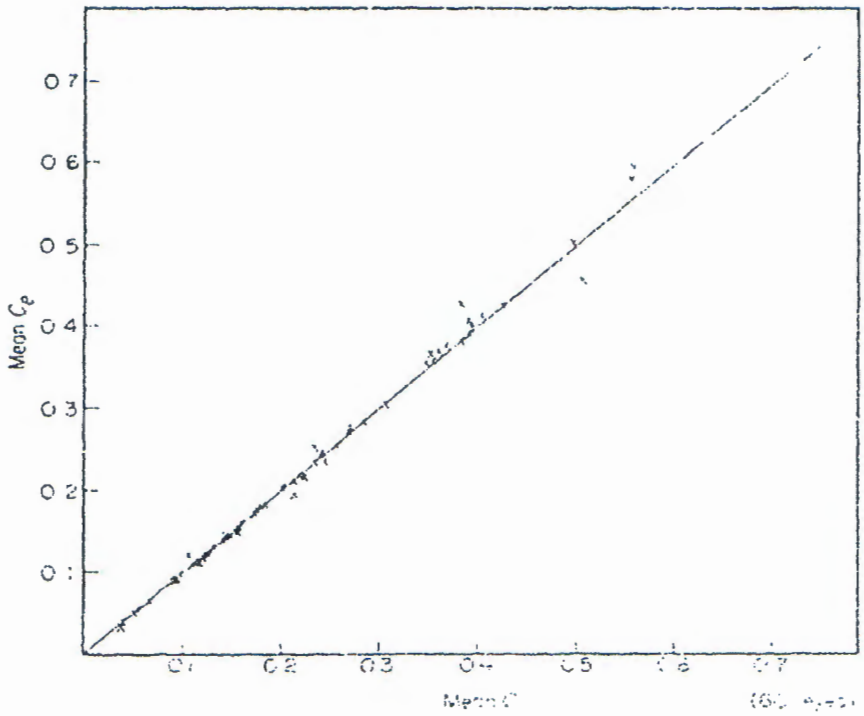

FIG. 7

Effect of the plunger weight on accuracy

The accuracy of the outflow coefficient depends partly on the form of the tonogram, especially its regularity, as shown in Fig. 6. However the overall gradient of the tonogram also has a considerable effect on accuracy, since when the gradient is small the short-period waves due to cardiac and respiratory rhythms, etc., tend to swamp the long-period trend, on which the outflow calculation is based. Ideally the tonogram should descend at least three Schiotz units to provide a sufficient change in pressure and volume for the calculation of outflow. When the outflow is low the accuracy can be increased by using a heavier plunger weight, and this is illustrated by patient (WEI 350) in whom, with a 5·5 g weight, the S.D. = 0·0169 (C_e = 0·0420) and, with a 10 g weight, the S.D. = 0·0086 (C_e = 0·0411), thereby halving the error.

Goldman (1963) has advised the use of the heavier weights in order to reduce the uveal blood volume and the increase in accuracy confirms this, although the present author finds that the 10 g weight is the heaviest that can be balanced with sufficient stability.

Effect of P_{ap} *and* ΔP_v *on accuracy*

If the tonogram descends to a level below that equal to the addition of the tonographic increase in episcleral venous pressure (ΔP_v) to the applanation pressure (P_{ap}), the outflow coefficient will become infinite or negative and the electronic computer may halt the program through overflow of its register. To prevent a complete clearing of the program from the computer, an instruction has been used and this identifies the error by printing P. LT. Q. (pressure less than applanation pressure).

Even when this does not occur, an erroneous measurement of the applanation pressure may produce a considerable elevation of the outflow coefficient if, as a result,

the total of $P_{ap}+\Delta P_e$ becomes almost equal to the lowest pressure on the tonogram (P_{tn}). One patient's tonogram (WEI 19) terminated at Schiotz 11 when the applanation pressure was 20 mmHg; the computed mean C_e was 2·7515 with a correlation coefficient of 0·832, but elimination of the ΔP_e value of 1·25 mmHg reduced the mean C_e to 0·8915 with a correlation coefficient of 0·993. This example does not argue against applanation in favour of a return to Schiotz tonometry, which can produce the same error. It does show the usefulness of the correlation coefficient, which should be at least 0·90 for an outflow result to be accepted, and it also shows that, however accurate applanation tonometry can be, errors will arise if the patient is not relaxed and co-operative.

Effect of prolonging the duration of the tonogram

Table 1 shows the computed outflow values using the Grant's C and the exponential C_e. Although there is sometimes a change in their values towards the end of the tonogram, this is almost always less than the random fluctuation. It can, however, be shown that the outflow value will increase along the tonogram if the P_0 value is erroneously elevated (tonogram 3).

Tonogram 4 shows the smaller variation in the values of C_e as compared with C.

Effect of a computed outflow coefficient on diagnosis

Tonography is only an aid in the diagnosis of glaucoma and cannot be a final arbiter when the other clinical signs have all proved equivocal. Since there are so many variables contributing to the errors of tonography (Gloster, 1966) it is not

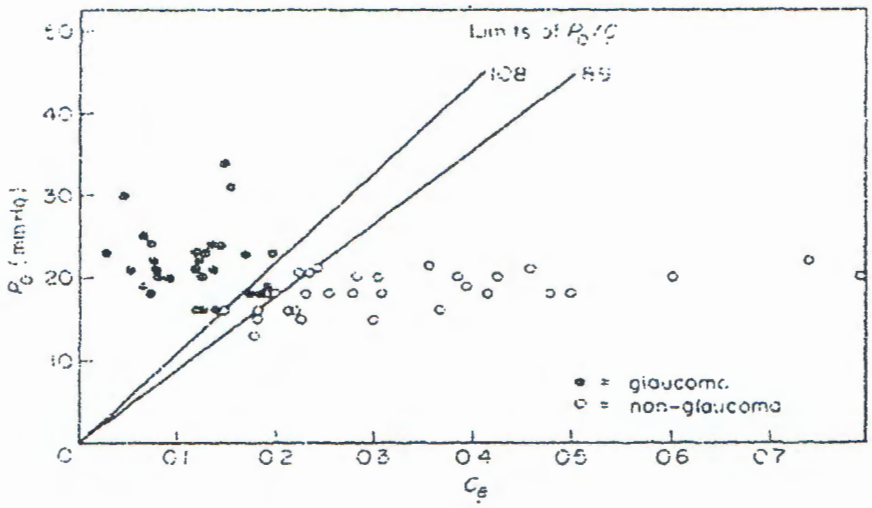

FIG. 8

likely that tonography in its present form will become completely reliable. The statistical analysis of the tonogram produces a measurement of these errors, and the significance of these has been illustrated. However, the repetition of calculations over the length of the tonogram is tedious and time consuming, and the high speed electronic computer provides a solution. It allows the computation of the outflow for a tonogram following an exponential curve, a problem considered by Langham and Maumenee (1964), Langham (1966) and Fox (1967), and the repetition of data along the curve of the tonogram increases the information used thereby reducing the uncertainty of

tonography (Kinchin, 1957). In practice the accuracy of tonography can often be less than satisfactory, and the calculated outflow results should include an estimate of their error.

The clinical application of the coefficient of facility of outflow requires an efficient test for comparing it with any previous tonography results on the same eye or with an accepted limit of clinical normality. For this the Student's t-test (Crow, et al., 1960) can be used where: $T = \dfrac{(\text{mean } C\text{-limiting value}).\sqrt{N}}{(\text{s.d.})}$.

Since all the C and C_e values are nearly identical within the usual range of clinical experience, the same clinical criteria apply to the values of C_e and P_0/C_e as to the

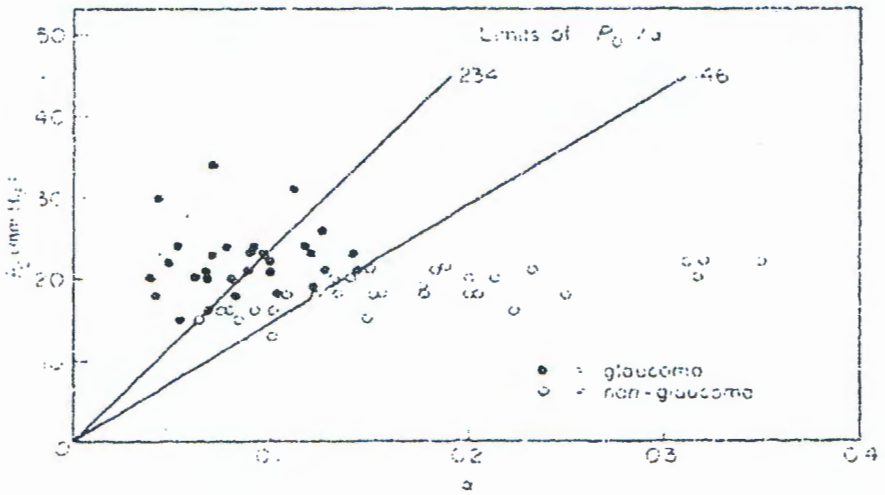

FIG. 9

values of C and P_0/C. Owing to differences in technique between various clinics, the levels of diagnostic significance should be established through the experience within each clinic and recorded; the two-dimensional scattergram used by Grant (1951). has been used by the present author (Figs 8 and 9), for C_e and α. From the point of view of diagnosis the precise physiological meaning of outflow is not relevant and it may include an element of reduced inflow.

5. Summary

A method of calculating the coefficient of facility of outflow using a high-speed electronic digital computer is described. The calculation has included a statistical estimation of the accuracy of the tonogram and a method of computing outflow, C_e, on an exponential tonogram, from the value of the coefficient of exponential decay of pressure, α. C_e has been shown to be equal to Grant's C for short duration tonography. The clinical significance of the results is briefly discussed, and it is emphasized that tonography may easily fall below the accuracy required, so that an error estimation is essential.

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Appendix A

The following symbols are used for the calculus of tonography.

P_0 is the steady-state intraocular pressure before tonometry.
P_{ap} is the intraocular pressure during applanation tonometry.
P_t is the intraocular pressure during Schiotz tonometry.
P_{t0}, P_{t4} are the intraocular pressures at the start of tonography and 4 min later.
$\bar{P}_t = P_{tm}$, is the arithmetical mean intraocular pressure during tonography.
P_v is the episcleral venous pressure.
ΔP_v is the change in episcleral venous pressure during tonography.
$\Delta V = \Delta V_c + \Delta V_s$ is the change in intraocular volume during tonography, where:
ΔV_c is the change in volume due to increasing corneal indentation.
ΔV_s is the change in volume due to corneoscleral elasticity where $\Delta V_s = (\log_{10} P_{t0} - \log_{10} P_{tm})/K$
$K = (\log_{10} P_1 - \log_{10} P_2)/\Delta V$ K being the coefficient of ocular rigidity (mean $K = 0{\cdot}0215$, Friedenwald, 1937).
ΔP, ΔV, dp, dv are changes in pressure and volume where: dp/dv is the limiting value of $\Delta P/\Delta V$ as ΔV tends to zero.
T is the time (min)
W is the Schiotz plunger weight (5·5, 7·5, 10·0 or 15·0 g).
C is the coefficient of the facility of aqueous outflow (in mm^3/min per mmHg).
C_e is the coefficient of the facility of aqueous outflow for an exponential tonogram.

P.P.D. is the percentage pressure decay over 15 min in perilimbal suction cup tonography.

$F = C(P_0 - P_t)$ is a measure of total aqueous flow.

α is the coefficient of exponential decay of pressure during tonography.

(pressures are usually measured in mmHg and volume in mm^3)

Statistical symbols

S.D. is the standard deviation of a sample.

$$\left[\text{S.D.} = \sqrt{\left\{\frac{\Sigma(x-\bar{x})^2}{(N-1)}\right\}}\right]$$

C.C. is the correlation coefficient of the tonogram;

$$\left[\text{C.C.} = \sqrt{\left\{\frac{\Sigma(x-\bar{x})(y-\bar{y})}{\{\Sigma(x-\bar{x})^2 \times \Sigma(y-\bar{y})^2\}}\right\}}\right]$$

N is the number of points on the tonogram used for Schiotz measurement.

Appendix B

Data symbols

NAM	is patient's name	LAT	is side of eye
NUM	is patient's number	AGE	is age in years
DIA	is diagnostic code		
N	is number of points used on tonogram		
IT	is the number of points summated to produce a pair		
VT	is the time in minutes between adjacent points		
W	is the plunger weight in g		
Q	is the applanation pressure, P_{app}		
R	is the coefficient of rigidity K		
E	is ΔP_v		
P(I)	is the Schiotz-vector derived for the tonogram.		
G	is α and CE is C_e		
*	may be used for multiplication;	/	for division.

Program. (C_e)

```
*JOB  EXPONENTIAL OUTFLOW EYE
*EXECUTE
*COMPILE
      DIMENSION P(40),V(40),X(40),DV(36),CE(36)
00001 READ 80,NAM,LAT,NUM,AGE,DIA,N,IT,VT,W,Q,R,E,(P(I),I = 1,N)
      M=N-IT
      R=R*2.30259
C     ASSESS VOLUME AND PRESSURE
      IF (7.5-W) 7,8,9
00007 B=4.971
      BN=2.300
      GO TO 3
00008 B=4.849
      BN=2.174
      GO TO 3
00009 B=4.642
      BN=2.064
```

```
00003   DO 4 J=1,N
        P(J)=W/(0.107+0.0138*P(J))
00004   V(J)=EXPF(BN*(B-LOGF(P(J))))
        DO 5 K=1,M
        L=K+IT
00005   DV(K)=V(L)-V(K)+(LOGF(P(K)/P(L)))/R
C       ASSESS GAMMA
        CM=0
        C2=0
        PS=0
        TS=0
        P2=0
        T2=0
        TP=0
        DO 2 J = 1,N
        P(J)=P(J)-Q-E
        IF (P(J)) 20,20,10
00010   X(J)=LOGF(P(J))
        F=FLOATF(J)
        PS=PS+X(J)
        TS=TS+F
        P2=P2+X(J)*X(J)
        T2=T2+F*F
00002   TP=TP+X(J)*F
        Z=FLOATF(N)
        G=(TP-PS*TS/Z)/(T2-TS*TS/Z)
        CC=G*SQRTF((T2-TS*TS/Z)/(P2-PS*PS/Z))
        G=G/VT
C       ASSESS OUTFLOW
        DO 6 K = 1,M
        CE(K)=DV(K)*G/P(K)/(1.-EXPF(G*VT*FLOATF(IT)))
        CM=CM+CE(K)
00006   C2=C2+CE(K)*CE(K)
        SD=SQRTF((C2-CM*CM/FLOATF(M))/FLOATF(M-1))
        CM=CM/FLOATF(M)
        OPRINT 90,NAM, LAT, NUM,AGE,DIA,M,IT,VT,W,Q,R,E,G,CC,CM,SD,
        (CE(J),J=1 1,M)
00080   FORMAT (A10,A4,A8,2A5,2I4,5F8.4,/(16F5.1))
00090 0 FORMAT (1HO,A10,A4,5X,A8,5X,A5,3H YR,5X,A5//5X,2H M,I3,5H IT,13,
      1 5H VT,F4.2,4H W,F3.1,4H Q,F4.1,4H R,F5.3,4H E,F4.2//5X,2,
      2 HG,F10.7,5X,3H CC,F10.7,5X,3H CM,F10.7,5X,3H SD,F10.7//6H CE(J)/
      3 (10F10.5))
        GO TO 1
00020   PRINT 30,NAM,NUM,(P(I),I=1,N)
00030   FORMAT (2A10,9H P. LT. Q//(10F10.5))
        GO TO 1
        STOP
        END
*DATA
```

Notes:

Statement 1 is the input statement and interprets the meaning of IBM punch cards (Fig. 3).

Statements 7, 8 and 9 are the constants selected by the IF statement according to the values of W(5·5, 7·5 or 10 cm) and are used in Friedenwald's calculation of V_e in statement 1:

$$V_e = \text{exponential } (N \times (B - \log P_t)).$$

Statement preceding 4 is Friedenwald's calculation of P_t from the Schiotz value:

$$P_t = W \div (0{\cdot}107 + 0{\cdot}0138 \text{ Schiotz}).$$

Statement 5 calculates the difference in V_e for two points on the tonogram and adds to this the ΔV_s.

$$\Delta V_s \quad \frac{\log (P_K \div P_1)}{K}.$$

Two statements before statement 10: the first subtracts $(P_{ap} \div \Delta P_e)$ from P_t and only continues calculation via statement 10 IF the result is positive. Otherwise the IF-statement jumps program to statement 20.

The next 6 statements (including statement 2) summate the values needed in the least-square calculation (in the statements following statement 2) z, G and the correlation coefficient, CC.

PS	is	$\Sigma(P_t - P_{ap} - \Delta P_e)$
P2	is	$\Sigma(P_t - P_{ap} - \Delta P_e)^2$
TS	is	Σ(Subscripts)
T2	is	Σ(Subscripts)^2
TP	is	$\Sigma[(\text{Subscripts}) \times (P_t - P_{ap} - \Delta P_e)]$.

F and Z are the floating-point (decimal) equivalents for integers J and N.

The statements following assess outflow: DO 6 $K = 1, M$ repeats the calculation of the following 3 statements for the subscript K successively from 1 to a value M

CE(K) evaluates the exponential outflow;

$$Ce = \frac{\Delta V_{XZ}}{(P_t - P_{ap} - \Delta P_e)} \cdot (1 - e^{z,d})$$

CM is ΣC_e and C2 is ΣC_e^2, used to calculate SD, which is the standard deviation. Finally CM is divided by the floating-form of M to give an arithmetical mean of C_e.

The print statement determines which values are to be printed out and the format statement controls the printed layout.

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ORIGINAL RESEARCH

The digital aqueous humor outflow meter: an alternative tool for screening of the human eye outflow facility

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Purpose: To develop, characterize, and validate a prototype digital aqueous humor outflow tonographer (DAHOM).

Material and methods: The DAHOM was developed, characterized, and validated in three phases. Phase 1 involved construction of the sensor. This was broadly based on the fundamental design of a typical Schiotz tonographer with a series of improvements, including corneal indentation, which was converted to an electrical signal via a linear variable differential transducer, an analog signal which was converted to digital via ADC circuitry, and digital data acquisition and processing which was made possible by a serial port interface. Phase 2 comprised development of software for automated assessment of the outflow facility. Automated outflow facility assessment incorporated a series of fundamental improvements in comparison with traditional techniques, including software-based filtering of ripple noise and extreme variations, rigidity impact analysis, and evaluation of the impact of patient age, central corneal thickness, and ocular axial length. Phase 3 comprised characterization and validation of DAHOM, for which we developed an experimental setup using porcine cadaver eyes. DAHOM's repeatability was evaluated by means of Cronbach's alpha and intraclass correlation coefficient. The level of agreement with a standard Schiotz tonographer was evaluated by means of paired *t*-tests and Bland-Altman analysis in human eyes.

Results: The experimental setup provided the necessary data for the characterization of DAHOM. A fourth order polynomial equation provided excellent fit (R square >0.999). DAHOM demonstrated high repeatability (Cronbach's alpha ≥ 0.997; intraclass correlation coefficient ≥ 0.987) and an adequate level of agreement with a standard Schiotz tonographer.

Conclusions: This study presents the development, characterization, and validation of a prototype digital tonographer. DAHOM demonstrates high repeatability and a sufficient level of agreement with a typical Schiotz tonographer, while its digital design remedies known vulnerabilities of conventional tonographers.

Keywords: glaucoma, tonography, pressure, outflow facility, aqueous humor

Introduction

The importance of aqueous humor tonography in research settings has been highlighted over many years.[1–3] Tonography outcomes provide essential information for a series of ophthalmic diseases, eg, the glaucomas, and facilitate exploration of the ocular manifestations of systemic diseases. However, tonography in daily clinical settings has yet to be applied, mainly due to time constraints in hospital departments. Moreover, prevalent tonographic settings suffer from poor repeatability which limits their clinical usefulness. Among the primary causes of variability is the fact that reliable measurements require continuous eye alignment, which is

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difficult to achieve in practice. On the other hand, data collection and processing using traditional tonographers is difficult, because they do not provide digital output, automated assessment of the outflow facility, or evaluation of the impact of a series of known modifiers of the outflow facility. Within this context, we demonstrate here the development, characterization, and validation of a novel digital aqueous humor outflow topographer (DAHOM) that addresses the series of vulnerabilities of traditional tonographers.

Materials and methods

Setting

The study adhered to the tenets of the Declaration of Helsinki and written informed consent was given by all participants. This was a prospective study conducted in the Department of Ophthalmology at the University Hospital of Alexandroupolis in Greece between 2004 and 2007.

Development of DAHOM

The digital outflow meter was designed at the Eye Institute of Thrace, in collaboration with the Electrical Engineering Department of the Technical University of Thrace. The development of the system was done in three phases.

Phase I

Phase 1 included construction of the electromechanical system with the sensor and the electronic circuitry (Figure 1). The sensor design was broadly based on the fundamental design of a typical Schiotz tonographer. The sensor converted corneal indentation to electrical signal with high sensitivity (1.719 mV/volt/0.0254 mm) using a linear variable differential transducer. All elements were connected to an aluminum alloy frame capable of retraction and sterilization. Analog to digital signal conversion was accomplished using ADC electronic circuitry providing interface via a serial port (RS232, Figure 2).

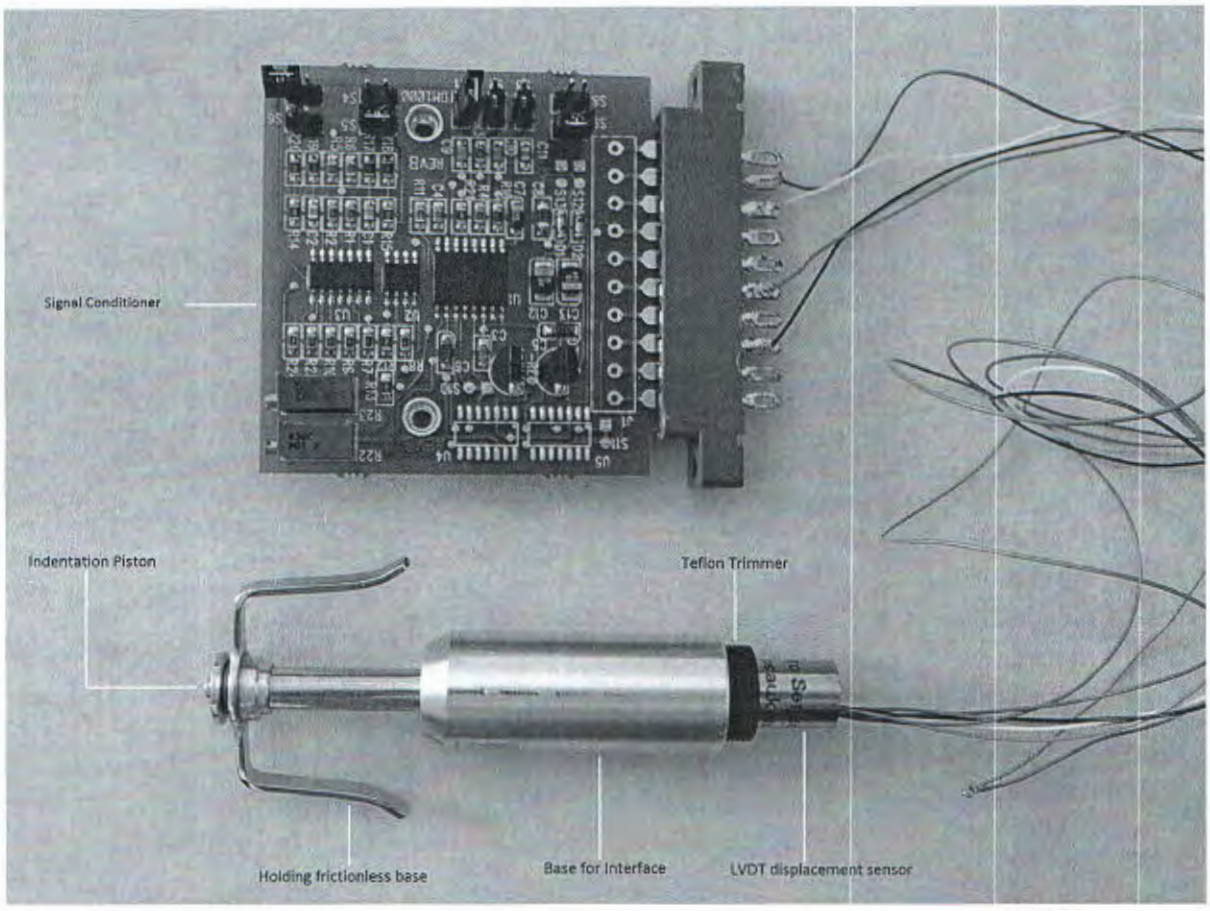

Figure 1 Digital outflow meter, including linear variable differential transducer and signal conditioner circuit.
The digital outflow transducer with the contact tip (indentation piston), the base (center), and the linear variable differential transducer sensor (right). Connector cables are used for power supply and data transfer to the DAQ board. The signal conditioning board is responsible for sinusoidal wave generation, signal rectification, and phase-sensitive demodulation processing.

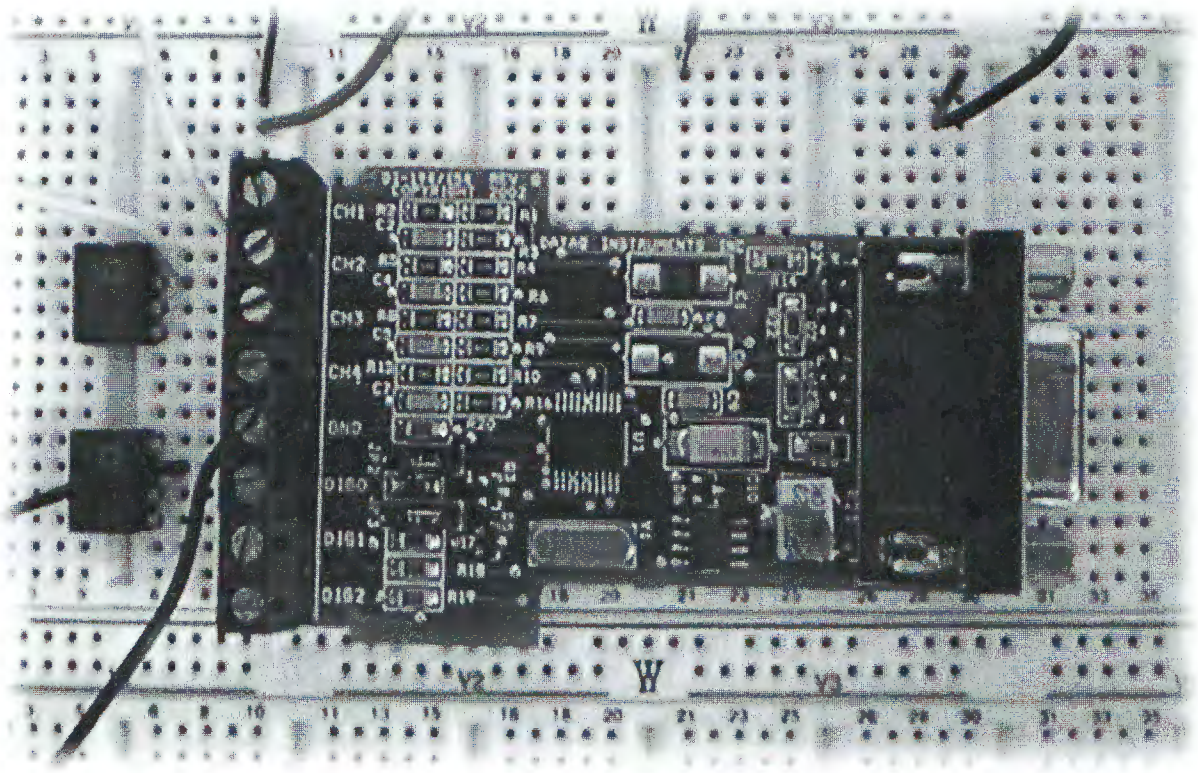

Figure 2 Data acquisition board with analog to digital converter and serial communication with a PC.
Electronic circuitry with data acquisition, analog to digital converter, and RS 232 communication interface.

Phase 2

Phase 2 involved development of the software and the conversion algorithm for the evaluation of the outflow facility. A software-based percentile filter was used to cut out ripple noise and random measurement variations (Figure 3). Observed differences in intraocular pressure (IOP) measurements between the DAHOM and Goldmann applanation tonometer (GAT) were used for assessment of ocular rigidity.

The outflow facility was calculated according to the following formula:

$$C_{out} = \frac{\Delta V}{\left(\frac{P_{t0}+P_{t4}}{2} - P_{applanation} - \Delta P_{indentation}\right)\cdot 4} = \frac{(V_{C4}-V_{C0}) + \frac{1}{K}\log\left(\frac{P_{t0}}{P_{t4}}\right)}{\left(\frac{P_{t0}+P_{t4}}{2} - P_{applanation} - \Delta P_{indentation}\right)\cdot 4}$$

where $V_{C4} - V_{C0}$ is the corneal volume displacement during the tonography study, K is the sclera rigidity factor or ocular rigidity factor, P_{t0}/P_{t4} is the hydrostatic pressure difference between the points of flow resistance, $P_{applanation}$ is the IOP measured by GAT, ΔP is the mechanical increase of IOP from the weight of the tonographer, and 4 is duration of the study in minutes.[4]

A software program was developed in Java language, capable of calculating the outflow facility (Figure 4). Rigidity impact analysis was incorporated in the software algorithm using GAT IOP measurement, as suggested by Friedenwald.[4]

The following formula was used to calculate rigidity:

$$\begin{aligned} Rigidity = {} & 4.5282E^{-5} + 6.7443E^{-4}X + 6.165E^{-6}X^2 \\ & - 2.18104E^{-7}X^3 - 2.07212E^{-8}X^4 + 2.7598E^{-9}X^5 \\ & - 1.1391E^{-10}X^6 + 2.26627E^{-12}X^7 \\ & - 2.20326E^{-14}X^8 + 8.45107E^{-17}X^9 \end{aligned}$$

where X is the mathematical arc tangent operator of the difference between the applanation and the indentation IOP, while the following three formulas (F1–F3) were used to define the indentational versus IOP measurement for 5.5, 7.5, and 10 g weight of the digital outflow meter:

$$\begin{aligned} IOP_{indent}^{5.5g} = {} & 51.081 - 5.887x + 0.479x^2 \\ & - 0.0215x^3 + 3.832E^{-4}x^4 \end{aligned} \quad \text{(F1)}$$

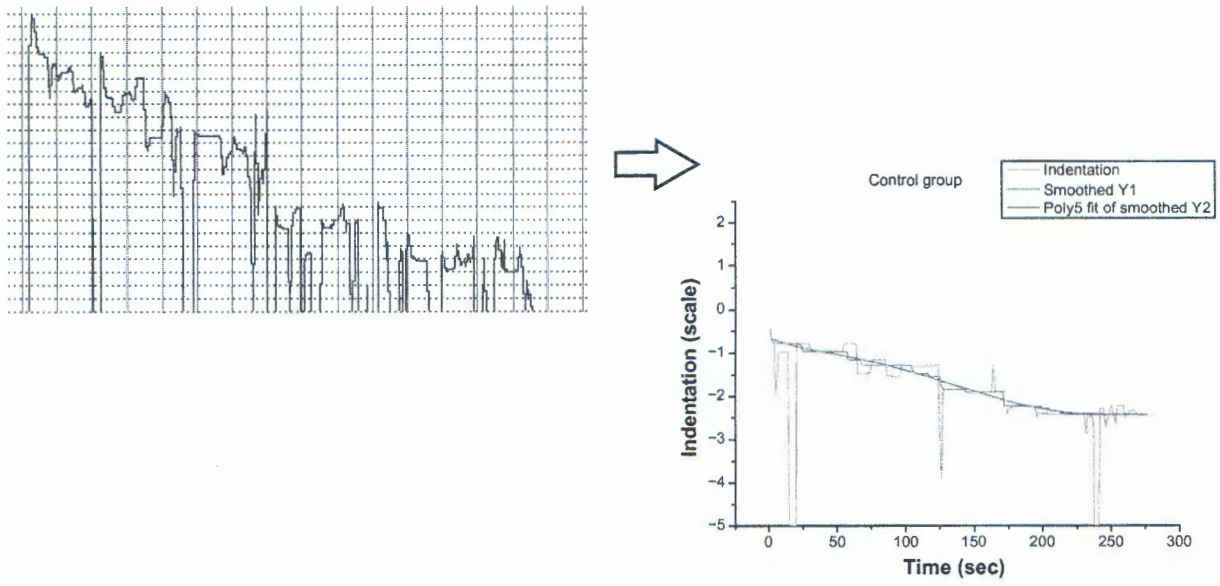

Figure 3 Data filtering and tonographic polynomial fit.
Data as recorded in real time by the data acquisition system (left graph) and data post-study analysis with digital filtering (red line) and polynomial fit (green line, right graph).

$$IOP_{indent}^{7.5g} = 69.668 - 8.045x + 0.655x^2 - 0.029x^3 + 5.204E^{-4}x^4 \quad \text{(F2)}$$

$$IOP_{indent}^{10g} = 92.89 - 10.717x + 0.872x^2 - 0.039x^3 + 6.937E^{-4}x^4 \quad \text{(F3)}$$

where x is the magnitude of indentation for the digital tonographer in mm.

A series of optional parameters were also incorporated in the algorithm in order to correct the rigidity measurements based on the influence of several biomechanical factors, including central cornea thickness, age of patient, and ocular axial length (Figure 4). These formulae were derived from previously published studies on ocular rigidity variation.[5,6]

$$K_{age} = 0.00526 + 1.09285E^{-4} \times Age$$

$$K_{cct} = -0.02055 + 6.33781E^{-5} \cdot CCT$$

$$K_{refraction} = 0.02056 + 6.6158E^{-4}L + 2.0559E^{-5}L^2 + 9.70044E^{-7}L^3 + 1.6981E^{-8}L^4$$

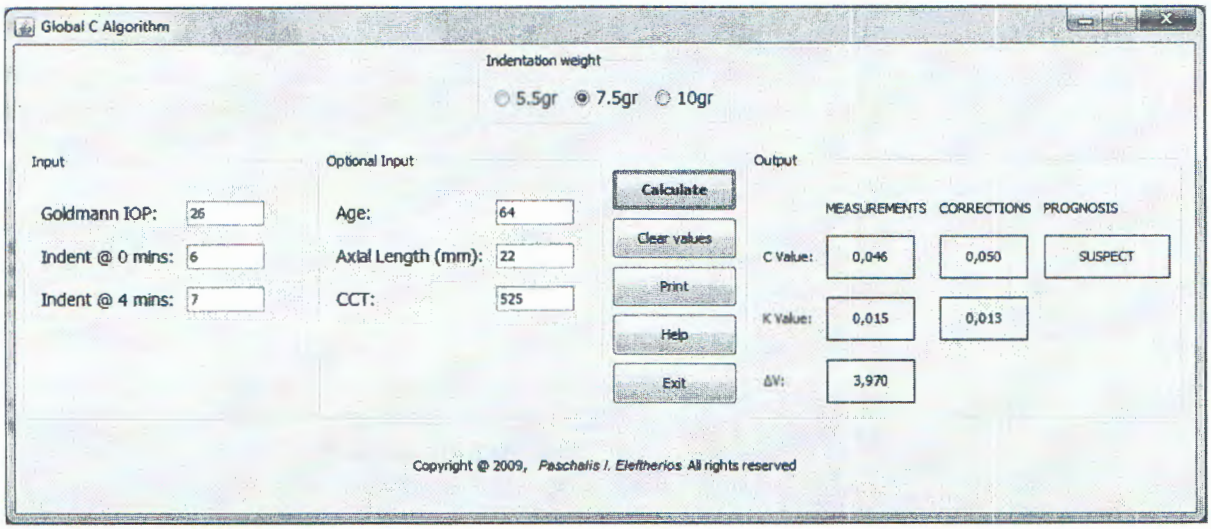

Figure 4 Outflow facility windows software based on Java language.
Outflow facility calculation software, designed in Java programming language with Windows® interface environment. Mandatory "inputs" are designed to measure the outflow facility, while "optional" inputs are designed to measure the ocular rigidity factor. "Corrected" outputs represent the outflow facility and rigidity measurements, corrected by the "optional" inputs. Correlation is a predictive algorithm of the severity of the condition from 0 to 3 for normal to acute angle closure, respectively.

where K_{age} is the rigidity variation based on the age of the patient;[5] K_{cct} is the rigidity variation based on central cornea thickness;[4] $K_{refraction}$ is the rigidity variation based on the ocular axial length;[4] age is patient age in years; CCT is the central corneal thickness (μm); and L is the ocular axial length (mm).

Phase 3

Phase 3 involved characterization and validation of the DAHOM. Characterization of the tonometer was accomplished using porcine cadaver eyes according to the following procedure. A microelectronic pressure sensor was implanted into the anterior chamber using a fine needle. A second needle was injected into the eye, connecting a water tank of balanced solution for IOP regulation, which was accomplished by altering the water tank height and thus affecting the hydrostatic pressure difference in the eye (Figures 5 and 6). Experimental IOP measurements were obtained in the range 5–90 mmHg, with a 1 mmHg increment.

Validation of the system was accomplished by comparing the measurement outcomes of the DAHOM with the corresponding ones of a Schiotz tonographer in a population of 30 volunteers according to the following procedure. Outflow facility measurements were obtained in one eye using a Schiotz tonographer and in the fellow eye by the DAHOM. Within one week, the procedure was repeated in a crossover manner. All tonography measurements were obtained by the same experienced operator (NF) who ensured proper eye fixation. Before each measurement, the Schiotz tonographer was calibrated according to the manufacturer's instructions. GAT IOP measurements determined the indentation weight for both systems. For IOPs less than 30 mmHg, a 5.5 g weight was used, while a 7.5 g weight was used for IOP between 30 and 45 mmHg. For IOPs higher than 45 mmHg, a 10 g weight was used. The level of agreement between the two systems was evaluated by means of paired *t*-test and by Bland-Altman analysis. DAHOM repeatability was evaluated

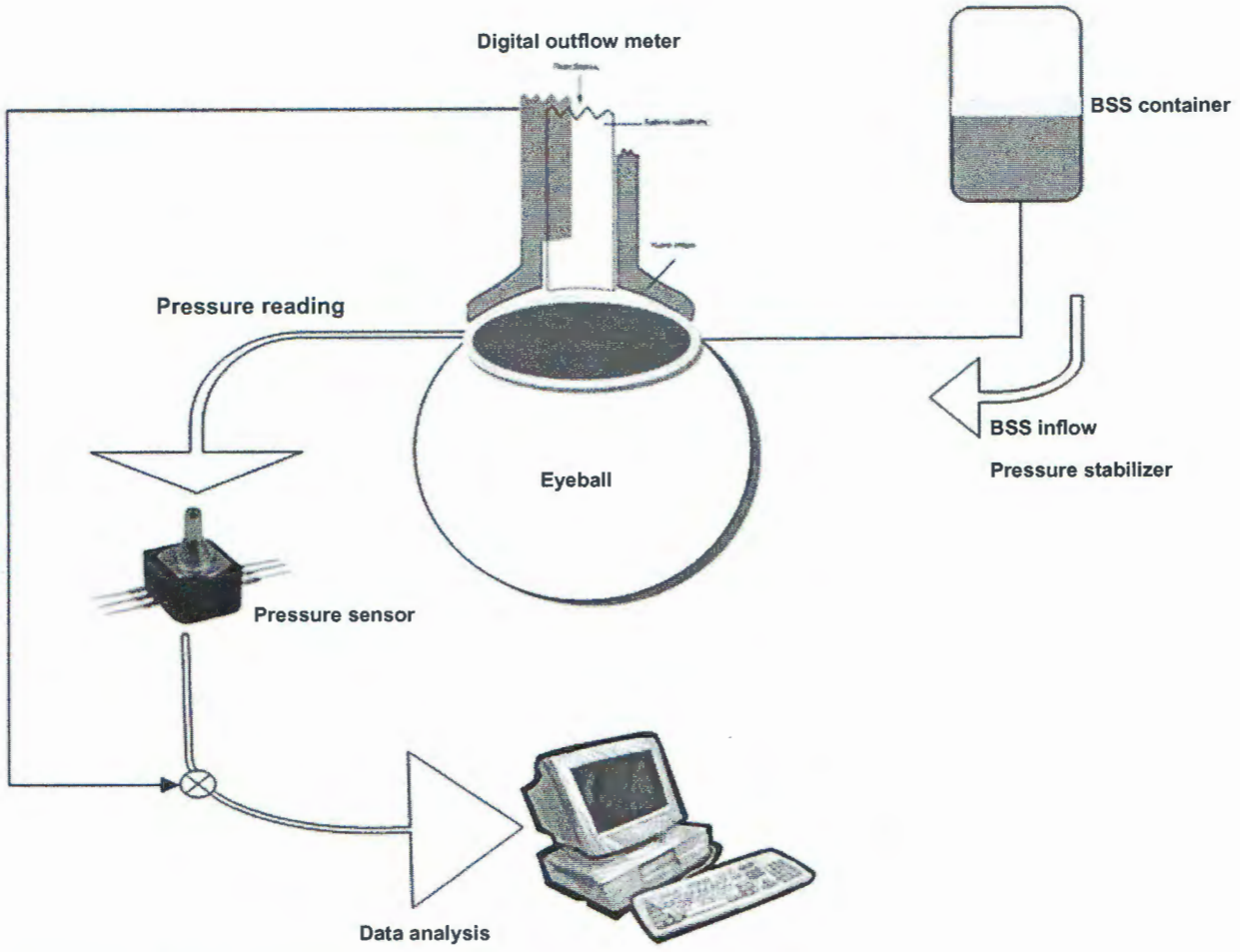

Figure 5 Laboratory setup for the characterization of the digital outflow meter.
Laboratory setup for the calibration of the system. The balanced solution (BSS) container is used for intraocular pressure regulation, the micropressure sensor is used for intracameral real-time intraocular pressure measurements, while the digital outflow meter performs tonography. All data are collected by the PC and analyzed.

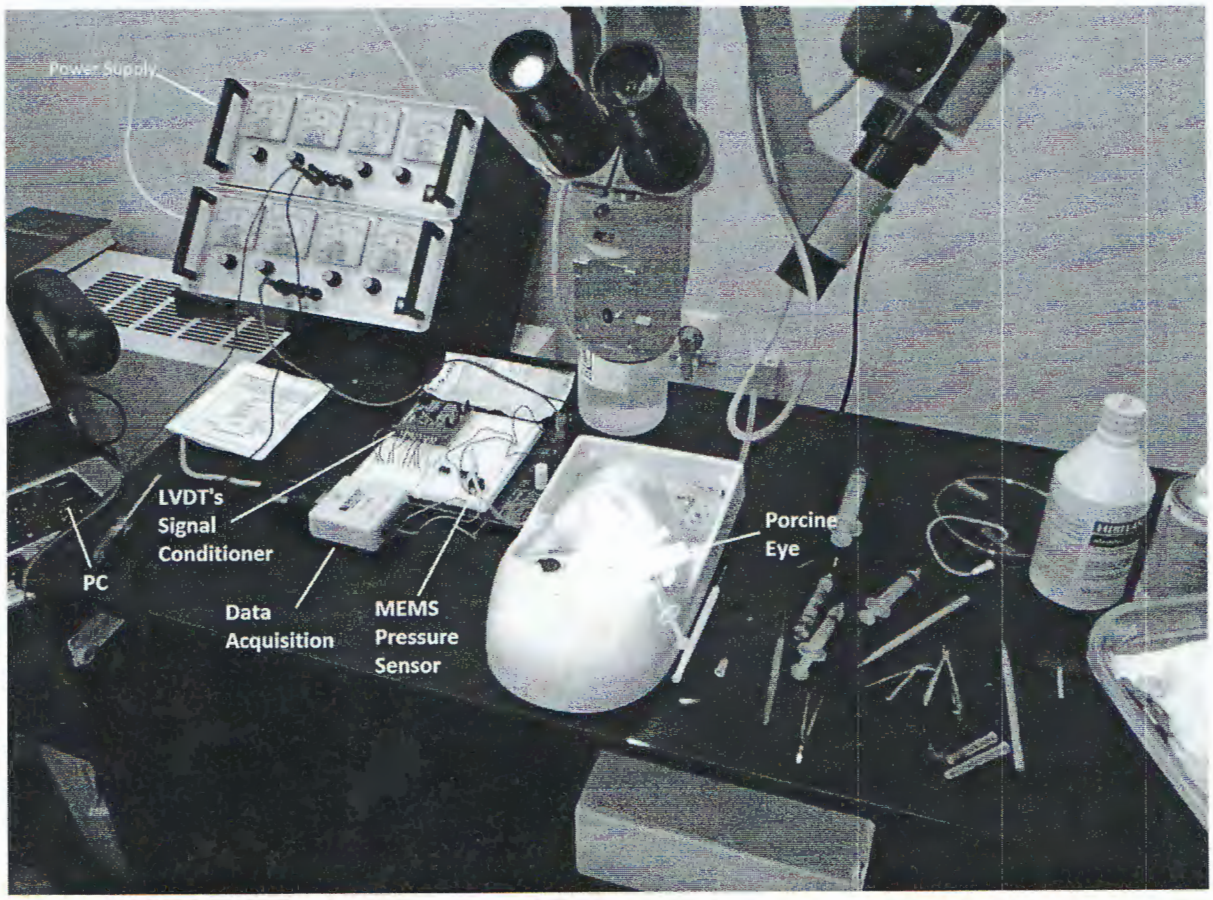

Figure 6 Experimental setup.
Experimental setup in porcine cadaver eyes using a microelectromechanic intracameral pressure sensor.

by both Cronbach's alpha test and the intraclass correlation coefficient (ICC) from three consecutive measurements prior to the tonography study.

Statistical analysis

Results were analyzed with the SPSS Version 17.0 (Statistical Package for the Social Sciences Inc., Chicago, IL). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Quantitative variables expressed as mean ± standard deviation (SD) and qualitative variables were expressed as frequencies and percentages. The Mann-Whitney test was used to assess outflow facility variations between the Schiotz and digital outflow meters. All tests were two-tailed, and statistical significance was considered as $P < 0.05$. Intrasession repeatability was tested using Cronbach's alpha test and the ICC. Agreement of the outflow facility measurements between the digital and Schiotz outflow meters was assessed with Bland-Altman plots and 95% limits of agreement. MedCalc version 9.0 software was used for the Bland-Altman plots.

Results

The experimental setup with the porcine eyes provided the necessary data for the characterization of the system's response, according to the following formulae:

$$IOP_{MEMS} = 51.081 - 117.735x + 191.649x^2 - 171.753x^3 + 61.131x^4 \quad \text{(F4)}$$

$$IOP_{MEMS} = 69.668 - 160.908x + 262.05x^2 - 234.266x^3 + 83.266x^4 \quad \text{(F5)}$$

$$IOP_{MEMS} = 92.89 - 214.339x + 348.911x^2 - 312.038x + 111x^4 \quad \text{(F6)}$$

where x is the magnitude of indentation for the DAHOM in mm.

In fact, the characterization of the DAHOM was accomplished using a fourth order polynomial equation (adjusted R-square >0.999 in all polynomial fittings, Figure 7). Three different polynomial equations were derived, each one

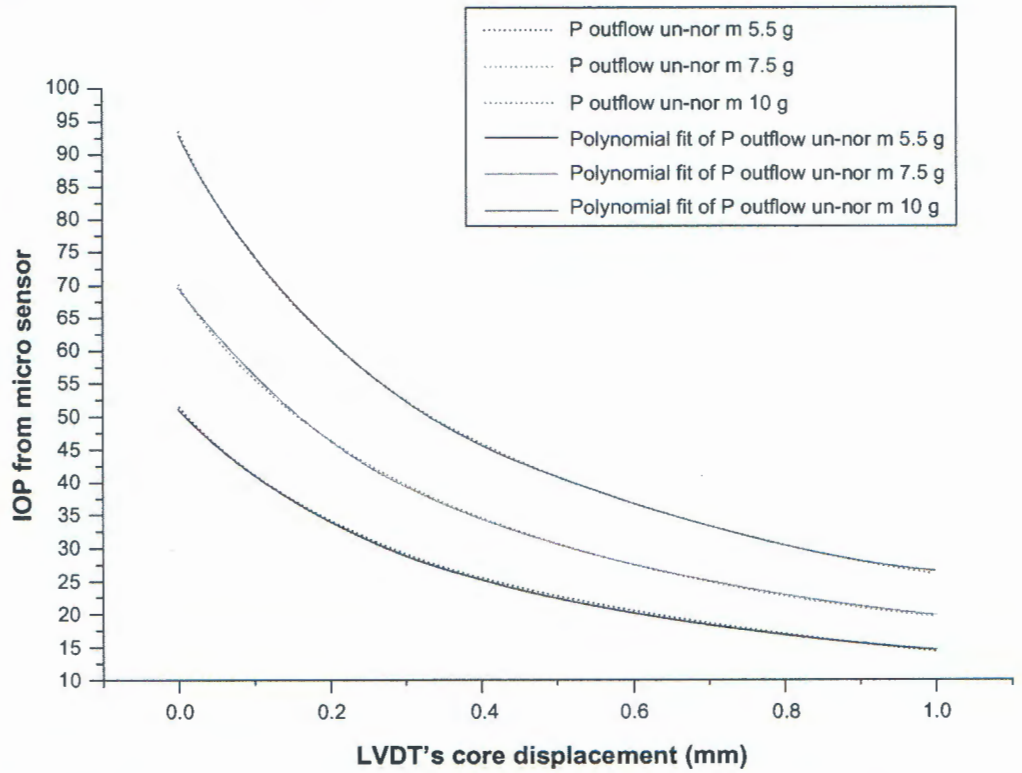

Figure 7 Indentation versus intraocular pressure intracameral readings from the microelectronic silicon-based pressure sensor.
Objective intraocular pressure versus indentation measurements in an experimental setup using extracted porcine cadaver eyes. Intraocular pressure measurements attained by a micropressure sensor, connected to the anterior chamber of the eye, while the indentation measurements attained by the digital outflow meter.

corresponding to a different plunger weight. Systems transfer functions are shown below. Equation F7 was used for a 5.5 g plunger weight, F8 for 7.5 g, and F9 for 10 g:

$$y(x) = 51.081 - 117.735x + 191.649x^2 - 171.753x^3 + 61.131x^4 \quad \text{(F7)}$$

$$y(x) = 69.668 - 160.908x + 262.05x^2 - 234.266x^3 + 83.266x^4 \quad \text{(F8)}$$

$$y(x) = 92.89 - 214.339x + 348.911x^2 - 312.0.8x^3 + 111x^4 \quad \text{(F9)}$$

It should be mentioned that all polynomials were derived by assessment of the best fitting of the experimental results in a Cartesian plot, with one axis representing the experimental measurements of interest and the second axis representing the values obtained by the DAHOM. The order of polynomial fitting was selected in a way to provide R-Square adjustment higher than 0.98, ensuring minimum calculation error.

DAHOM demonstrated a sufficient level of agreement with the Schiotz tonographer. Specifically, the results for DAHOM were: $C_{Digital} \pm SD_{Digital} = 0.168 \pm 0.08\ \mu L \times min^{-1} \times mmHg^{-1}$ and for the Schiotz tonometer were: $C_{schiotz} \pm SD_{schiotz} = 0.163 \pm 0.09\ \mu L \times min^{-1} \times mmHg^{-1}$; Paired sample *t*-test validated measurements conformity ($P > 0.12$). Sufficient level of agreement was also confirmed by Bland-Altman analysis. According to the plot in Figure 8, with the exception of two outlying values, the plot points are distributed in a symmetric manner about the "zero difference" line.

Regarding DAHOM's measurement repeatability, the Cronbach's alpha was 0.997 and the ICC was 0.987, both tests suggesting high intrasession reliability.

Discussion

The objective of this study was to develop a digital aqueous humor tonographer that could provide valid information about the outflow facility and address a series of technical and design limitations of the conventional tonographers.

Various tonographers have been introduced during the past 60 years. First, Schiotz,[7] then Bock et al[8] and others[9,10] introduced tonographers for measuring the outflow coefficient, and in 1951, Gant reported the use of an electronic tonographer connected to a paper strip.[11]

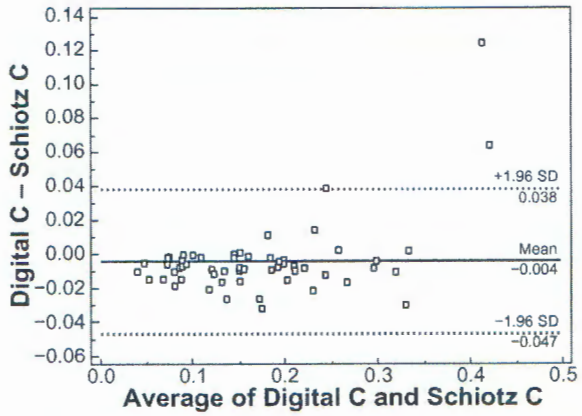

Figure 8 Bland-Altman plot showing interdevice difference plotted against mean measurements for each eye.
Bland-Altman plot showing interdevice difference plotted against mean measurements for each eye. Dotted line, zero line. Blue solid line, mean difference and boundaries of the 95% limits of agreement.

Among the difficulties in the development of a reliable tonographer is its characterization. For characterization of the DAHOM, we developed an experimental setup introducing an intracameral pressure sensor in porcine cadaver eyes. Although cadaver porcine eyes have biomechanical properties similar to those of human eyes, a number of differences should be taken into consideration, ie, cadaver eyes may introduce measuring errors due to lack of blood volume displacement during the tonography study, and despite similar stress-strain patterns, human and porcine corneas demonstrate different stress relaxation properties.[12] However, neither of these differences interfered with the characterization or the validation process. In fact, both the Schiotz tonographer and DAHOM demonstrated very similar results in the majority of cases. The observed nonsignificant differences may well be attributable to the known Schiotz vulnerabilities regarding ocular rigidity assessment rather than to the design and/or implementation of the DAHOM project.[13] Specifically, the average indentation values obtained by both systems (Schiotz and DAHOM) did not reveal any significant differences. However, the outcomes of the DAHOM are corrected by a series of rigidity impact algorithms (which is not the case for the Schiotz tonographer). Regarding outflow facility, the DAHOM demonstrated similar results in a series of former studies that used different tonographers.[14–20]

Regarding DAHOM's intrasession variability, both Cronbach's alpha and ICC tests suggested excellent repeatability. Specifically, the ICC value of 0.987 is well above the minimal ICC value of 0.90 that the literature suggests to be adequate.[21] It is known that in tonography studies the intrasession variability is exacerbated mainly due to the loss of eye alignment when retracting and placing the tonographer. In the software development of the DAHOM, we incorporated a software-based filter for automatic rejection of tracing irregularities that result in outlying values (Figure 3). However, hysteresis of the DAHOM was mainly attributed to the nonlinear semielastic properties of the eye, as shown in the report by Luce.[22]

Following the introduction of a reliable and valid tonographer like the DAHOM, its enhancements over the traditional tonographers should be underscored. The capability to provide raw data and outcomes measured in a digital format facilitates the processing and reprocessing of the data (both real-time and at a later time), allows introduction of different filters for cutting off measurement irregularities, and facilitates tonographic follow-up of patients because point-to-point comparisons can be made over time. The capability to calculate ocular rigidity and incorporate its impact on every single measurement on final measured outcome is a major advance over traditional designs that assume a mean ocular rigidity value for their calculations. Moreover, there is the capability to correct the measured outcome of the DAHOM by estimation of the impact of a series of optional ocular biomechanical factors and patient age.

In summary, in this report we present a characterization and validation of the DAHOM, a novel digital aqueous humor tonographer that attempts to address the known inherent vulnerabilities of the traditional tonographers. Addressing these vulnerabilities will allow the implementation of future relevant studies with high clinical significance in diseases with disrupted aqueous humor outflow, eg, the glaucomas. Among them are the qualitative outflow profile analysis that could provide detail information of the dynamic regulation of the outflow facility,[23–26] and the development of a glaucoma risk assessment algorithm, capable of identifying preclinical patterns of glaucoma development.

Disclosure

The authors report no conflict of interest in this work.

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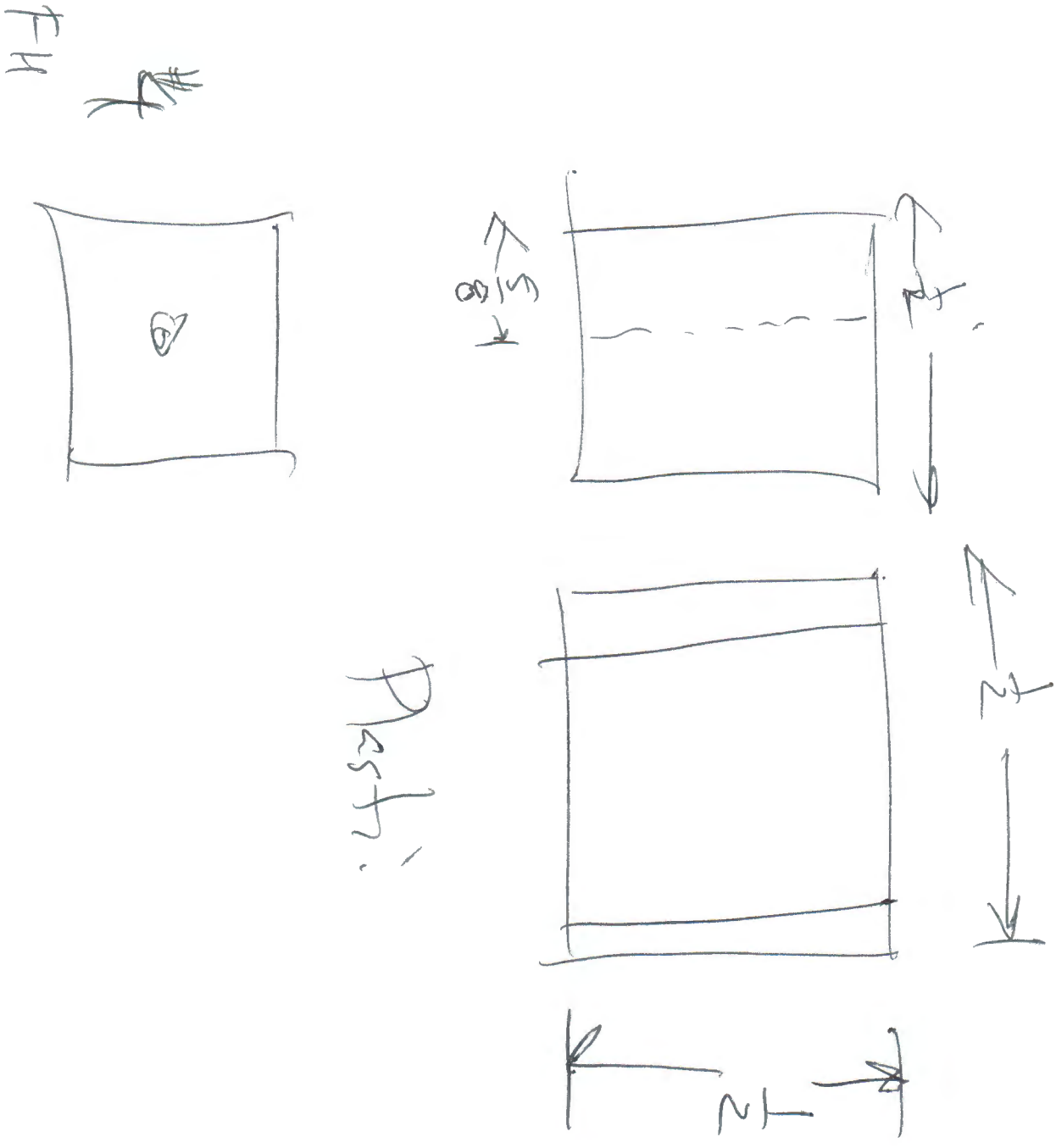
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Patented Aug. 22, 1950 2,519,681

UNITED STATES PATENT OFFICE

2,519,681

TONOMETER HEAD

Morris Mages, Chicago, Ill., assignor to V. Mueller & Company, Chicago, Ill., a corporation of Illinois

Application July 27, 1946, Serial No. 686,702

2 Claims. (Cl. 73—80)

1

My invention relates to tonometers. These instruments are used in the medical profession for making measurements of the pressure of liquid in the eyeball. The instruments now used for this purpose, with which I am familiar, are quite difficult to handle being of such construction that it is quite a delicate task to make the measurement. The scale for measurement is limited in size, and there is quite a problem of keeping the plunger that engages the eyeball from being influenced by friction and by inaccuracies that result from use.

It is the purpose of my invention to provide a novel tonometer which is so constructed that application of it to the human eye and the measurement of the pressure can be accomplished easily, and to any sensitivity that is desired, the measurement being translated into current flow that can be measured to whatever accuracy is desired by a suitable meter.

It is a further purpose of my invention to provide an improved tonometer wherein the head thereof is capable of being set directly on the eye and supported entirely by the eye in a stable position while the measurement is being made.

Another purpose of the invention is the provision of a novel supporting means for the tonometer whereby, when it is being applied, free movement in all directions is provided, thereby assuring perfect alignment of the tonometer head with the curvature of the eyeball.

It is a further purpose to provide such an instrument in which a calibrated "standard" is incorporated in the circuit by means of which any deviation in the accuracy of the tonometer head, changes in line voltage, or aging of tubes, can be easily detected. Provision is made for easily compensating for any normal changes, so that the accuracy of the instrument can be maintained over a long period of time.

A further purpose of my invention is to provide a simple means of mounting the plunger whereby to avoid cams, pivots and the like, and thus reduce frictional errors to a minimum.

Other objects and advantages of the invention will appear from the following detailed description and the accompanying drawings disclosing a preferred embodiment of my invention. It should be understood, however, that the drawings and description are illustrative only and are not to be taken as limiting the invention except insofar as it is limited by the claims.

In the drawings:

Figure 1 is a vertical sectional view showing the tonometer in use;

2

Figure 2 is a sectional view taken on the line 2—2 of Figure 1;

Figure 3 is a wiring diagram illustrating the electrical connections of the tonometer, and

Figure 4 is a fragmentary view illustrating the manner of clamping the tonometer plunger in place for initially adjusting the instrument.

Referring now to the tonometer as illustrated in Figures 1 and 2, the parts shown are on an enlarged scale. The eye under test is indicated at 5. No attempt is made herein to discuss the reasons for testing the liquid pressure within the eyeball since the testing and the use made of the knowledge gained thereby are matters for the medical profession. The measurement is, for example, important in the diagnosis of Glaucoma. The present invention is directed entirely to perfection of the instrument for making the pressure measurements so that the measurement may be made with greater accuracy, and the accuracy is maintainable throughout the life of the instrument. All dimensions, curvatures and weights conform to American Medical Association (A. M. A.) standards.

The tonometer comprises a head 6 of a suitable non-magnetic metal such as brass. This head has its lower end 7 cupped out to substantially conform to the shape of the eyeball surface. A central passage 8 is provided through the head for a plunger 9. This plunger has its lower end also cupped to fit the eyeball as indicated at 10. The plunger is composed at least in part of a magnetic material such as iron, for a purpose that will presently appear.

The upper portion of the head 6 is cut out at 11 to form a spool for the coils 12. A sleeve 13 is fitted snugly over the spool portion of the head 6. The sleeve encloses the coil and has an opening at 14 for the leads to the coil. A shoulder 15 is formed on the sleeve at its lower end. A similar shoulder 16 is formed on the sleeve near its upper end. These shoulders serve as stops for a ring 17 that fits loosely around the sleeve 13. The sleeve 13 projects above the upper end of the head 6 somewhat as shown as 18, to form a stop for a head 19 on a stem 20 which carries the plunger 9. The stem 20 and the head 19 are of brass, and the stem is threaded into the upper end of the plunger. The proportions are preferably such that the lower limit of movement of the plunger and stem assembly at which the head 19 rests on the part 18 of the sleeve 13 will bring the lower cupped end 10 of the plunger substantially level with the lower edge of the head 6. This prevents the plunger from being let down

too far, and protects the eye. A reduced extension 21 projects above the head 19 for the addition of auxiliary weights to measure higher pressures.

The ring 17 is secured to a handle 22 by a bent rod 23, one end of which is integral with the ring 17, and the other end of which is threaded into a sleeve 24 fixed in the handle 22. The handle is also provided with a pocket 25 in which a connector strip 26 is mounted. The wires in the coil 12 are fine wires, and leads of fine wires are brought from the coil in a cable form through a passage 27 in the handle to the strip 26. A cord 28 having wires of the size usually employed for appliances is used to make connection from the strip 26 to the metering circuit and current source. The pocket 25 is closed by a plate 29, and the connector strip 26 has end flanges 30—31 for positioning it in the pocket.

In Figure 3 of the drawings, the measuring circuit is shown diagrammatically as an induction bridge type of measuring circuit. In this circuit the tonometer head coil is shown at 32, a standard coil is shown at 33, and the balance coil is shown at 34. Each coil is shown as comprising a primary coil and a secondary coil. The primary coils are connected to a source 35 of alternating current. The output leads 36 and 37 of the secondary coils are connected through a phase adjuster 38 to an amplifier tube 39. This tube and a second tube 40 form an amplifier by which the signal is amplified and transmitted to a third tube 41, the plate circuit of which includes a meter 42, and a source 43 of current. The sensitivity or compensation control is obtained by a variable connection 44 to the grid of the tube 41.

The phase adjustment unit 38 is merely to bring the unbalance signal in phase with the plate voltage of the indicator tube 41. Normally when the plunger 9 is positioned so that its surface 10 coincides with the curved face 7 of the head 6, the voltage in the secondary of coil 32 (wound oppositely to the coils 33 and 34) is balanced against the voltage of the standard and balance coils so that the leads 36 and 37 are at the same potential. When the tonometer head is placed on the cornea of the eye, the weight of the plunger bearing against the eye causes the plunger to sink downward against the fluid pressure within the eyeball. The change in the position of the iron plunger in the coil 12 will cause a change in the secondary voltage so that a balance condition will no longer exist, and one of the leads 36—37 will be at a different potential than the other. This will cause a signal to be transmitted through the amplifier tubes the intensity of which is measurable by the meter 42.

In practice the instrument is first checked for accuracy and adjusted by comparison with the internal "standard" so as to insure accurate measurement. This is done as follows:

A holding member 45 (of brass) of the proper curvature is clamped to the bottom of the tonometer head to align the plunger with the "foot" of the tonometer head. This member (see Figure 4) is pivoted loosely on two pivot pins 46 and 47 that extend from two rods 48 and 49 toward each other. The rods are carried by a split ring 50 that can be clamped upon the head 6 when the member 45 is in proper position. With the instrument plugged in, the adjustment for the "standard" coil is set at its zero or normal position. The meter pointer is then set at zero on the scale by manipulation of the control for the "balance" coil. The "standard" coil 33 is now adjusted to change its value a predetermined amount, and this should result in a meter needle movement of a certain number of divisions—also marked on the meter dial by a red line. If the adjustment of the "standard" does not check with the required movement of the meter needle, they are made to coincide by means of the sensitivity control 44. The member 45 is then detached from the tonometer head, and the instrument is ready for use.

From the foregoing description it is believed that the nature and advantages of my invention will be clear to those skilled in the art.

Having thus described my invention, I claim:

1. In a tonometer, a substantially cylindrical head of nonmagnetic material, said head having a cupped lower face to engage the eyeball surface, said head having a central passage from said face to the upper end of the head, said head also having a spool portion on the exterior thereof intermediate its ends, an electrically conductive coil wound upon said spool portion, a plunger composed in part of magnet material slidable in said passage, indicating means connected with the coil to indicate changes in the magnetic circuit about said coil effected by movement of the plunger, a sleeve covering the spool portion of said head and projecting above the head, a handle having a head supporting ring portion in which said sleeve is loosely suspended and cooperating stop members on the sleeve and plunger limiting downward movement of the plunger, but leaving the plunger free for removal upwardly out of said head.

2. A tonometer comprising a head having a cupped lower face for resting on an eyeball, an electrically conductive coil carried by said head, a plunger freely slidable in said head and extending through the coil and having an end face for engaging an eyeball upon which the head is resting, said plunger having a part of magnetic material, means connected with said coil for indicating changes in the magnetic circuit about said coil effected by movement of the plunger, a ring encircling the head loosely, spaced upper and lower shoulders on the head retaining the ring, and a handle to which the ring is fixed.

MORRIS MAGES.

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Aug. 22, 1950 M. MAGES 2,519,681

TONOMETER HEAD

Filed July 27, 1946

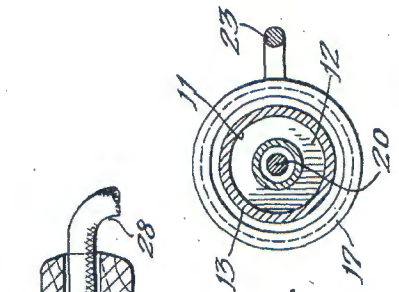


Fig. 2.

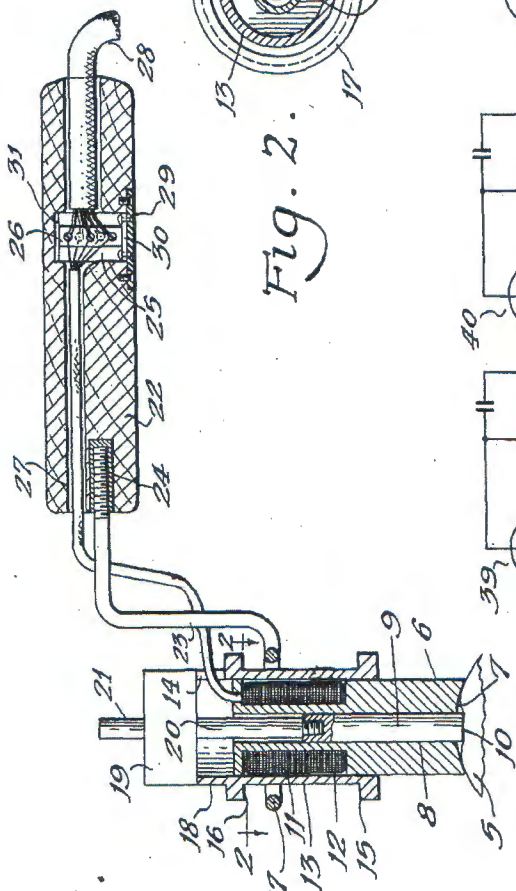


Fig. 1.

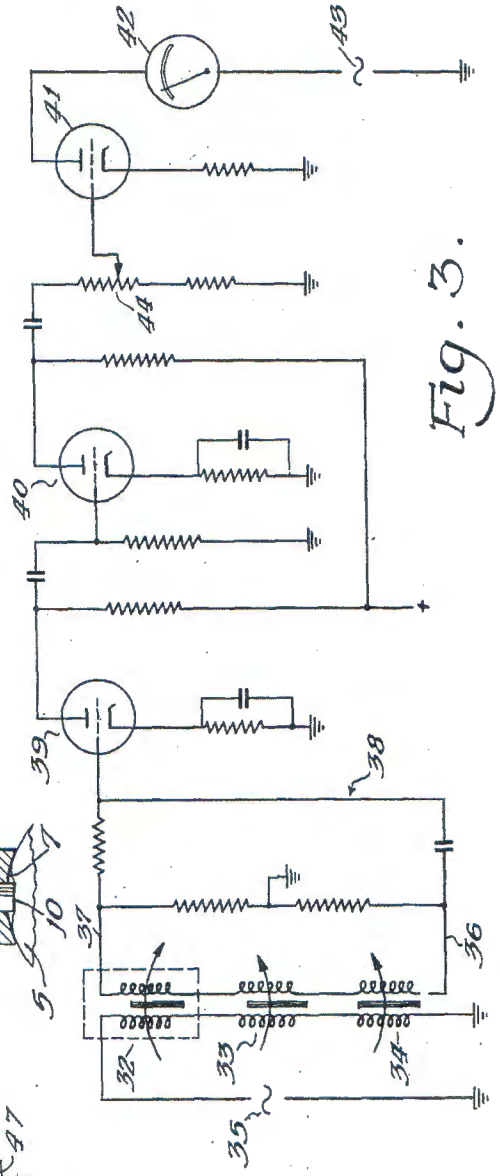


Fig. 3.

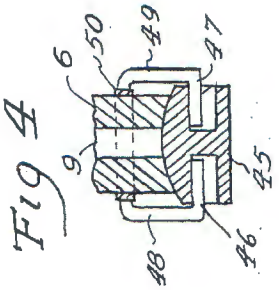


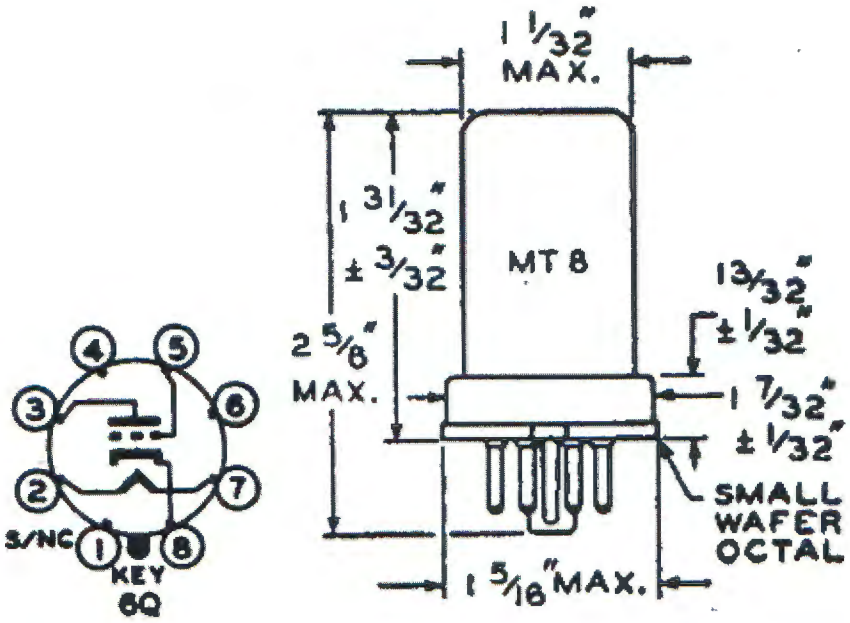
Fig 4

INVENTOR.
Morris Mages
BY Greek Wells
Attorney

NJ7P Tube Database Search

6J5
Medium-Mu Triode

Base & Bulb (RCA RC-15 - 1947)



Substitute Data

Preferred Substitutes 6C5
Substitutes 6AE5 6L5

Application

Metal type used a detectors, amplifiers, or oscillators in radio equipment. This type features high transconductance together with comparatively high amplification factor. Requires octal socket and may be mounted in any position.

Mechanical Data

Bulb MT-8
Base ..... Small Wafer Octal 6-Pin
Outline 8-3
EIA Base 6Q
Mounting Position ..... Any

Electrical Data

Heater Voltage ..... 6.3 V

Heater Current ..... **0.3 A**
Maximum Heater-Cathode Voltage
Heater Positive with Respect to Cathode
DC Component ..... **90 V**
Heater Negative with Respect to Cathode
DC Component ..... **90 V**

Direct Interelectrode Capacitances (approx)

Triode
Input ..... **3.4 pf**
Output ..... **3.6 pf**
Grid to Plate ..... **3.4 pf**

Maximum Ratings (Design Center Values)

Triode
Plate Voltage ..... **300 V**
Positive Grid No. 1 Voltage ..... **0 V**
Plate Dissipation ..... **2.5 W**
Cathode Current ..... **20 mA**
Grid No. 1 Circuit Resistance
Self Bias ..... **1M Ω**

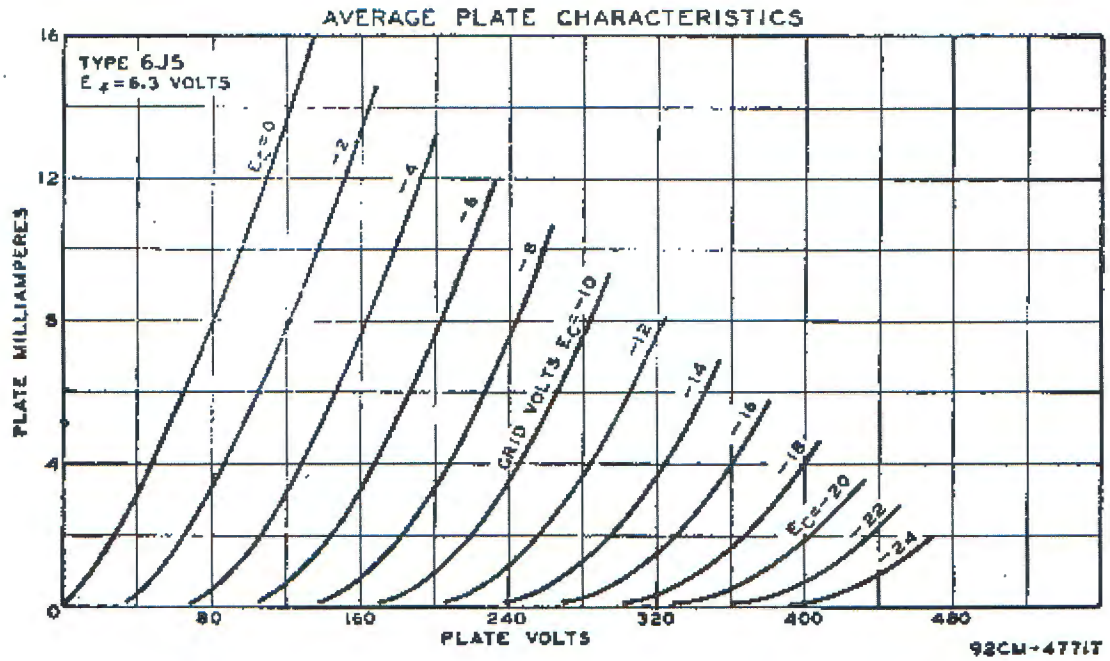
Characteristics and Typical Operation

Class A Amplifier
Plate Voltage ..... **250 V**
Grid No. 1 Voltage ..... **-8 V**
Amplification Factor **20**
Plate Resistance (approx) ..... **7.7K Ω**
Transconductance ..... **2600 μ℧**
Plate Current ..... **9 mA**

Characteristics and Typical Operation

Class A Amplifier
Plate Voltage ..... **90 V**
Grid No. 1 Voltage ..... **0 V**
Amplification Factor **20**
Plate Resistance (approx) ..... **6.7K Ω**
Transconductance ..... **3000 μ℧**
Plate Current ..... **10 mA**

Characteristic Curves



Searched 20770 records on 3667 tube types

Please enter the tube number: 6J5

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Other Tube Search Engines:
Duncan Amps
Frank's Electron Tube Pages
KBApps partial 195X RCA Receiving Tube Manual

Complete Tube Manuals:
Tube Manual Index from NJ7P

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